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Health-related quality of life in children and adolescents born very preterm and its correlates: a cross-sectional study

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Data Sharing Statement: Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to Susi Kriemler susi.kriemlerwiget@uzh.ch.

Abbreviations: BPD (Bronchopulmonary dysplasia), FLiP ("Frühgeborenen Lungen Projekt" / Premature Infant Lung Project), HRQOL (health-related quality of life), SES (Socio-economic status)

Contributors Statement:

Sarah R Haile, PhD conceptualized and designed the study, conducted the statistical analysis, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Gabriela P Peralta, PhD acquired funding, collected and cleaned the data and critically reviewed and revised the manuscript.

Mark Adams, PhD, Dirk Bassler, MD, Alexander Moeller, MD, and Giancarlo Natalucci, MD acquired funding, collected data and critically reviewed and revised the manuscript.

Ajay N Bharadwaj, BSc collected data and critically reviewed and revised the manuscript.

Thomas Radtke, PhD acquired funding, conceptualized and designed the study, and critically reviewed and revised the manuscript for important intellectual content.

Susi Kriemler, MD acquired funding, conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objective We aimed to assess health-related quality of life (HRQOL) in a cohort of very preterm born children and adolescents (aged 5-16), and to compare it with their fullterm born siblings and the general population. We also explored correlates of HRQOL among the very preterm born.

Design Cross-sectional survey

Patients Children born <32 weeks gestation

Main outcome measures Primary outcome was KINDL total score (0 worst - 100 best), a validated measure of HRQOL in children and adolescents.

Methods Linear mixed models accounted for family unit. Secondary analysis compared very preterm born children to another cohort of healthy children from the same time period. A classification tree analysis explored potential correlates of HRQOL.

Results On average, preterm children, both <28 and 28-31 weeks gestational age, had similar KINDL total score to fullterm sibling controls (-2.3, 95% CI -3.6 to -0.6), and to population controls (+1.4, 95% CI 0.2 to 2.5). Chronic health conditions, age, and respiratory symptoms affecting daily life were key correlates of HRQOL among very preterm born children.

Conclusions Very preterm birth in children and adolescents was not associated with a relevant reduction in HRQOL compared to their fullterm born peers. However, lower HRQOL was explained by other factors, such as older age, the presence of chronic health conditions, but also by current respiratory symptoms that may be modifiable. The influence of respiratory symptom amelioration and its potential influence on HRQOL needs to be investigated further.

What is already known on this topic As infants born very preterm become more likely to survive, the importance of health-related quality of life (HRQOL) increases. Research on HRQOL in very preterm born children and adolescents often focuses on non-modifiable risk factors without potential interventions.

What this study adds HRQOL in very preterm born children and adolescents is similar to that of their siblings and to the general population. Age, respiratory symptoms, and chronic health conditions were associated with HRQOL. Better control of respiratory symptoms could improve HRQOL in very preterm born children and adolescents.

How this study might affect research, practice or policy A better understanding of the complex picture of pulmonary disease following prematurity throughout life and interventions to treat respiratory symptoms may be leveraged to improve HRQOL as very preterm born children and adolescents grow.

Introduction

Recent decades have seen an increased prevalence of very preterm birth (<32 weeks gestation)[1]. These infants are born more and more premature but also increasingly likely to survive the neonatal period[2]. While much research on school-age children born very preterm has focused on neurodevelopment or somatic disease[3], outcomes such as mental health and health-related quality of life (HRQOL) are of similar importance. It has been suggested that very preterm born children have lower HRQOL than their fullterm counterparts throughout childhood[4,5], but that these differences do not necessarily persist through adolescence or adulthood[4,6,7]. Some research has specifically focused on HRQOL in preterm children with chronic health conditions, where HRQOL was even found to be similar or only slightly lower than that of their fullterm counterparts[8]. Yet, the many systematic reviews[4,5,7,8] on HRQOL in the premature born often cannot account for important potentially modifiable factors, and are likely to suffer from inadequate comparison groups or selection bias, including but not limited to selective dropout.

Studies of such correlates with HRQOL have identified factors as gender, maternal education, socio-economic status, nationality[5,9–11], motor, cognitive or neurodevelopment impairment[6,12,13], and also behavioral or non-adaptive coping difficulties[12,14]. Although a wide range of potential correlates have been explored previously, few of them are modifiable. Accordingly, it has been recommended that studies exploring long-term outcomes in the preterm born examine lifestyle factors, such as physical activity and diet, and other modifiable factors which could be leveraged to improve HRQOL in this population[15]. In this study, we aimed to compare HRQOL in very preterm born school-age children (<32 weeks gestation) to that of control fullterm siblings (37 weeks or longer), as well as to a population-based cohort from the same time and geographic

region. Further, we examined possible correlates, both modifiable and non-modifiable, of HRQOL, using conditional inference trees.

Methods

In the cross-sectional study FLiP ("Frühgeborenen Lungen Projekt" / Premature Infant Lung Project)[16], children born less than 32 weeks gestation between January 2006 and December 2019, in the greater Zurich area, Switzerland were recruited. They were all included in the Swiss Neonatal Network & Follow-Up Group (SwissNeoNet), a nationwide registry of very preterm children[17]. Parents of 1401 of 1720 potentially eligible children with valid postal addresses were invited (May - December 2021) to complete an online survey for their preterm child as well as for a term born (37 weeks gestation or later) sibling aged 1 to 18 years, referred as controls hereafter. Families who did not complete the survey within 2 weeks received a reminder call or a second invitation letter, if the phone number was not available. They could also complete a paper version and the questionnaire was available in German, English, French, and Italian. Our analysis included those participants who were at least 5 years of age or older. The study was approved by the Ethics Committee of the Canton of Zurich, Switzerland (2020–02396). Filling out the online survey was considered as providing consent. The FLiP study was powered to assess the prevalence of respiratory symptoms among children born <32 weeks gestation.

As an additional comparison to schoolchildren from the general population, we used data from the Ciao Corona study, which was part of the Swiss-wide research network Corona Immunitas[18,19]. Ciao Corona was a school-based cohort of randomly selected public and private schools and classes in the canton of Zurich, Switzerland. With 1.5 million inhabitants, the canton of Zurich is largest of 26 cantons in Switzerland by population and is home to a linguistically and ethnically diverse population in both urban and rural settings. While the primary endpoint of Ciao

Corona was seropositivity, questionnaires included a range of other measures, including the KINDL[20], assessed repeatedly between June 2020 and December 2022. For comparison with FLiP, the KINDL total score from September 2021 was used, as this best matched the timeframe of the FLiP assessment period. The Ciao Corona study was approved by the Ethics Committee of the Canton of Zurich, Switzerland (2020-01336). All participants provided written informed consent before being enrolled in the study.

The primary outcome was the KINDL total score[21], a validated instrument for assessing HRQOL ranging from 0 (worst) to 100 (best) (for further details, see Supplementary Material and Table S1). Secondary outcomes included all the KINDL subscales (physical, emotional, self-esteem, family, friends, and school). Additional data collected included participants' age and gender, gestational age (in weeks, range 24 - 31), birthweight (in grams), diagnosed bronchopulmonary dysplasia (BPD), socio-economic status (SES), family unit, chronic health conditions, hours of physical activity per week, hours of screen time per week, participation in music lessons, participation in scouts, participation in sports, and need for various types of therapy. Prematurity-related diagnosis of BPD was taken from personal history of the premature born children included in the SwissNeoNet registry (none to mild vs moderate to severe). SES was determined according to each parent's education level (1 university, 2 vocational university, 3 apprenticeship, 4 job requiring minimal training, 5 compulsory education, 6 less than compulsory education), and then summed over both parents (range 2 highest education - 12 lowest education). Chronic health conditions were categorized as respiratory, non-respiratory or cerebral palsy. Respiratory conditions included asthma and cystic fibrosis. Non-respiratory conditions included heart conditions, diabetes, intestinal issues, low/high blood pressure, attention deficit hyperactivity disorder, epilepsy, joint disorders, and depression. Cerebral palsy was reported separately along with its severity (none; mild, no to minimal restriction to daily activities; mild, limitations in daily activities but without the need for aids; moderate, needs

prostheses, medication or technical aids to manage daily activities; severe, requires a wheelchair and has significant difficult in daily activities). Types of therapy included speech, physical, occupational, psychomotor, curative or psychological therapy, as well as early support programs. To assess whether respiratory symptoms affected daily life, parents were asked about several questions related to whether their child had cough or wheezing due to physical exertion in the last 12 months or whether cough, or wheezing restricted their daily activities. Other included variables were: number of siblings, presence of house pets, whether parents smoked (no/outside/in the home), number of therapies used, use of assistive devices (e.g hearing aids, walking aids, wheelchair), hours of physical activity per day, hours of screen time per day, and participation in sports, scouts, or musical activities (see Supplementary Material for wording of selected questions).

Key demographic variables were summarized as median (range), n (%), or in the case of socio-economic status, median [IQR]. Outcomes were compared between FLiP preterm and FLiP control participants using linear mixed models, including family unit as a random effect. Comparisons of FLiP preterm and Ciao Corona control participants were made using linear regression, after 2:1 matching on age in years, sex and nationality. Sensitivity analyses included a) excluding participants with chronic health conditions, b) restricting to preterm born children with control siblings, c) stratification by age, and d) adjusting for SES. Coefficients and corresponding 95% confidence intervals were interpreted according to their possible relevance, rather than with p-values[22,23]. To explore other potential correlates, both modifiable and non-modifiable, of HRQOL among very preterm born children, we used conditional inference trees[24,25] estimated by binary recursive partitioning. To handle missing predictor values, the conditional inference trees used up to 3 surrogate splits[24]. The algorithm stopped if no split with $\alpha < 0.05$ could be constructed or if a subgroup had less than 25 participants. For further details, see Supplementary Material.

The statistical analysis was performed using R (R version 4.4.1 (2024-06-14)). Linear mixed models were fit using the `lmerTest` package[26], and tables were produced with `gtsummary`[27]. The classification trees were fit using the `ctree` function from `partykit`[28]. Matching to the Ciao Corona data was performed using the `MatchIt` package[29].

Patient and Public Involvement

Patients or their parents were not involved in the planning of the FLiP survey. In the Ciao Corona study, several school principals were consulted during the development of the protocol to ensure feasibility of the planned study procedures. Feedback was continuously collected from invited and enrolled children and parents to adapt the communication strategies and channels. Online informational sessions, which encouraged open exchange and feedback, were organised at the onset of the study for invited and enrolled school principals, staff, and parents of the children.

Results

After inviting 1401 very preterm born children and their parents to participate in FLiP, data from 681 40% preterm children and 205 fullterm control siblings was available. Among the very preterm born, we excluded 199 children that were younger than 5 years of age and 40 had not filled out KINDL, leaving 442 preterm participants. Among their fullterm born siblings, 56 were younger than 5 years of age and 4 had not filled out KINDL, leaving 145 fullterm siblings (see **Supplementary Figure S1**). We also included 1058 participants from Ciao Corona (total n=4435, 2020 - 2022, of whom 2974 had participated prior to September 2021[30]) with a KINDL total score in September 2021. Characteristics of the included participants are found in **Table 1**, and not included participants were similar regarding most morbidities typical for the very preterm (**Supplementary Table S2**).

Very preterm born children with gestational age 24-27 weeks (n = 130) had an average total KINDL score of 77.3 ± 10.0 points out of 100, while those with gestational age 28-31 weeks (n = 312) had an average total KINDL score of 78.9 ± 10.5, compared to 80.8 ± 8.7 among fullterm born control siblings. On average, preterm children born at 24-27 weeks had a 2.3 point lower KINDL total score than fullterm controls (95% CI -4.4 to -0.2), when accounting for family unit. Similarly, those born at 28 weeks had a 2.3 point lower KINDL total score than fullterm controls (95% CI -3.9 to -0.7) (**Figure 1, Supplementary Table S3**). The pattern was similar for the KINDL subscales (**Supplementary Figure S2**), and when comparing those with birthweight <1000g with those at least 1000g (**Supplementary Figures S3 and S4, Supplementary Table S4**). Results were similar when examining all preterm born children together for both KINDL total score and its subscales (**Supplementary Figures S5 and S6, Table S5**), and did not change in any of the sensitivity analyses.

A number of other potential non-modifiable and modifiable correlates for HRQOL were further considered in a classification tree analysis (**Supplementary Table S6**). It indicated that respiratory symptoms affecting daily activities as well as age and chronic non-respiratory conditions were the primary correlates of HRQOL among very preterm born children and adolescents in our sample (Figure 2), with mean KINDL total score ranging from 68.2 ± 13.1 (among those 10 years of age or older with chronic non-respiratory conditions) to 80.5 ± 8.8 (among those with no chronic health conditions and no respiratory symptoms affecting daily activities). 67% (296 / 442) of the sample was in the latter group that could not be further differentiated with the selected variables. Notably, gestational age, birthweight and BPD were not identified as correlates of HRQOL in our sample.

Discussion

We observed no relevant difference in HRQOL (KINDL total score) when comparing very preterm children to their fullterm siblings, even after accounting for gestational age or birthweight, chronic health conditions, including respiratory conditions or cerebral palsy, and did not change in any of the sensitivity analyses. HRQOL among very preterm children was also similar to that of the general population of schoolchildren. When considering possible variables associated with HRQOL beyond prematurity, respiratory symptoms affecting daily activities, chronic non-respiratory conditions, and age group appeared to play a role and were identified as more important correlates of HRQOL than gestational age. Two points out of 100 difference in the total KINDL score represent a marginal difference in HRQOL that was not clinically relevant. Comparing KINDL in children with and without various chronic health conditions, differences ranging from 1.9 (children with asthma) to 6.2 (cancer survivors) points have been observed[31–33]. The 2 point difference in our study was thus quite small, and based on the variability of the KINDL total score (SD=10.3), likely not meaningful.

In a classification tree analysis the most important factors correlated with HRQOL appeared to be age group, chronic health conditions and the existence of respiratory symptoms affecting daily activities. While age and chronic health conditions are not modifiable, the presence of respiratory symptoms may be modifiable, indicating that improvement of respiratory symptoms may potentially improve HRQOL in the very preterm born.

Children with respiratory symptoms should be investigated for their phenotype profile and potentially treatable traits by a pediatric pulmonologist to understand the complex picture of prematurity associated respiratory symptoms, and whether or not the child may benefit from treatment at all or treatment optimization[34]. This is important as up to 40% of the premature population are prescribed asthma medication during childhood[34], although there is a lack of

objective evidence on how to treat these individuals and whether treatment improves symptoms[34–36]. Thus, individual treatment needs to be based on the phenotype or underlying mechanisms of prematurity-associated lung disease as proposed by for instance the wheel-and-spoke model that combines components of a phenotype classification including structural, physiological, inflammatory and clinical traits[34]. Non-pharmaceutical interventions such as exercise to improve cardiopulmonary function might likewise be of benefit[37]. Our finding that respiratory symptoms are correlated with HRQOL could imply that interventions targeting those symptoms may potentially also improve HRQOL in the very preterm born. This hypothesis of course should be tested in future studies.

Our analysis has several strengths. It used a relatively large registry of very preterm born children in Switzerland and included fullterm born siblings as a control group. Family unit was accounted for in the analysis. The Ciao Corona study provided a school-based random sample of school children in the same geographic region and time period. We considered a broad range of possible correlates of HRQOL in a classification tree analysis. A key limitation is that longitudinal data on HRQOL was not available for this sample of children, and not all very preterm born participants had control siblings. We did not have information on other potentially important variables, for example, on participants' mental health status (e.g. sadness or anxiousness[38]) or on social support[39], which could have provided useful information in the conditional inference tree analysis. There were also not many fullterm born children with chronic health conditions in the FLiP sample, which would have allowed us to further explore the associations between very preterm birth, chronic health conditions and HRQOL. Like other studies of very preterm born children, our sample may have had selection bias[5,7]. Although this research took place during the COVID-19 pandemic which may have affected HRQOL of the children, but if so, this was likely true for all included groups. Nevertheless, we cannot exclude that premature born children were especially shielded, which would compromise HRQOL even

more. Yet, this was not the case and HRQOL was similar in normal school children and previously premature children.

It is a gift of medicine that children born <32 weeks gestation generally have a HRQOL comparable to fullterm born children[6]. Nevertheless, there are children that clearly show compromised HRQOL. While an association between HRQOL and older age or chronic health conditions such as cerebral palsy may often be expected and considered plausible, the association with respiratory symptoms may be neglected and often not addressed[40]. A better understanding of the complex picture of pulmonary disease following prematurity throughout life and interventions to treat respiratory symptoms, such as medical treatment or those targeting aerobic exercise and physical activity, may be leveraged to improve HRQOL as very preterm born children and adolescents grow.

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Figures and Tables

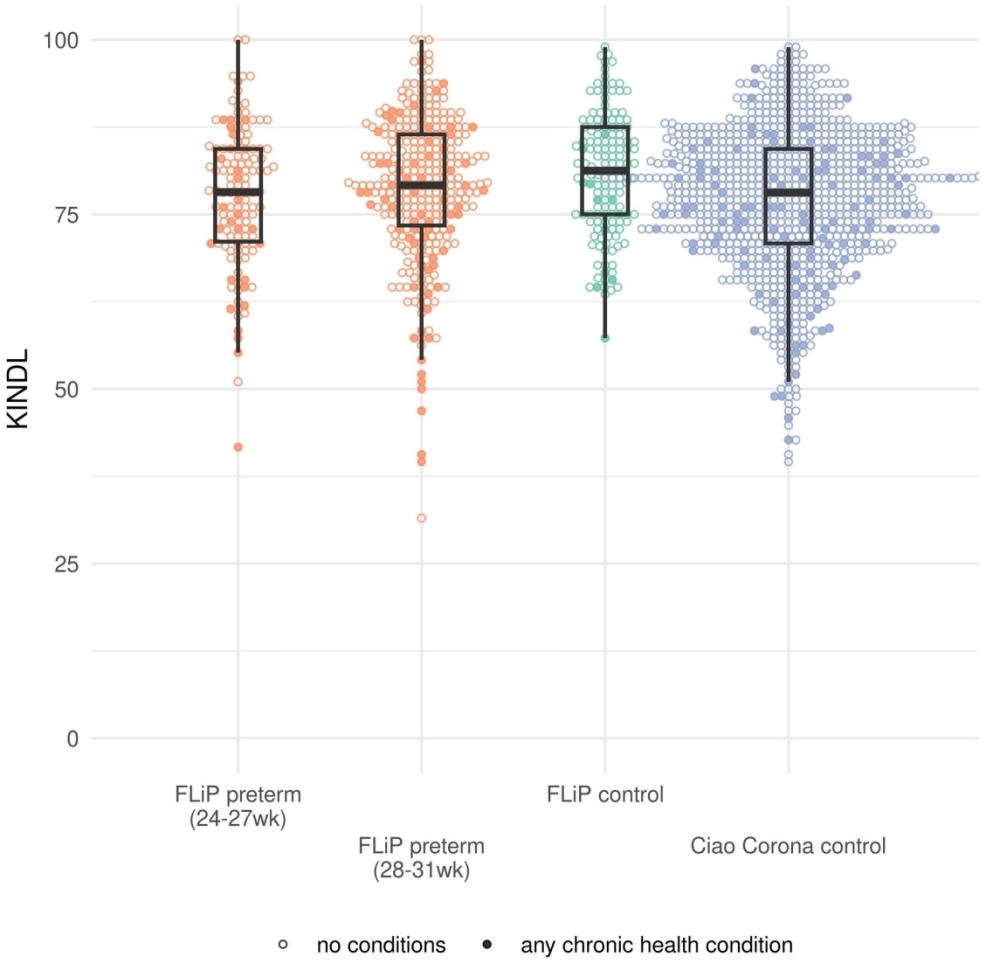
Figure 1: KINDL total score, for very preterm born children (FLiP preterm, stratified by gestational age 24-27 weeks or 28-31 weeks) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control). Solid circles indicate participants without chronic health conditions, while empty diamonds indicate those with any chronic health condition, respiratory or non-respiratory.

Figure 2: Classification tree for KINDL total score in very preterm born children, based on a range of possible correlates (see Table S7). Identified correlates are chronic non-respiratory conditions, age group (5-9 vs 10+), and whether respiratory symptoms negatively affect daily life. For each identified subgroup, mean ± standard deviation for KINDL total score is given, along with the number of participants.

Table 1: Key characteristics of FLiP very preterm born children and adolescents, their control siblings, and age, sex and nationality matched control participants from Ciao Corona. BPD indicates bronchopulmonary dysplasia. Chronic health conditions included asthma, cystic fibrosis, congenital heart defects, heart disease, celiac, diabetes, inflammatory bowel disease, high blood pressure, attention deficit hyperactivity disorder, epilepsy, joint disorders, depression/anxiety, and cerebral palsy. Socio-economic status is measured on the basis of parents' education from 2 (both parents having university education) to 12 (both parents less than compulsory education) points, though the

categories differed somewhat in FLiP and Ciao Corona. As physical activity was assessed using different questions in Ciao Corona than in FLiP that were not comparable, we did not include physical activity in Ciao Corona here.

Characteristic	FLiP preterm N = 442	FLiP control N = 145	Ciao Corona control N = 882
age (years)	10 (5 - 16)	9 (5 - 19)	10 (6 - 16)
sex (male)	236 (53%)	84 (59%)	472 (54%)
gestational age (weeks)			
24-27 wks	130 (29%)		
28-31 wks	312 (71%)		
birthweight			
<1000g	158 (36%)		
1000+g	284 (64%)		
multiple gestation	140 (32%)		
socio-economic status	5 [3, 6]	5 [3, 6]	4 [3, 5]
non-Swiss nationality	66 (15%)	20 (14%)	121 (14%)
moderate to severe BPD	55 (12%)		
coughing / wheezing restrict daily activities	13 (2.9%)	1 (0.7%)	
any chronic health condition	104 (24%)	12 (8.3%)	122 (14%)
chronic non-respiratory conditions	67 (15%)	11 (7.6%)	96 (11%)
chronic respiratory conditions	24 (5.4%)	3 (2.1%)	34 (3.9%)
cerebral palsy	33 (7.5%)	1 (0.7%)	0 (0%)
physical activity (hours per day)	0.71 [0.50, 1.00]	0.71 [0.57, 1.14]	



KINDL total score, for very preterm born children (FLiP preterm, stratified by gestational age 24-27 weeks or 28-31 weeks) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control). Solid circles indicate participants without chronic health conditions, while empty diamonds indicate those with any chronic health condition, respiratory or non-respiratory.

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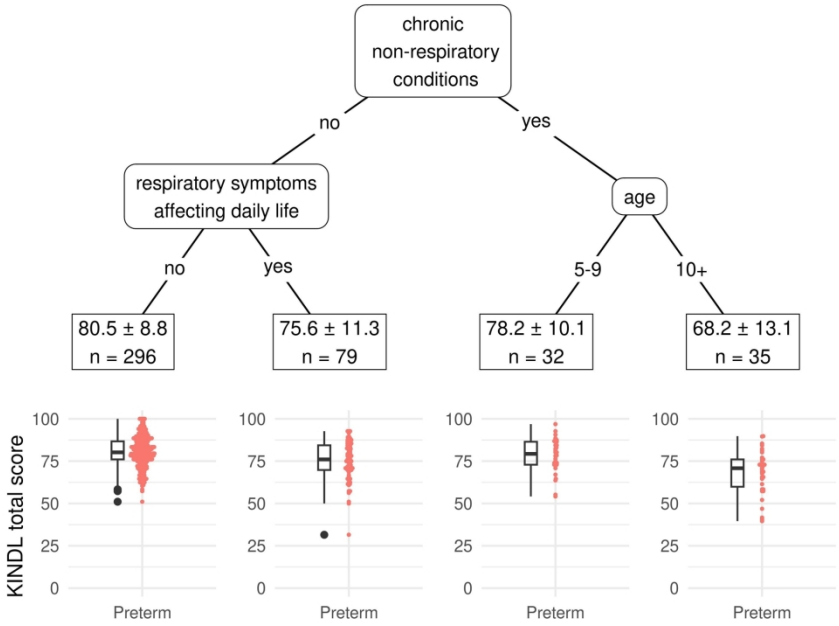

Classification tree for KINDL total score in very preterm born children, based on a range of possible correlates (see Table S7). Identified correlates are chronic non-respiratory conditions, age group (5-9 vs 10+), and whether respiratory symptoms negatively affect daily life. For each identified subgroup, mean ± standard deviation for KINDL total score is given, along with the number of participants.

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Health-related quality of life in children and adolescents born very preterm and its correlates - supplementary material

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Supplementary Methods

The KINDL score

The KINDL-R score (hereafter, KINDL) is a validated instrument for measuring health-related quality of life} [1], with scores ranging from 0 (worst) to 100 (best). In FLiP, we used slightly adapted versions of the parent (proxy) versions for 4-6 year olds and for 7-17 year old children and adolescents (https://www.kindl.org/contacts/english/). In Ciao Corona, we used the parent (proxy) version, for 7-17 year old children and adolescents. All questions as asked are listed in Table S1. The KINDL contains 24 items, 4 in each of 6 subscales: physical well-being, emotional well-being, self-esteem, family, social contacts / friends, and school. To compute the KINDL score, certain items are first recoded. A subscale can be analysed as long as no more than 30% of its items are missing. Mean value replacement is used to deal with missing item scores. The 6 subscales are then added and rescaled to 0-100 to form the KINDL total score. Sample code is available at https://www.kindl.org/english/analysis/.

Table S1: KINDL questions as used in the FLiP and Ciao Corona studies. Item are noted with an asterisk (*) if the wording has been adapted for FLiP.

item	FLiP (age 3 - 6 years)	FLiP (age 7 – 17 years)	Ciao Corona
1. Physical Well-being			
	During the past week. . .	During the past week. . .	During the past week. . .
1	. . . my child felt ill.	. . . my child felt ill.	. . . my child felt ill.
2	. . . my child had a headache or tummyache.	. . . my child had a headache or tummyache.	. . . my child had a headache or tummyache.
3	. . . my child my child was tired and worn-out.	. . . my child my child was tired and worn-out.	. . . my child my child was tired and worn-out.
4	. . . my child felt strong and full of energy.	. . . my child felt strong and full of energy.	. . . my child felt strong and full of energy.
2. Emotional Well-being			
	During the past week. . .	During the past week. . .	During the past week. . .
1	... my child had fun and laughed a lot	... my child had fun and laughed a lot	... my child had fun and laughed a lot
2	... my child didn't feel much like doing anything	... my child didn't feel much like doing anything	... my child didn't feel much like doing anything
3	... my child felt alone	... my child felt alone	... my child felt alone
4	... my child felt alone	... my child felt alone	... my child felt alone
3. Self-esteem			
	During the past week. . .	During the past week. . .	During the past week. . .
1	... my child was proud of him-/herself	... my child was proud of him-/herself	... my child was proud of him-/herself
2	... my child felt on top of the world	... my child felt on top of the world	... my child felt on top of the world
3	... my child felt pleased with him-/herself	... my child felt pleased with him-/herself	... my child felt pleased with him-/herself
4	... my child had lots of good ideas	... my child had lots of good ideas	... my child had lots of good ideas
4. Family			
	During the past week. . .	During the past week. . .	During the past week. . .
1	... my child got on well with us as parents	... my child got on well with us as parents	... my child got on well with us as parents

Table S1: KINDL questions as used in the FLiP and Ciao Corona studies. Item are noted with an asterisk (*) if the wording has been adapted for FLiP. *(continued)*

item	FLiP (age 3 - 6 years)	FLiP (age 7 – 17 years)	Ciao Corona
2	... my child felt fine at home	... my child felt fine at home	... my child felt fine at home
3	... we quarrelled at home	... we quarrelled at home	... we quarrelled at home
4	... my child felt that I was bossing him/her around	... my child felt that I was bossing him/her around	... my child felt that I was bossing him/her around
5. Social Contacts			
	During the past week. . .	During the past week. . .	During the past week. . .
1*	... my child played or did things together with friends	... my child played or did things together with friends	... my child did things together with friends
2	... my child was liked by other kids	... my child was liked by other kids	... my child was liked by other kids
3	... my child got along well with his/ her friends	... my child got along well with his/ her friends	... my child got along well with his/ her friends
4	... my child felt different from other children	... my child felt different from other children	... my child felt different from other children
6. School			
	During the past week. . .	During the past week. . .	During the last week in which my child was at school . . .
1*	... my child coped well with the assignments set in nursery school/ kindergarten	... my child easily coped with schoolwork	... my child easily coped with schoolwork
2*	... my child enjoyed the nursery school/ kindergarten	... my child enjoyed the school lessons	... my child enjoyed the school lessons
3*	... my child looked forward to nursery school/kindergarten	... my child worried about his/her future	... my child worried about his/her future
4*	... my child made lots of mistakes when doing minor assignments or homework	... my child was afraid of bad marks or grades	... my child was afraid of bad marks or grades

Chronic health conditions listed on the surveys

- **FLiP**: asthma, cystic fibrosis, congenital heart defects, heart disease, celiac / gluten allergy , lactose intolerance, allergies (other than hay fever), diabetes mellitus, chronic inflammation of the bowel (ulcerative colitis or Crohn's disease), high blood pressure (hypertension), attention deficit disorder (ADHD, ADD), epilepsy, joint disease (e.g. arthritis), depression/anxiety disorder, other [comment field], cerebral palsy [with severity]
- **Ciao Corona**: asthma, hay fever, celiac, lactose intolerance, allergies (other than hay fever), neurodermatitis / excema, Diabetes Mellitus, chronic inflammation of the bowel (ulcerative colitis or Crohn's disease), high blood pressure (hypertension), attention deficit disorder (ADHD, ADD), epilepsy, joint disease (e.g. arthritis), depression/anxiety disorder, other [comment field]

The following conditions were not counted as chronic health conditions for the purposes of this analysis: hay fever, celiac, gluten allergy, lactose intolerance, allergies (other than hay fever). The Ciao Corona study did not ask specifically about cerebral palsy, but it was also not reported under "other".

Selected Questions from FLiP

- **Respiratory symptoms affecting daily life**: Yes to any of the following questions:
  a) *In the last 12 months, has your child ever had whistling or wheezing breathing during or after physical exertion?*
  b) *Have any of the following situations triggered a cough in your child in the last 12 months? Physical exertion (running, sports)*
  c) *Have any of the following situations triggered whistling or wheezing in your child in the last 12 months? Physical exertion (running, sports)*
  d) *Does your child sometimes have difficulty breathing during physical exertion?*
  e) *In the last 12 months, how much was your child's daily activities (or play behaviour) restricted by the cough?*
  f) *In the last 12 months, how much was your child restricted in his/her daily activities (or play behaviour) because of whistling or wheezing breathing or shortness of breath?*
- **Physical Activity**: *On average, how many hours per week does your child spend in physical activity that causes at least some sweating or heavy breathing? (School sport INCLUDED)* This value was converted to hours per day.
- **Screen Time**: These values were converted to average hours per day.
  a) *How many hours per day does your child CURRENTLY spend using electronic devices on a typical weekday? NOT counting school lessons and schoolwork. For example: Mobile phone, tablet, Playstation, Xbox, Nintendo, computer, TV*
  b) *How many hours per day does your child CURRENTLY spend using electronic devices on a typical weekend day? NOT counting school lessons and schoolwork. For example: Mobile phone, tablet, Playstation, Xbox, Nintendo, computer, TV*
- **Sports**: *Does your child participate regularly (at least once every 2 weeks) in the following activities? Yes, sport activities such as gymnastics club, ballet, dance, tennis, basketball, football club etc.*
- **Music**: *Does your child participate regularly (at least once every 2 weeks) in the following activities? Yes, music lessons, musical activities, theatre, circus, etc.*
- **Scouts**: *Does your child participate regularly (at least once every 2 weeks) in the following activities? Yes, other activities such as Scouts, Cevi [YMCA / YWCA], Blauring / Jungwacht [similar Catholic organization], etc.*
- **SES**: Sum of *What is the highest educational qualification of the mother?* and *What is the highest educational qualification of the father?* as defined by SwissNeoNet https://app.swissneonet.ch/data/live/structure/38/show
  1. University
  2. University of applied science, technical college, higher level job training, college of education, university entrance qualification (Matura or Berufsmatura)
  3. Apprenticeship or secondary school diploma
  4. Job requiring minimal training
  5. Regular school without job training
  6. No education, or unfinished regular school

Detailed Statistical Methods: Conditional Inference Trees

We used conditional inference trees [2, 3] estimated by binary recursive partitioning to identify possible determinants of health-related quality of life (HRQOL) in very preterm born children and adolescents. These models seek to make homogeneous subgroups, i.e. clusters, of the sample with respect to the outcome of interest. Generally, the algorithm 1) searches for the variable with the strongest association to the outcome, and then 2) splits the values of that variable into two groups, and repeats this process until some stopping criteria (in this analysis, p-value < 0.05 or sample size < 25) are reached. While all types of variables can be selected in step 1 of this algorithm, categorical and continuous variables have more flexibility in terms of selected thresholds in step 2 than binary variables do. Conditional inference trees select variables in an unbiased manner, without being affected by overfitting [2]. Such models identify subgroups defined by combinations of covariates, without needing to *a priori* specify interaction terms or consider multicollinearity [4], and thresholds do not need to be prespecified. Standard regression models, even when combined with model selection, do not identify homogenous subgroups. Due the presence of missing observations in some of the variables, we employed so-called surrogate splits to account for this missingness without excluding subjects [2].

The conditional inference trees were fit using `ctree` from the R package `partykit` [2, 5]. Missing covariate information was handled by `ctree` directly. All analysis was performed in R (R version 4.4.1 (2024-06-14)).

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Supplementary Results

Analysis Population

Flowchart

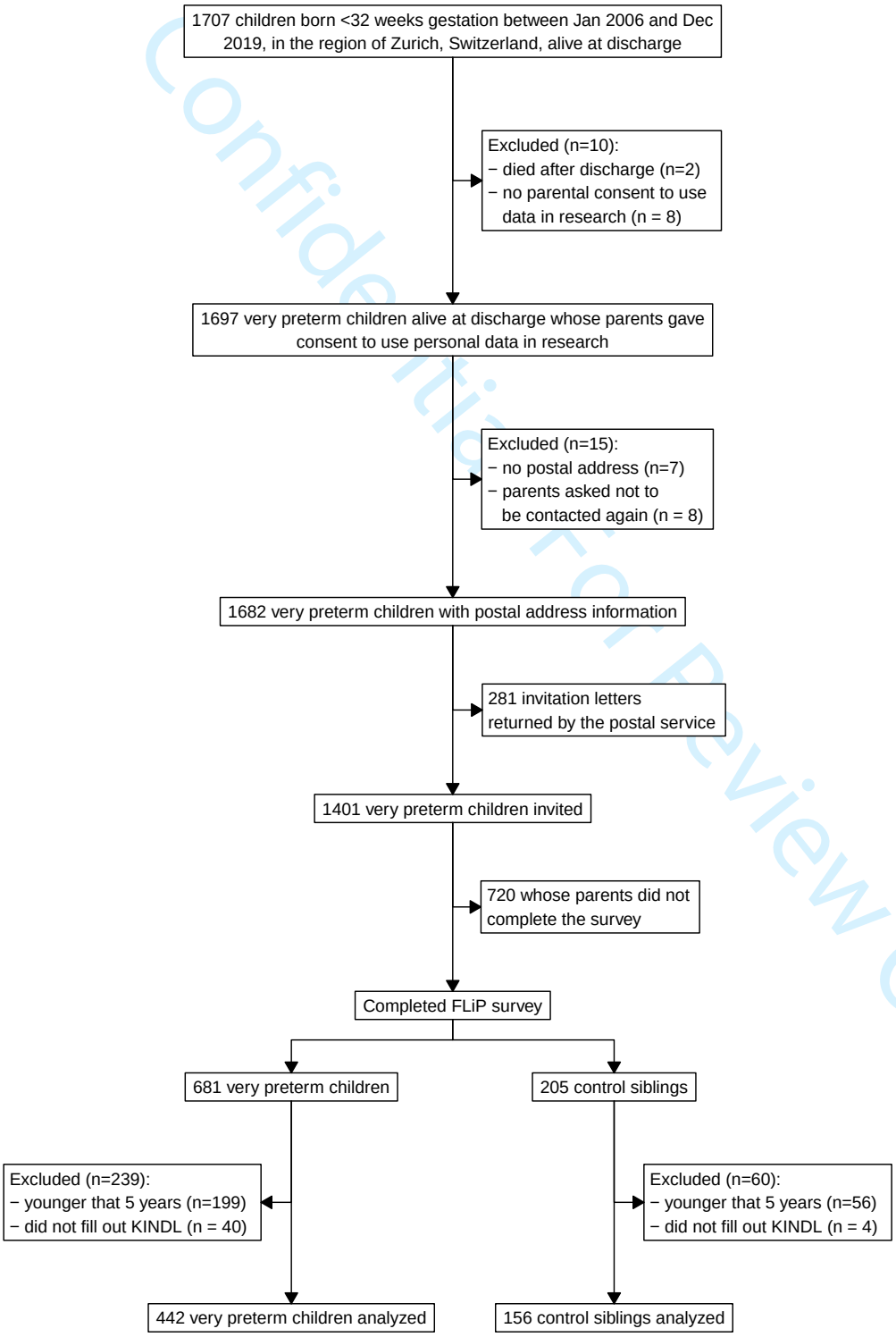

Figure S1: Flowchart of children and adolescents included in the FLiP cohort study.

Analyzed vs not analyzed very preterm born children

Very preterm born children included in our analysis were generally comparable to those not included, though with slightly lower gestational age and birthweight, and more likely to have had supplemental oxygen at 36 weeks, as moderate to severe BPD is often defined. Notably, none of the other morbidities typical for very preterm children are different between participants and non-participants (**Supplementary Table S2**).

Table S2: Comparisons of very preterm born children included in this analysis ('analyzed') vs not included in this analysis. IVH indicates intraventricular hemorrhage, PVL periventricular leukomalacia, NEC necrotizing enterocolitis, ROP retinopathy of prematurity, and NDI neurodevelopmental impairment.

variable	not analyzed	analyzed	p-value	Total
N	1031 (70%)	442 (30%)		1473
Gestational age (IQR)	30.6 (28.6 to 31.7)	29.4 (27.4 to 30.7)	<0.0001	30.1 (28.1 to 31.4)
Birth weight z-score (Voigt 2006) (IQR)	-0.2 (-1.2 to 0.4)	0 (-0.6 to 0.4)	<0.0001	-0.1 (-1 to 0.4)
Sex male N (%)	563 (54.6 %)	236 (53.4 %)	0.710	799 (54.2 %)
Outborn N (%)	29 (2.8 %)	9 (2 %)	0.495	38 (2.6 %)
Multiple births N (%)	376 (36.5 %)	140 (31.7 %)	0.088	516 (35 %)
Any antenatal steroids N (%)	910 (91.6 %)	397 (92.5 %)	0.642	1307 (91.9 %)
Caesarean section N (%)	889 (86.2 %)	382 (86.4 %)	0.985	1271 (86.3 %)
Congenital malformation (validated) N (%)	20 (1.9 %)	7 (1.6 %)	0.799	27 (1.8 %)
Severe IVH N (%)	35 (3.4 %)	18 (4.1 %)	0.625	53 (3.6 %)
Cystic PVL N (%)	9 (0.9 %)	4 (0.9 %)	1.000	13 (0.9 %)
Supplemental oxygen at 36 weeks GA* N (%)	72 (7 %)	55 (12.4 %)	0.001	127 (8.6 %)
NEC stage >=2 N (%)	16 (1.6 %)	7 (1.6 %)	1.000	23 (1.6 %)
Severe ROP* N (%)	21 (2.8 %)	12 (3 %)	0.977	33 (2.9 %)
Moderate to severe NDI at 2 years corr. N (%)	147 (24.4 %)	85 (22.1 %)	0.450	232 (23.5 %)
Cerebral palsy at 2 years corr. N (%)	36 (6.3 %)	18 (4.8 %)	0.394	54 (5.7 %)

Main Analyses

Stratified by Gestational Age

Table S3: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP or participants from Ciao Corona, stratified by gestational age (24-27 weeks vs 28-31 weeks). Mean differences denote either differences in health-related quality of life between FLIP very preterm born siblings and their control siblings, or between FLIP very preterm born siblings and controls from Ciao Corona. Negative mean differences indicate that very preterm born children had lower HRQOL than controls. Mean differences and 95% confidence intervals account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

Gestational Age	cohort	Preterm	Control	difference	confidence interval
Total					
24 - 27 weeks	FLiP	77.6 (10.0)	80.8 (8.7)	-2.27	(-4.36 to -0.17)
	Ciao Corona		77.2 (10.2)	0.45	(-1.42 to 2.32)
28 - 31 weeks	FLiP	78.9 (10.5)	80.8 (8.7)	-2.29	(-3.86 to -0.73)
	Ciao Corona		77.2 (10.2)	1.72	(0.40 to 3.04)
Physical					
24 - 27 weeks	FLiP	77.4 (17.7)	82.9 (14.7)	-5.17	(-9.02 to -1.31)
	Ciao Corona		77.6 (14.9)	-0.19	(-3.02 to 2.63)
28 - 31 weeks	FLiP	82.3 (15.0)	82.9 (14.7)	-0.44	(-3.08 to 2.20)
	Ciao Corona		77.6 (14.9)	4.74	(2.81 to 6.67)
Emotional					
24 - 27 weeks	FLiP	79.5 (13.0)	83.6 (11.6)	-3.35	(-6.10 to -0.61)
	Ciao Corona		80.5 (14.1)	-0.99	(-3.55 to 1.56)
28 - 31 weeks	FLiP	80.8 (14.0)	83.6 (11.6)	-3.12	(-5.49 to -0.75)
	Ciao Corona		80.5 (14.1)	0.32	(-1.50 to 2.14)
Self-esteem					
24 - 27 weeks	FLiP	73.9 (13.3)	76.8 (12.9)	-2.25	(-5.25 to 0.75)
	Ciao Corona		72.3 (13.5)	1.64	(-0.83 to 4.11)
28 - 31 weeks	FLiP	73.2 (13.8)	76.8 (12.9)	-3.68	(-5.98 to -1.37)
	Ciao Corona		72.3 (13.5)	0.87	(-0.87 to 2.60)
Family					
24 - 27 weeks	FLiP	80.5 (12.6)	80.3 (12.8)	1.18	(-1.60 to 3.96)
	Ciao Corona		79.1 (12.8)	1.44	(-0.91 to 3.79)
28 - 31 weeks	FLiP	80.2 (13.3)	80.3 (12.8)	-0.84	(-2.83 to 1.15)
	Ciao Corona		79.1 (12.8)	1.25	(-0.41 to 2.92)
Friends					
24 - 27 weeks	FLiP	75.5 (14.2)	78.4 (13.1)	-2.20	(-5.34 to 0.95)
	Ciao Corona		77.8 (13.5)	-2.22	(-4.73 to 0.29)
28 - 31 weeks	FLiP	76.7 (15.4)	78.4 (13.1)	-2.07	(-4.76 to 0.61)
	Ciao Corona		77.8 (13.5)	-1.06	(-2.88 to 0.75)
School					
24 - 27 weeks	FLiP	77.5 (16.5)	82.5 (13.6)	-4.02	(-7.63 to -0.41)
	Ciao Corona		75.6 (15.9)	1.58	(-1.44 to 4.60)
28 - 31 weeks	FLiP	80.5 (14.8)	82.5 (13.6)	-2.11	(-4.59 to 0.36)

	Ciao Corona	75.6 (15.9)	4.81 (2.83 to 6.80)

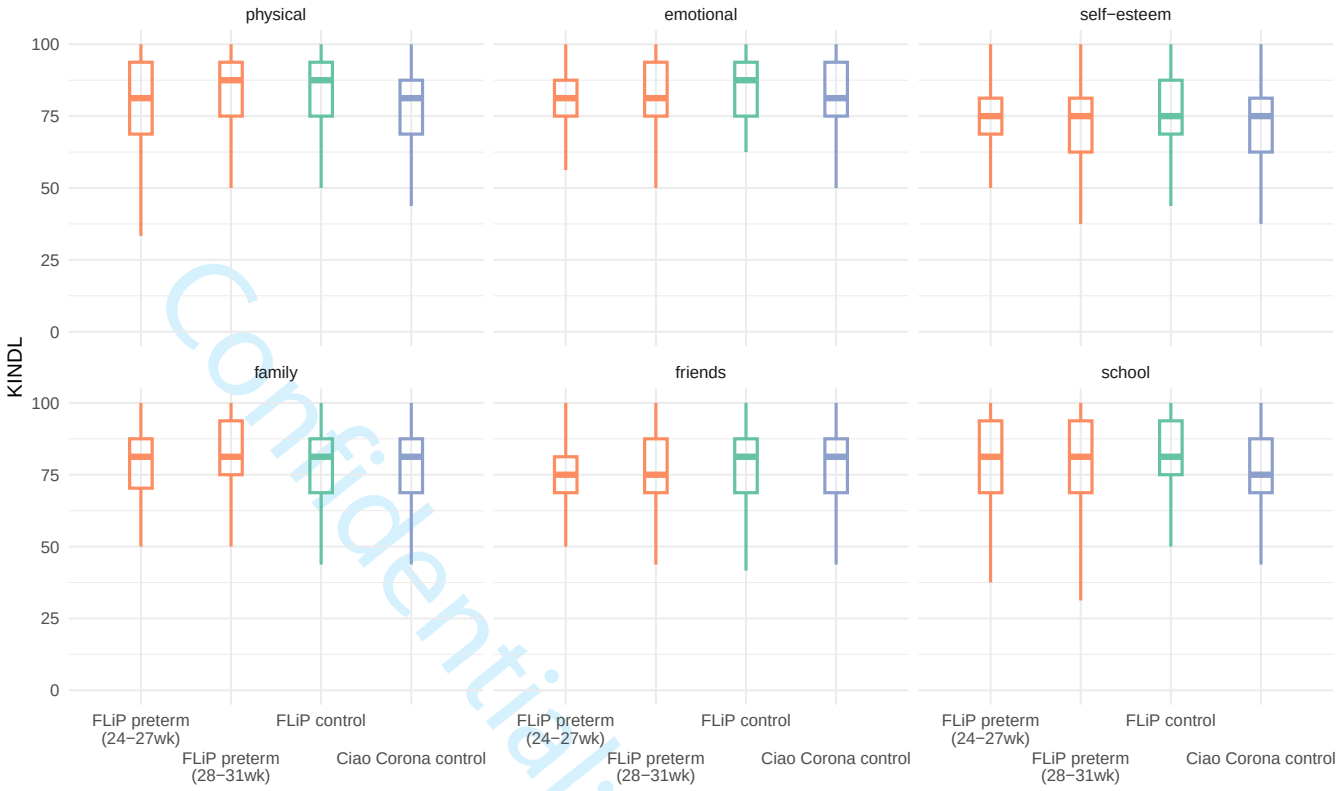

Figure S2: KINDL subscales, for very preterm born children (FLiP preterm, stratified by gestational age 24-27 weeks vs 28-31 weeks) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control).

Stratified by Birthweight

Table S4: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP and participants from Ciao Corona, stratified by birthweight ($<$ 1000g vs $\geq$ 1000g). Mean differences denote either differences in health-related quality of life between FLIP very preterm born siblings and their control siblings, or between FLIP very preterm born siblings and controls from Ciao Corona. Mean differences and 95% confidence intervals account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

Birthweight	cohort	Preterm	Control	difference	confidence interval
Total					
< 1000g	FLiP	76.6 (10.4)	80.8 (8.7)	-3.44	(-5.48 to -1.41)
	Ciao Corona		77.2 (10.2)	-0.54	(-2.27 to 1.19)
1000g +	FLiP	79.5 (10.1)	80.8 (8.7)	-1.46	(-3.05 to 0.12)
	Ciao Corona		77.2 (10.2)	2.40	(1.04 to 3.76)
Physical					
< 1000g	FLiP	77.0 (16.9)	82.9 (14.7)	-5.33	(-8.84 to -1.83)
	Ciao Corona		77.6 (14.9)	-0.58	(-3.17 to 2.01)
1000g +	FLiP	83.0 (15.1)	82.9 (14.7)	0.43	(-2.35 to 3.21)
	Ciao Corona		77.6 (14.9)	5.43	(3.43 to 7.43)
Emotional					
< 1000g	FLiP	79.8 (13.8)	83.6 (11.6)	-2.99	(-5.72 to -0.27)
	Ciao Corona		80.5 (14.1)	-0.72	(-3.10 to 1.65)
1000g +	FLiP	80.8 (13.6)	83.6 (11.6)	-3.10	(-5.46 to -0.74)
	Ciao Corona		80.5 (14.1)	0.30	(-1.58 to 2.17)
Self-esteem					
< 1000g	FLiP	72.3 (13.4)	76.8 (12.9)	-3.90	(-6.73 to -1.06)
	Ciao Corona		72.3 (13.5)	-0.01	(-2.278 to 2.25)
1000g +	FLiP	74.0 (13.8)	76.8 (12.9)	-2.71	(-5.08 to -0.33)
	Ciao Corona		72.3 (13.5)	1.72	(-0.076 to 3.52)
Family					
< 1000g	FLiP	80.0 (12.6)	80.3 (12.8)	-0.01	(-2.65 to 2.63)
	Ciao Corona		79.1 (12.8)	0.94	(-1.21 to 3.09)
1000g +	FLiP	80.5 (13.3)	80.3 (12.8)	-0.19	(-2.20 to 1.82)
	Ciao Corona		79.1 (12.8)	1.52	(-0.22 to 3.25)
Friends					
< 1000g	FLiP	73.6 (16.0)	78.4 (13.1)	-4.51	(-7.79 to -1.22)
	Ciao Corona		77.8 (13.5)	-4.17	(-6.53 to -1.82)
1000g +	FLiP	77.9 (14.2)	78.4 (13.1)	-0.93	(-3.46 to 1.60)
	Ciao Corona		77.8 (13.5)	0.15	(-1.68 to 1.98)
School					
< 1000g	FLiP	76.4 (16.8)	82.5 (13.6)	-5.20	(-8.73 to -1.67)
	Ciao Corona		75.6 (15.9)	0.67	(-2.08 to 3.41)
1000g +	FLiP	81.3 (14.3)	82.5 (13.6)	-1.61	(-4.02 to 0.81)
	Ciao Corona		75.6 (15.9)	5.63	(3.58 to 7.68)

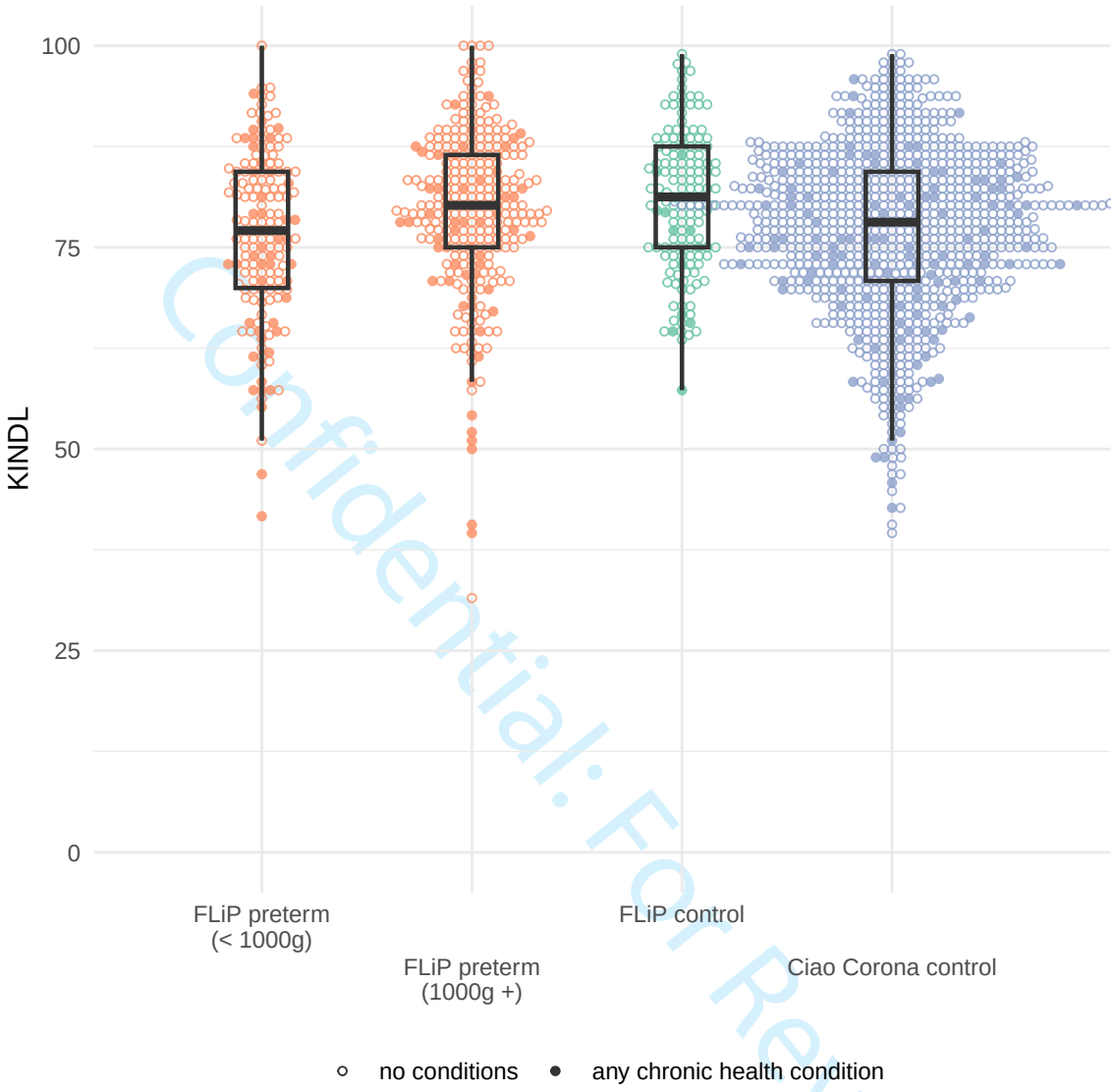

Figure S3: KINDL total score, for very preterm born children (FLiP preterm, stratified by birthweight $<$ 1000g vs $\geq$ 1000g) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control). Solid circles indicate participants without chronic health conditions, while empty diamonds indicate those with any chronic health condition.

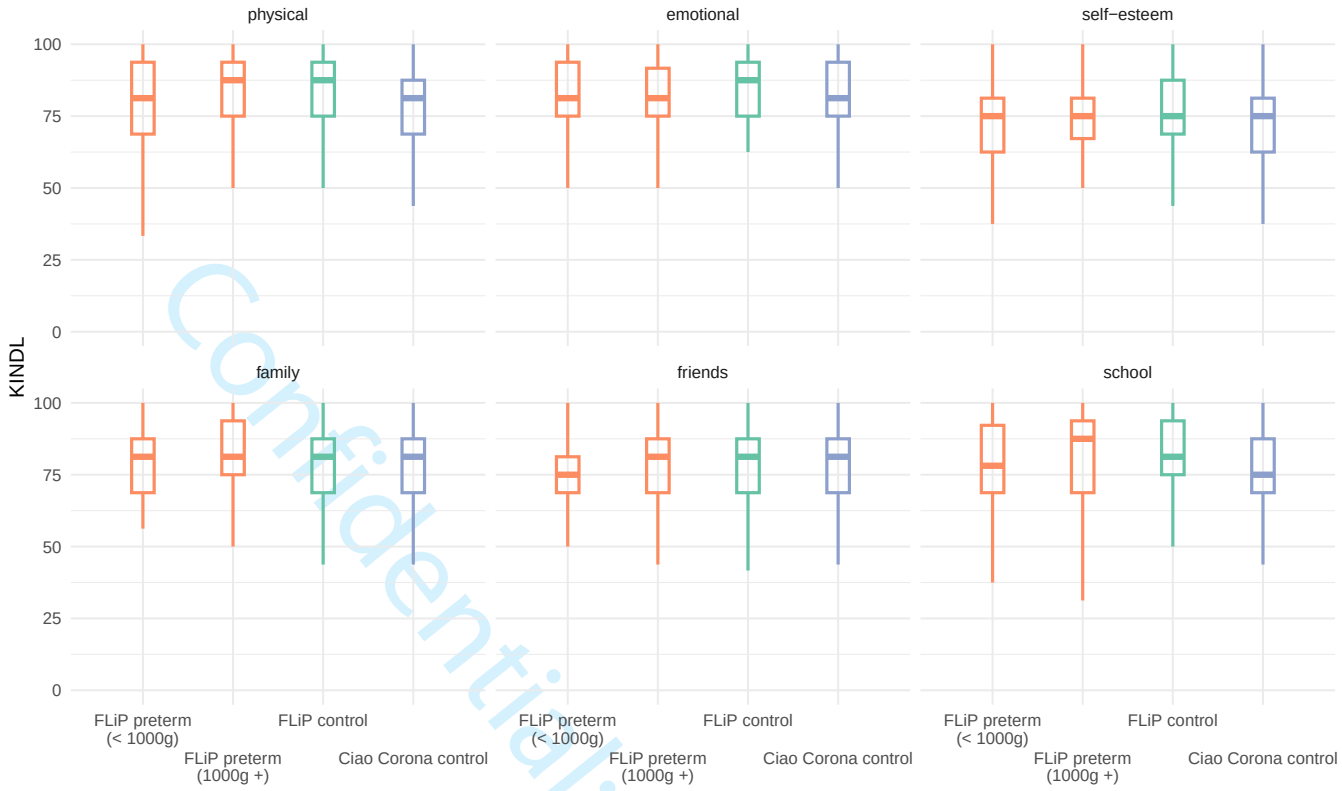

Figure S4: KINDL subscales, for very preterm born children (FLiP preterm, stratified by birthweight: <1000g vs >1000g) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control).

All very preterm born children, regardless of gestational age or birthweight

Table S5: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP and participants from Ciao Corona. Mean differences denote either differences in health-related quality of life between FLIP very preterm born siblings and their control siblings, or between FLIP very preterm born siblings and controls from Ciao Corona. Mean differences and 95% confidence intervals account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

cohort	Preterm	Control	difference	confidence interval
Total				
FLiP	78.5 (10.3)	80.8 (8.7)	-2.09	(-3.56 to -0.62)
Ciao Corona		77.2 (10.2)	1.35	(0.19 to 2.51)
Physical				
FLiP	80.9 (16.0)	82.9 (14.7)	-1.34	(-4.02 to 1.34)
Ciao Corona		77.6 (14.9)	3.28	(1.53 to 5.03)
Emotional				
FLiP	80.4 (13.7)	83.6 (11.6)	-3.16	(-5.31 to -1.00)
Ciao Corona		80.5 (14.1)	-0.08	(-1.67 to 1.52)
Self-esteem				
FLiP	73.4 (13.6)	76.8 (12.9)	-3.22	(-5.39 to -1.06)
Ciao Corona		72.3 (13.5)	1.10	(-0.42 to 2.61)
Family				
FLiP	80.3 (13.1)	80.3 (12.8)	-0.20	(-2.04 to 1.64)
Ciao Corona		79.1 (12.8)	1.31	(-0.16 to 2.77)
Friends				
FLiP	76.4 (15.0)	78.4 (13.1)	-2.21	(-4.68 to 0.26)
Ciao Corona		77.8 (13.5)	-1.40	(-3.01 to 0.20)
School				
FLiP	79.7 (15.3)	82.5 (13.6)	-2.49	(-4.87 to -0.11)
Ciao Corona		75.6 (15.9)	3.94	(2.19 to 5.69)

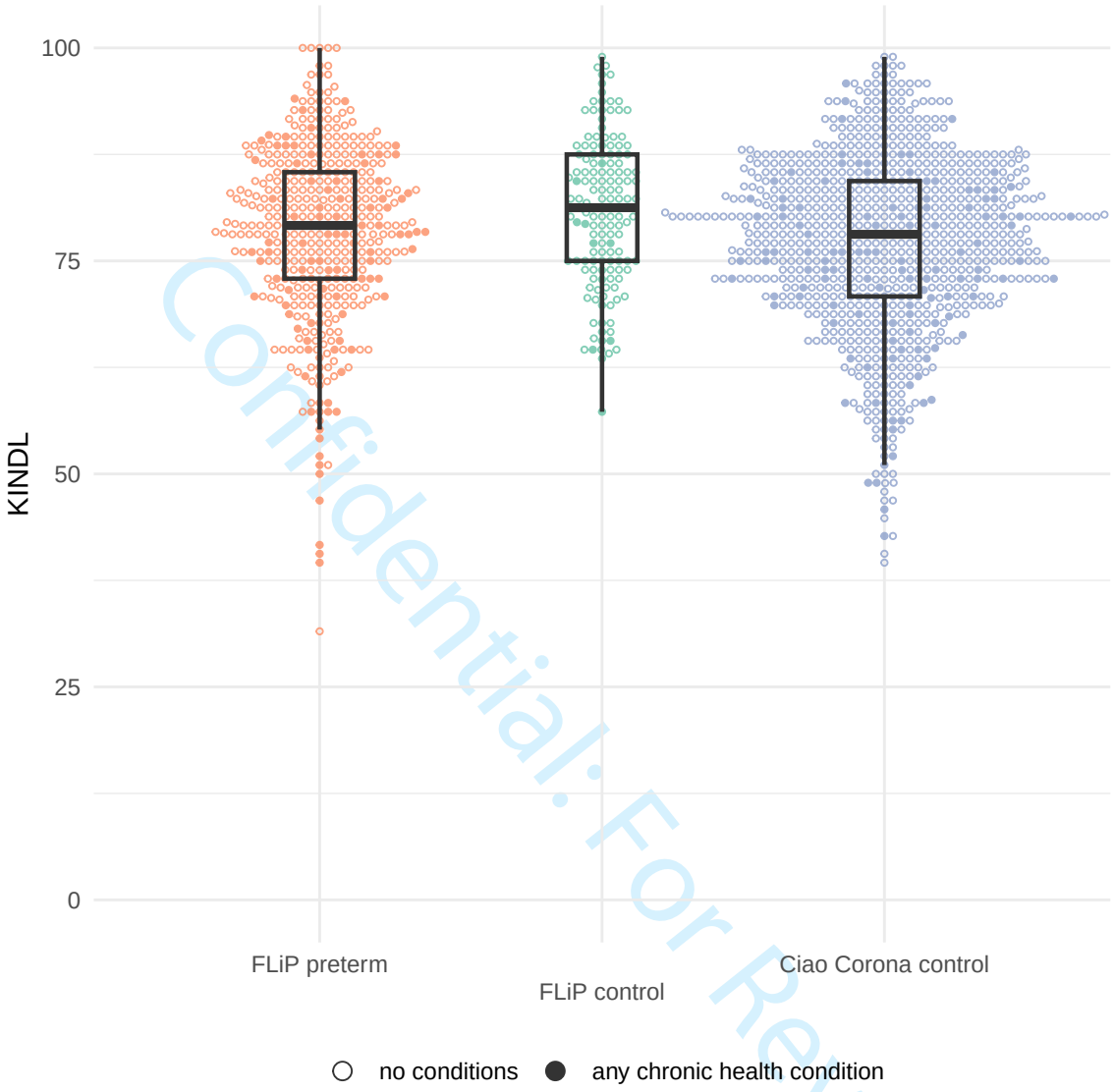

Figure S5: KINDL total score, for very preterm born children (FLiP preterm) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control). Solid circles indicate participants without chronic health conditions, while empty diamonds indicate those with any chronic health condition.

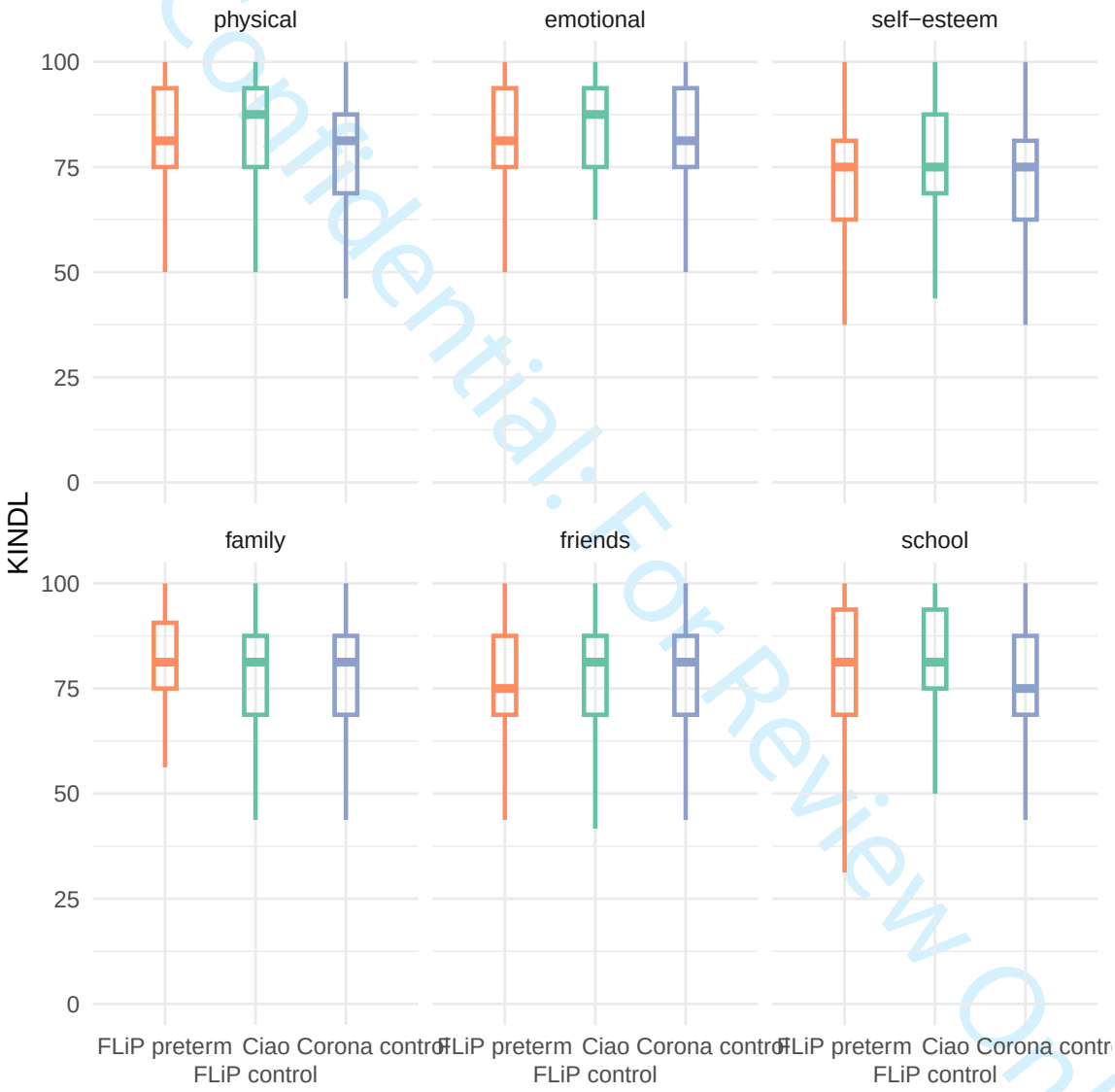

Figure S6: KINDL subscales, for very preterm born children (FLiP preterm) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control).

Table of potential determinants

Table S6: Table of potential determinants of health-related quality of life in FLiP among very preterm born children and adolescents, by age group.

Characteristic	**Overall**, N = 442	**5-9**, N = 227	**10+**, N = 215	**p-value**
KINDL total score	79 (73, 85)	80 (74, 85)	79 (72, 86)	0.11
sex (male)	236 (53%)	116 (51%)	120 (56%)	0.3
overweight	56 (13%)	26 (12%)	30 (15%)	0.5
Unknown	27	17	10	
non-Swiss nationality	66 (15%)	39 (17%)	27 (13%)	0.2
Unknown	1	1	0	
socio-economic status	5 (3, 6)	5 (3, 6)	5 (3, 6)	0.14
Unknown	12	1	11	
unemployed	103 (24%)	50 (22%)	53 (25%)	0.4
Unknown	6	1	5	
siblings				0.6
0	91 (21%)	49 (22%)	42 (20%)	
1	229 (53%)	120 (54%)	109 (52%)	
2+	114 (26%)	54 (24%)	60 (28%)	
Unknown	8	4	4	
smoking				0.007
no	349 (79%)	174 (77%)	175 (81%)	
outside	84 (19%)	52 (23%)	32 (15%)	
in the house	9 (2.0%)	1 (0.4%)	8 (3.7%)	
pets	169 (38%)	59 (26%)	110 (51%)	<0.001
physical activity (hrs / day)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	0.4
Unknown	5	2	3	
screen time (hrs / day)	1.1 (0.6, 2.0)	0.8 (0.5, 1.1)	1.9 (1.0, 2.6)	<0.001
Unknown	11	6	5	
Participation in sports outside of school	319 (73%)	167 (74%)	152 (72%)	0.7
Unknown	3	0	3	
Participation in music lessons or activities	128 (29%)	58 (26%)	70 (33%)	0.085
Unknown	3	0	3	
Participation in scouts or similar	48 (11%)	20 (8.8%)	28 (13%)	0.14
Unknown	3	0	3	
Gestational age				0.006
24-27 wks	130 (29%)	80 (35%)	50 (23%)	
28-31 wks	312 (71%)	147 (65%)	165 (77%)	
birthweight				0.2
<1000g	158 (36%)	87 (38%)	71 (33%)	
1000+g	284 (64%)	140 (62%)	144 (67%)	
BPD	55 (12%)	29 (13%)	26 (12%)	0.8
chronic non-respiratory conditions	67 (15%)	32 (14%)	35 (16%)	0.5
chronic respiratory conditions	24 (5.4%)	9 (4.0%)	15 (7.0%)	0.2
cerebral palsy	33 (7.5%)	12 (5.3%)	21 (9.8%)	0.073
therapy				0.032
no therapy	307 (69%)	145 (64%)	162 (75%)	
1-2	116 (26%)	70 (31%)	46 (21%)	
3+	19 (4.3%)	12 (5.3%)	7 (3.3%)	
assistive devices	15 (3.4%)	7 (3.1%)	8 (3.7%)	0.7
respiratory symptoms affecting daily life	99 (22%)	54 (24%)	45 (21%)	0.5

[1] Median (IQR); n (%)

Sensitivity Analyses

Sensitivity analyses included

a) excluding participants with chronic health conditions;

- Because very preterm born children were much more likely to report chronic non-respiratory conditions, respiratory conditions or cerebral palsy than fullterm children (24% vs 8% in our sample), we also examined a subset of FLiP participants that did not report any chronic health condition. In this subset, preterm children had on average a 1.3 point lower total KINDL score that their fullterm siblings (95% CI -2.8 to 0.2) and 2.0 points higher KINDL total score (0.7 to 3.2) than controls in Ciao Corona (**Table S7, Figures S7 and S8**).

b) restricting to preterm born children with control siblings;

- To ensure comparable groups with respect to family characteristics, including socioeconomic status and general level of physical activity, we restricted to those families with both preterm and fullterm siblings as a sensitivity analysis, leaving 119 preterm children and 119 controls (**Table S8**). Among those families, very preterm born children had on average 2.0 points lower KINDL total score than their fullterm born siblings (95% CI -3.7 to -0.3, **Table S9, Figure S9**).

c) stratification by age; and

- We noted similar patterns in both younger and older children (**Figures S10 and S11, Table S10**). The mean difference in KINDL total score between preterm and controls was -2.1 (95% CI -4.0 to -0.1) among children 5-9 years of age, and -1.7 (-4.2 to 0.7) among those 10 and older.

d) adjusting for SES.

- SES was directly influenced by family unit, and likely contributes to HRQOL. We therefore considered models with and without SES. The two models showed similar fit (BIC 4194 vs 4201), and the estimates were of very similar magnitude (-2.1 [-3.6 to -0.6] in both cases).

None of the sensitivity analyses led to a different conclusion regarding HRQOL in very preterm born children compared to their peers.

a) excluding participants with chronic health conditions

Table S7: Differences in KINDL total score between very preterm born children, their fullterm born siblings, and Ciao Corona participants (stratified by presence of any chronic health conditions). In FLiP, 104 of very preterm born children had chronic health conditions (24%), while n = 12 of their control siblings did (8%). Among controls from Ciao Corona, 122 (14%) reported chronic health conditions. Mean differences denote either differences in health-related quality of life between FLIP very preterm born siblings and their control siblings, or between FLIP very preterm born siblings and controls from Ciao Corona. Mean differences and 95% confidence intervals account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

chronic health conditions	cohort	Preterm	Control	difference	confidence interval
Total					
any chronic health condition	FLiP	74.5 (12.2)	73.8 (8.7)	-4.50	(-10.39 to 1.39)
	Ciao Corona		73.8 (10.3)	0.69	(-2.26 to 3.65)

no chronic health conditions	FLiP	79.7 (9.4)	81.4 (8.5)	-1.30	(-2.82 to 0.21)
	Ciao Corona		77.7 (10.1)	1.99	(0.74 to 3.23)
Physical					
any chronic health condition	FLiP	77.0 (17.2)	75.5 (10.8)	0.58	(-9.44 to 10.60)
	Ciao Corona		74.0 (14.3)	3.17	(-0.96 to 7.30)
no chronic health conditions	FLiP	82.1 (15.4)	83.5 (14.9)	-0.75	(-3.59 to 2.09)
	Ciao Corona		78.2 (15.0)	3.87	(1.93 to 5.81)
Emotional					
any chronic health condition	FLiP	78.4 (15.2)	77.6 (17.2)	-2.36	(-10.72 to 5.99)
	Ciao Corona		77.3 (14.7)	1.31	(-2.63 to 5.24)
no chronic health conditions	FLiP	81.0 (13.1)	84.1 (10.9)	-3.14	(-5.38 to -0.89)
	Ciao Corona		81.1 (13.9)	-0.09	(-1.81 to 1.64)
Self-esteem					
any chronic health condition	FLiP	68.1 (16.7)	70.3 (10.0)	-5.38	(-14.27 to 3.52)
	Ciao Corona		68.7 (13.3)	-0.52	(-4.48 to 3.43)
no chronic health conditions	FLiP	75.0 (12.2)	77.3 (13.0)	-1.93	(-4.03 to 0.16)
	Ciao Corona		72.9 (13.5)	2.03	(0.38 to 3.67)
Family					
any chronic health condition	FLiP	78.9 (14.1)	76.0 (12.5)	-1.92	(-9.49 to 5.66)
	Ciao Corona		75.9 (13.8)	3.25	(-0.43 to 6.93)
no chronic health conditions	FLiP	80.7 (12.7)	80.6 (12.8)	0.37	(-1.50 to 2.24)
	Ciao Corona		79.6 (12.5)	1.15	(-0.44 to 2.75)
Friends					
any chronic health condition	FLiP	71.4 (15.6)	69.6 (14.9)	1.05	(-8.22 to 10.33)
	Ciao Corona		73.2 (15.7)	-1.80	(-5.85 to 2.24)
no chronic health conditions	FLiP	77.9 (14.5)	79.2 (12.7)	-1.28	(-3.84 to 1.28)
	Ciao Corona		78.5 (13.0)	-0.57	(-2.30 to 1.16)
School					
any chronic health condition	FLiP	72.6 (18.0)	72.2 (19.2)	-3.29	(-12.48 to 5.89)
	Ciao Corona		73.8 (16.8)	-1.44	(-6.08 to 3.20)
no chronic health conditions	FLiP	81.9 (13.7)	83.5 (12.7)	-1.52	(-4.05 to 1.00)
	Ciao Corona		75.9 (15.8)	5.77	(3.89 to 7.66)

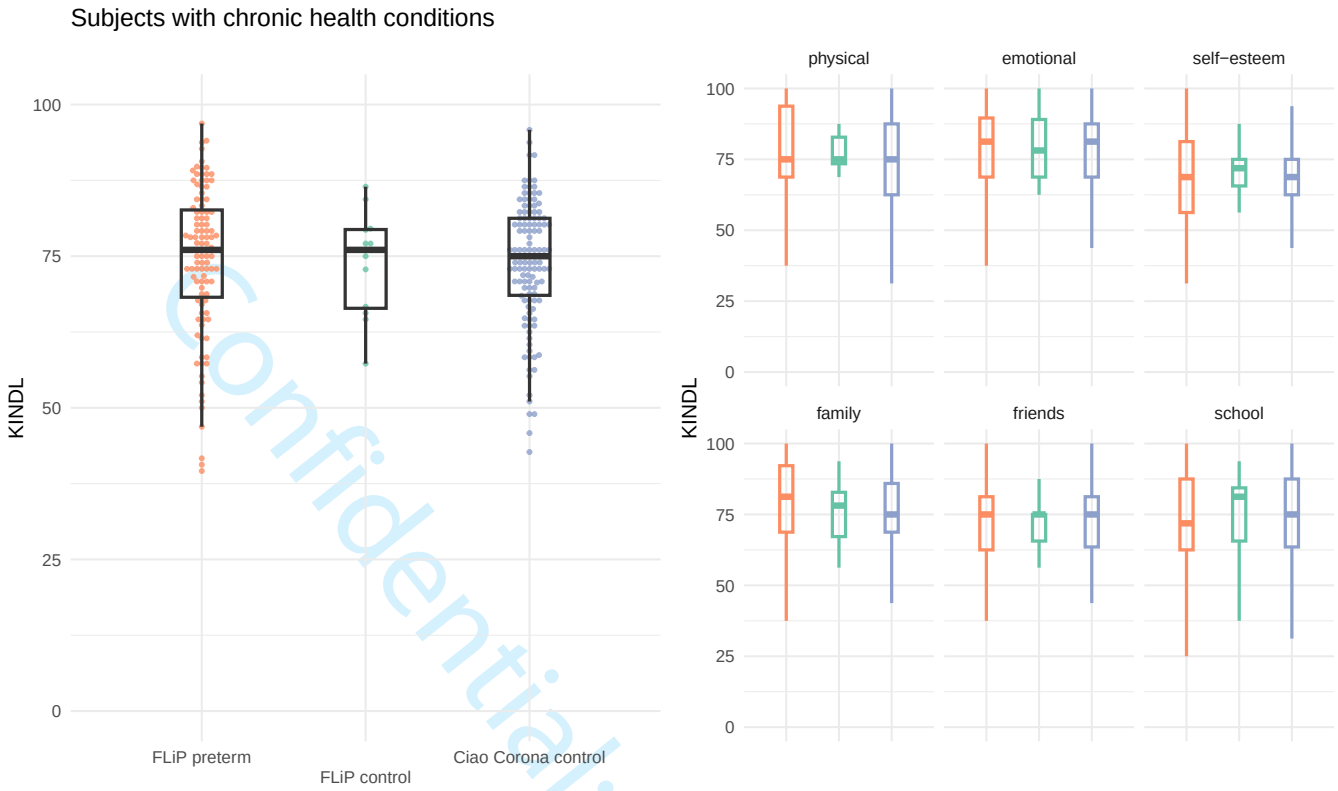

Figure S7: KINDL total score and its subscales, for preterm children and their fullterm siblings (with any chronic health condition)

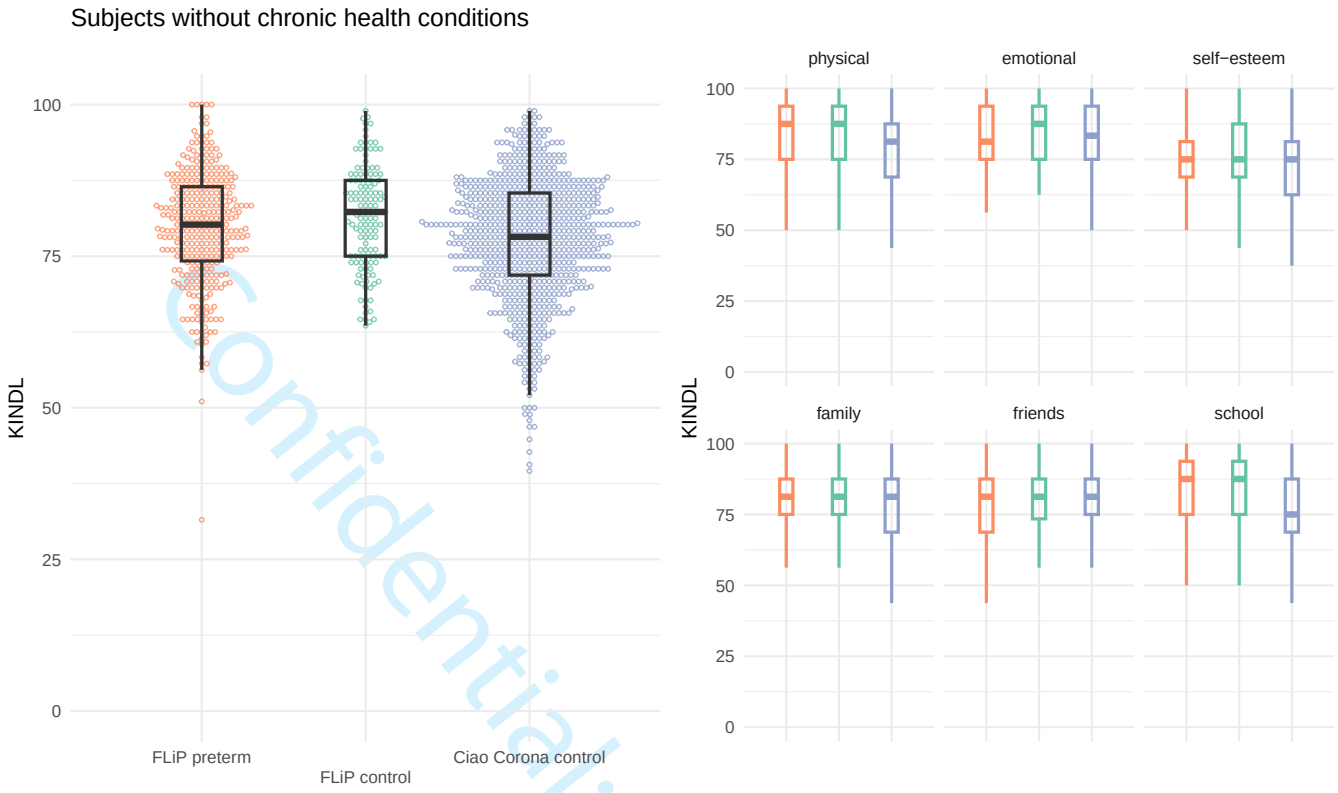

Figure S8: KINDL total score and its subscales, for preterm children and their fullterm siblings (with no chronic health conditions)

b) restricting to preterm born children with control siblings

Table S8: Differences in KINDL total score between preterm children and their fullterm siblings (only matched siblings).

KINDL	Preterm	Control	difference	confidence interval
total	78.5 (10.5)	80.6 (8.9)	-1.99	(-3.66 to -0.32)
physical	82.1 (15.0)	81.9 (15.6)	0.19	(-3.08 to 3.45)
emotional	80.5 (13.7)	83.6 (11.5)	-3.02	(-5.66 to -0.38)
self-esteem	72.6 (14.0)	76.3 (13.1)	-3.26	(-5.79 to -0.74)
family	80.1 (12.8)	80.9 (12.5)	-0.52	(-2.52 to 1.48)
friends	75.8 (15.3)	78.2 (13.2)	-2.46	(-5.36 to 0.45)
school	79.4 (14.7)	82.5 (13.7)	-2.67	(-5.58 to 0.23)

Table S9: Key characteristics of preterm and control participants in full data (preterm children with included control siblings)

Characteristic	**FLiP preterm**, N = 119	**FLiP control**, N = 119
age (years)	11 (5 - 16)	10 (5 - 19)
sex (male)	62 (52%)	71 (61%)
gestational age (weeks)		
24-27 wks	25 (21%)	
28-31 wks	94 (79%)	
birthweight		
<1000g	28 (24%)	
1000+g	91 (76%)	
multiple gestation	28 (24%)	
socio-economic status	5 [3, 6]	5 [3, 6]
non-Swiss nationality	15 (13%)	12 (10%)
moderate to severe BPD	15 (13%)	
coughing / wheezing restrict daily activities	4 (3.4%)	1 (0.8%)
any chronic health condition	31 (26%)	10 (8.4%)
chronic non-respiratory conditions	21 (18%)	9 (7.6%)
chronic respiratory conditions	9 (7.6%)	2 (1.7%)
cerebral palsy	8 (6.7%)	1 (0.8%)
physical activity (hours per week)	0.71 [0.57, 1.00]	0.75 [0.57, 1.14]

[1] Median (Range); n (%); Median [IQR]

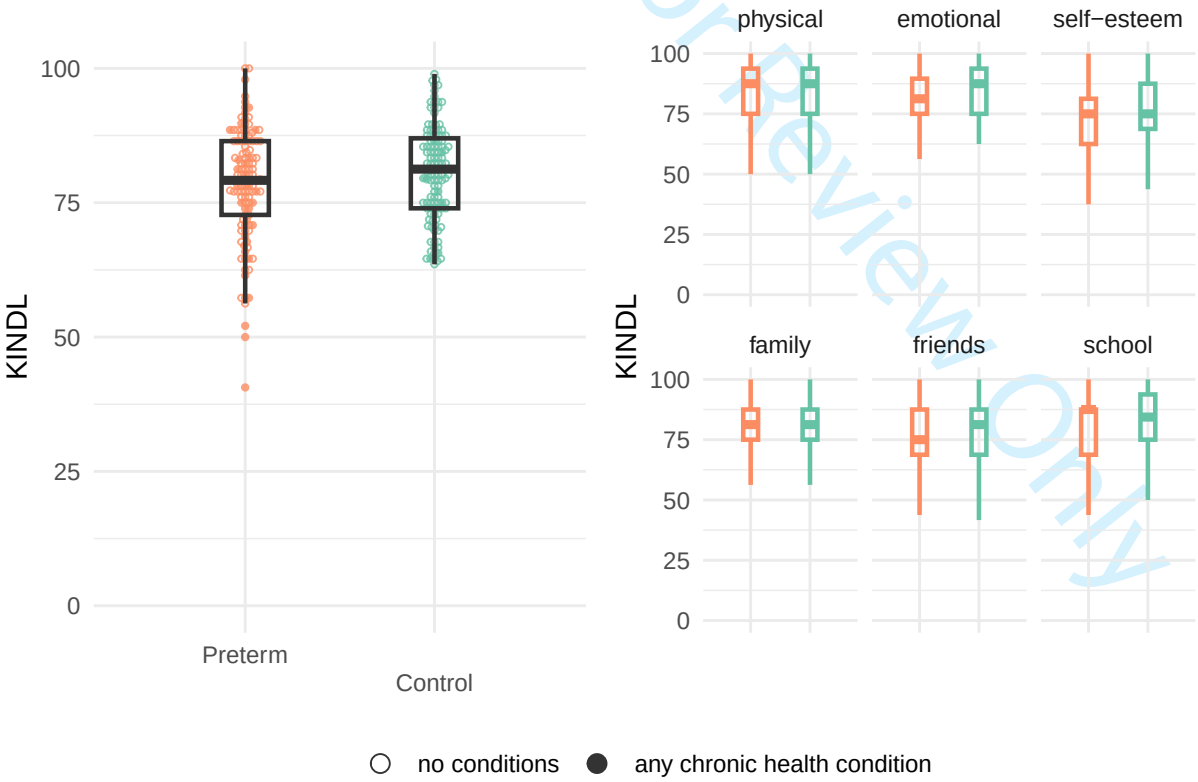

Figure S9: KINDL total score and its subscales, for preterm children and their fullterm siblings (matched siblings only)

c) stratification by age

Table S10: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP and participants from Ciao Corona, by age group (5-9, 10+). Mean differences, 95% confidence intervals and p-values account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

age	cohort	Preterm	Control	difference	confidence interval
Total					
5-9	FLiP	79.6 (8.7)	82.1 (8.0)	-2.06	(-3.97 to -0.14)
	Ciao Corona		79.8 (9.0)	-0.07	(-1.49 to 1.35)
10+	FLiP	77.3 (11.7)	78.8 (9.5)	-1.73	(-4.18 to 0.73)
	Ciao Corona		75.3 (10.7)	2.00	(0.24 to 3.75)
Physical					
5-9	FLiP	81.2 (16.1)	85.5 (13.1)	-4.14	(-7.74 to -0.54)
	Ciao Corona		80.9 (13.6)	0.37	(-2.05 to 2.79)
10+	FLiP	80.5 (16.0)	79.1 (16.1)	2.09	(-2.01 to 6.20)
	Ciao Corona		75.2 (15.4)	5.29	(2.83 to 7.76)
Emotional					
5-9	FLiP	81.0 (12.6)	84.3 (11.0)	-3.31	(-6.14 to -0.49)
	Ciao Corona		82.3 (13.0)	-1.19	(-3.29 to 0.92)
10+	FLiP	79.8 (14.8)	82.6 (12.5)	-3.23	(-6.65 to 0.19)
	Ciao Corona		79.3 (14.7)	0.52	(-1.83 to 2.87)
Self-esteem					
5-9	FLiP	74.9 (12.1)	78.8 (11.4)	-3.51	(-6.35 to -0.68)
	Ciao Corona		74.4 (13.0)	0.51	(-1.48 to 2.51)
10+	FLiP	71.8 (15.0)	73.8 (14.4)	-2.76	(-6.45 to 0.94)
	Ciao Corona		70.8 (13.7)	1.05	(-1.17 to 3.27)
Family					
5-9	FLiP	79.0 (12.2)	79.7 (12.8)	-0.43	(-3.13 to 2.27)
	Ciao Corona		79.0 (12.2)	0.08	(-1.91 to 2.07)
10+	FLiP	81.7 (13.8)	81.1 (12.7)	-0.22	(-2.97 to 2.54)
	Ciao Corona		79.1 (13.2)	2.59	(0.48 to 4.71)
Friends					
5-9	FLiP	77.9 (12.5)	79.3 (12.0)	-1.28	(-4.22 to 1.66)
	Ciao Corona		79.4 (12.5)	-1.60	(-3.67 to 0.47)
10+	FLiP	74.8 (17.1)	77.0 (14.5)	-2.29	(-6.43 to 1.84)
	Ciao Corona		76.6 (14.1)	-1.74	(-4.15 to 0.66)
School					
5-9	FLiP	84.4 (12.4)	85.2 (11.9)	0.03	(-2.93 to 2.99)
	Ciao Corona		82.5 (13.1)	1.85	(-0.30 to 4.00)
10+	FLiP	74.5 (16.5)	78.7 (14.9)	-3.50	(-7.29 to 0.29)
	Ciao Corona		70.7 (16.0)	3.85	(1.20 to 6.50)

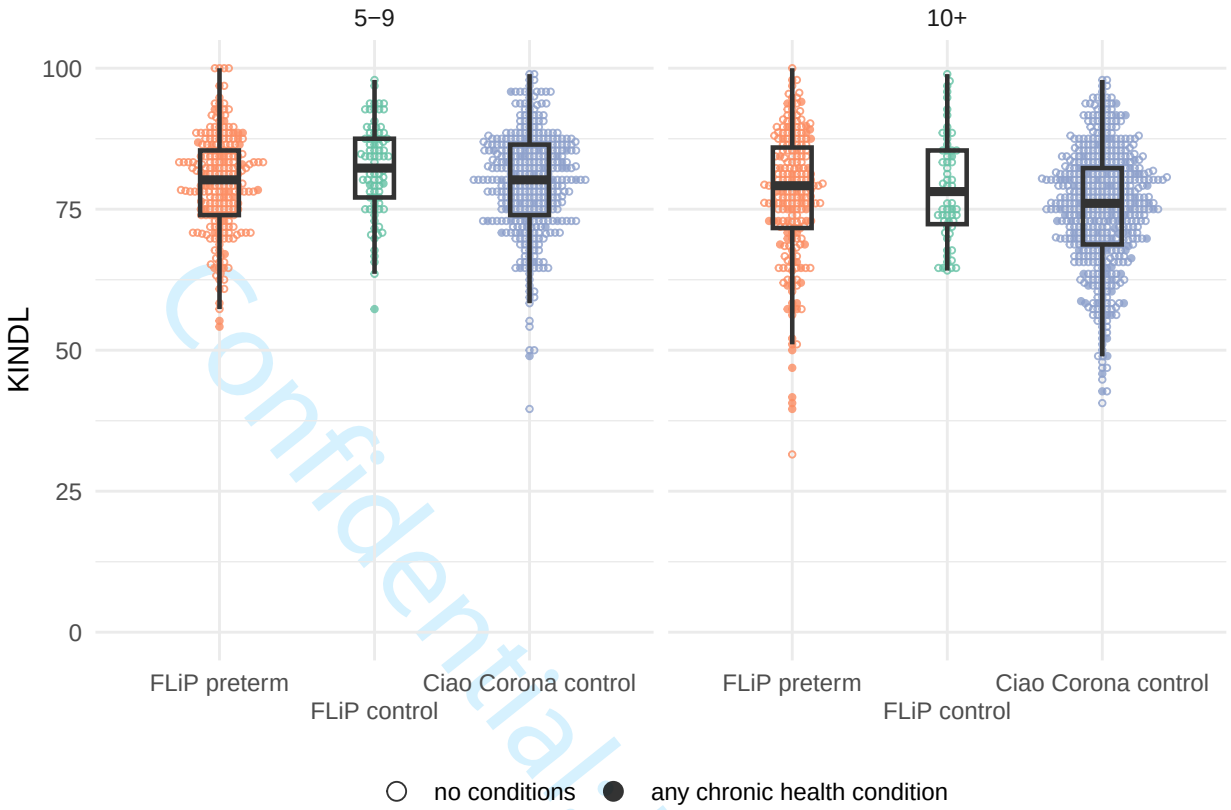

Figure S10: KINDL total score in very preterm born children and fullterm born controls from FLiP, as well as controls from Ciao Corona, by age group. Solid circles indicate participants without chronic health conditions, while empty circles indicate those with any chronic health condition.

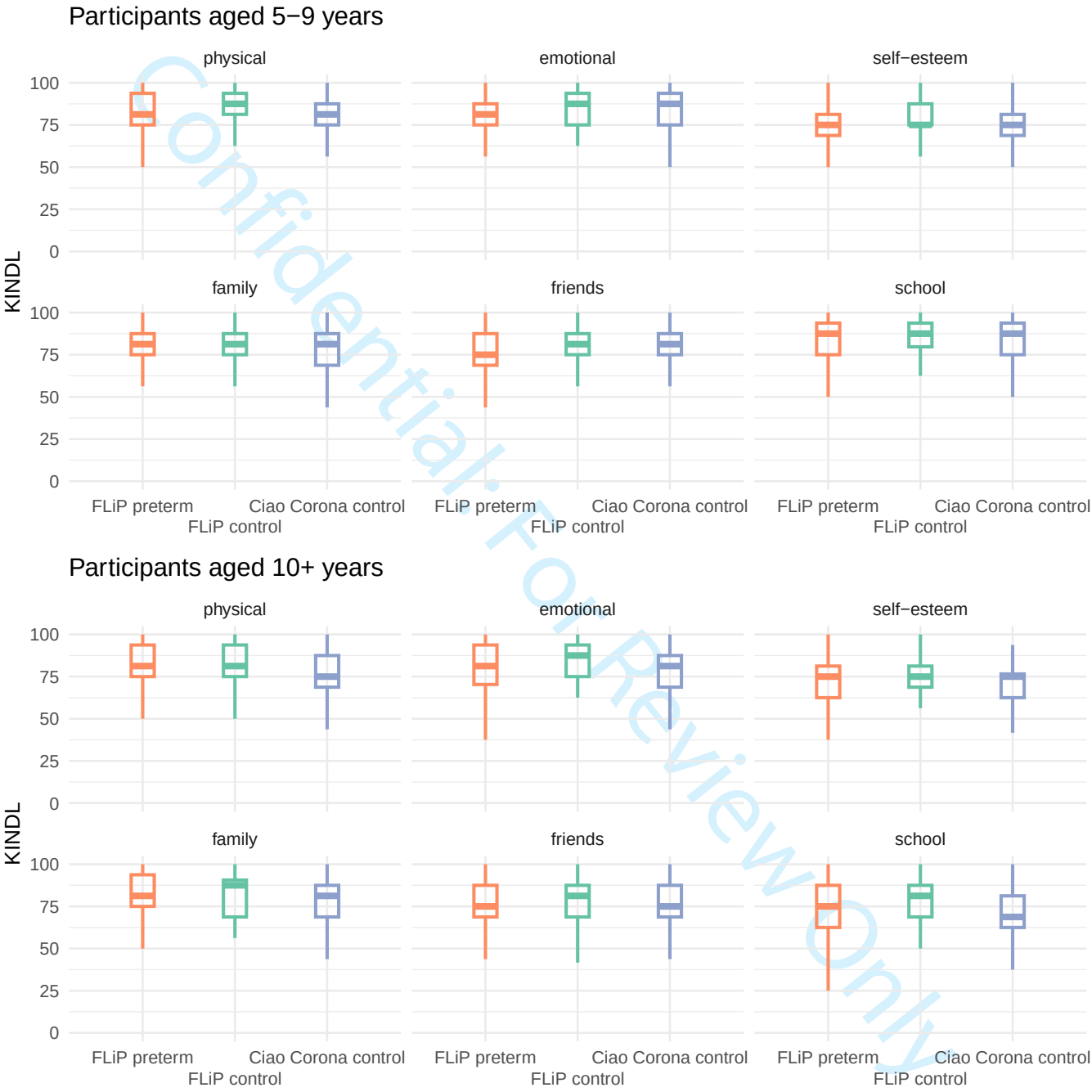

Figure S11: KINDL subscales in very preterm born children and fullterm born controls from FLiP, as well as controls from Ciao Corona, by age group.

d) adjusting for SES

SES was directly influenced by family unit, and likely contributes to HRQOL. We therefore considered models with and without SES. The two models showed similar fit (BIC 4194 vs 4201), and the estimates were of very similar magnitude (-2.1 [-3.6 to -0.6] in both cases).

```
sm2 <- sm %>%
  ungroup() %>%
  select(kindl_total, group, family_id, SES_Score_total) %>%
  filter(complete.cases(.))
mod_noSES <- lmer(kindl_total ~ group + (1 | family_id), data = sm2)
tidy(mod_noSES, conf.int = TRUE) %>%
  filter(term == "groupPreterm") %>%
  select(term, estimate, conf.low, conf.high, p.value) %>%
  mutate(BIC = BIC(mod_noSES),
         AIC = AIC(mod_noSES))
```

```
## # A tibble: 1 x 7
##   term         estimate conf.low conf.high p.value   BIC   AIC
##   <chr>           <dbl>    <dbl>     <dbl>   <dbl> <dbl> <dbl>
## 1 groupPreterm    -2.10    -3.59    -0.613 0.00581 4194. 4176.
```

```
mod_SES <- lmer(kindl_total ~ group + SES_Score_total + (1 | family_id), data = sm2)
tidy(mod_SES, conf.int = TRUE) %>%
  filter(term == "groupPreterm") %>%
  select(term, estimate, conf.low, conf.high, p.value) %>%
  mutate(BIC = BIC(mod_SES),
         AIC = AIC(mod_SES))
```

```
## # A tibble: 1 x 7
##   term         estimate conf.low conf.high p.value   BIC   AIC
##   <chr>           <dbl>    <dbl>     <dbl>   <dbl> <dbl> <dbl>
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Computational Details

- R version: R version 4.4.1 (2024-06-14)
- Base packages: grid, stats, graphics, grDevices, utils, datasets, methods, base
- Other packages: consort 1.2.1, kableExtra 1.4.0, ggparty 1.0.0, partykit 1.2.20, mvtnorm 1.2.4, libcoin 1.0.10, patchwork 1.2.0, ggdag 0.2.12, gtsummary 1.7.2, lmerTest 3.1.3, lme4 1.1.35.3, Matrix 1.6.5, broom.mixed 0.2.9.5, broom 1.0.5, ggbeeswarm 0.7.2, lubridate 1.9.3, forcats 1.0.0, stringr 1.5.1, dplyr 1.1.4, purrr 1.0.2, readr 2.1.5, tidyr 1.3.1, tibble 3.2.1, ggplot2 3.5.1, tidyverse 2.0.0

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Characterization of prevalence, type, treatment, burden of disease and predictors of respiratory symptoms in very prematurely born children in the Zurich area (Frühgeborenen Lungen Projekt - FLiP)

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	A

Project Leader:

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PROTOCOL SIGNATURE FORM

Study Title Characterization of prevalence, type, treatment, burden of disease and predictors of respiratory symptoms in very prematurely born children in the Zurich area **(FLiP)**

The project leader and the collaborators have approved the protocol version 2, 04 December 2020, and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [2,3], current version of the World Medical Association Declaration of Helsinki [4] and the principles and procedures for integrity in scientific research involving human beings.

Project leader:

Site: Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich. Hirschengraben 84, 8001 Zürich

Name: Prof. Dr. med. Susi Kriemler

Date: 04.12.2020 Signature: S. Kriemler

Collaborators:

Responsible for the SwissNeoNet, expert in epidemiology and data management:

Site: Department of Neonatology, University Hospital Zurich. Wagistr. 12, 8952 Schlieren

Name: Dr. sc. nat. Mark Adams

Date: 04.12.2020 Signature: Mark Adams

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Site: Department of Neonatology, University Hospital Zurich. Frauenklinikstr. 10, 8091 Zurich

Name: Prof. Dr. med. Dirk Bassler
Date: 04.12.2020 Signature: D. Bassler

Responsible for recruitment and the follow-up of neonates:

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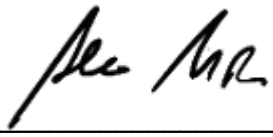
Name: Prof. Dr. med. Giancarlo Natalucci

Date: 04.12.2020 Signature: 

Responsible for expert opinion in pulmonology:

Site: Division of Respiratory Medicine, University Children's Hospital. Steinwiesstr. 75, 8032 Zurich

Name: Prof. Dr. med. Alexander Möller

Date: 04.12.2020 Signature: 

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
BPD	*Bronchopulmonary Dysplasia*
CPAP	*Continuous Positive Airway Pressure*
CRF	*Case report form*
EBPI	*Epidemiology, Biostatistics and Prevention Institute (EBPI)*
ERS	*European Respiratory Society*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
QR code	*Quick Response code*
SOPs	*Standard Operating Procedures*
SPAC	*Swiss Paediatric Airway Cohort*
SwissNeoNet	*Swiss Neonatal Network & Follow-Up Group*
UZH	*University of Zurich*

1 BACKGROUND AND PROJECT RATIONALE

Over the last three decades the prevalence of premature birth has risen due to changing demographics, higher mean age of pregnant mothers, and a progressive use of reproductive medicine [5]. Due to technological advances, improved care has further risen prevalence rates of very premature birth, particularly of the very immature newborns. Thus, the rate of children born with a birth weight below 1500g has doubled, summing up to about 800 preterm infants with a gestational age below 32 weeks per year in Switzerland [6]. Surviving children are susceptible to severe neonatal morbidity that leads to long-term medical and social sequelae, often including respiratory disease [7]. Lung injury due to immaturity, artificial ventilation, oxygen therapy and other factors can result in a wide range of pulmonary conditions from mild transient pulmonary impairment to severe bronchopulmonary dysplasia (BPD) as chronic structural lung disease of infancy [8,9].

Fortunately, BPD-related mortality has declined over time [10]. Yet, the prevalence of BPD - but also other respiratory symptoms unrelated to BPD - have remained high and are among the most common morbidities of prematurity [11,12]. Respiratory limitations often extend beyond the neonatal period even into adulthood [13], and require re-hospitalization more often compared to full-term children [13,14]. For instance, 25% of children born extremely preterm (<26 weeks of gestation) were diagnosed with asthma and half of them had abnormal spirometry values at the age of 11 years[15]. Children born very preterm (<32 weeks of gestation) had also three times higher risk of showing wheezing disorders [16] and higher bronchial hyper-responsiveness compared to term-born children with differences being highest for those who had BPD [17].

Despite several studies assessing the respiratory consequences of prematurity, there is significant variation in observed long-term pulmonary outcomes of premature birth. Most of these studies included heterogenous populations, frequently relatively small and selected samples, often focused mainly on severe respiratory outcomes, and only a few studies assessed predictors of prematurity-related pulmonary sequelae [18]. In addition, previous studies have used changing definitions of BPD [8]. Advances in perinatal management of premature birth have led to BPD phenotypes with different pathophysiological characteristics than the previously defined ‘classic’ BPD. The ways in which these ‘new’ forms of BDP influence pulmonary health in childhood are poorly studied and understood. It becomes more and more evident that even prematurity per se - without a history of BPD - can lead to pulmonary symptoms and disease in children [13,19,20]. Studies that focused specifically on premature samples and with exhaustive perinatal care characterization covering different periods of standard treatment regimens over the last decades (for instance antenatal or postnatal steroids) are scarce and cannot explain respiratory morbidity associated with prematurity.

Although the prevalence of altered pulmonary function and respiratory symptoms is high, symptoms and function usually improve during growth, but the burden of disease still remains high and even expands until adulthood [21]. Survivors with and without BPD and ongoing respiratory symptoms have decreasing lung function with age and may have a higher risk of lung disease in later life [18,22]. In some studies, up to 75% of children with a history of prematurity show abnormal lung function, and up to half of them are reported to have asthma or an asthma-like disorder [15]. About 20% of youth with a history of prematurity have measurable bronchial hyperresponsiveness, which is often unrelated to atopic status and inflammation [17]. The majority of preterm born children, however, suffer from fixed obstructive airway disease that mimic asthma-like symptoms, but is unrelated to allergy and inflammation [17]. It is likely that a large proportion of these premature children may therefore not substantially respond to asthma medication (e.g., beta-mimetics, anti-inflammatory steroid therapy) with an improvement in airway function or a relief in respiratory symptoms [21,23], but this patient-relevant feature has barely been studied.

Irrespective of the underlying lung pathology, type of treatment and treatment burden for children and their parents are poorly studied and previous research is often limited to studies addressing the effects of steroids on the improvement of respiratory symptoms [23,24]. There is no report of

other medications, no description of dosage, no treatment history, and no information of other treatment modalities as for example inhalation therapy with saline or the use of physiotherapy. Thus, there is a clear lack of information on treatment of respiratory symptoms of premature children, response to treatment, and in particular how this affects children and their parents in respect to the disease and treatment burden [24]. Although the negative effects of pulmonary sequelae on patients and their families decrease over the years, they do not disappear completely and continue to affect quality of life even into adulthood [14,24–29]. Just a few studies, and none of it conducted in Switzerland, have addressed this burden of disease to the child and even less to their caregivers and/or parents.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Primary objective and hypothesis

The aim of this project is to characterize prevalence, type, treatment, burden of disease and predictors of respiratory symptoms in children born very prematurely (<32 weeks of gestation), using data of the larger Zurich area collected by the population-based registry of children born at preterm, the Swiss Neonatal Network & Follow-Up Group (SwissNeoNet). We hypothesize that 1) children born very prematurely have a higher prevalence of respiratory symptoms under a considerable treatment burden in comparison to their term-born siblings and that 2) specific sociodemographic and perinatal characteristics are related with onset, type and severity of respiratory symptoms in this subset of very preterm children.

The *specific* research objectives of this study are

- to assess the prevalence, type and severity of respiratory symptoms in children born <32 completed weeks of gestation between 2006 and 2019 (now 1 to 14 years old) from the Swiss national cohort of preterm children in comparison to their siblings born at full-term,
- to characterize the treatment and treatment burden of children and parents for respiratory symptoms (e.g., medication, dosage and other procedures) perceived by these very preterm children,
- to determine whether treatment (e.g., inhaled steroids, leukotriene receptor antagonists) of respiratory symptoms is related to respiratory improvement,
- to assess the neonatal and sociodemographic predictors of respiratory symptoms of very preterm children.

2.2 Primary and secondary endpoints

Primary endpoints are the prevalence, type and severity of respiratory symptoms in children born <32 completed weeks of gestation between 2006 and 2019 (now 1 to 14 years old) from the Swiss national cohort of preterm children in comparison to their siblings born at full-term. We will assess the overall history of respiratory symptoms since they occurred. Respiratory symptoms (wheezing, coughing, chest tightness, breathing difficulties at rest and exercise) will be assessed using a symptom score (summary from night and daytime score) that has been proven sensitive to detect lower respiratory tract symptoms (Table 1) [30]. Wheeze is defined as a whistling or squeaky noise from the chest that is audible to a parent. Each respiratory symptom (wheezing, coughing, chest tightness, breathing difficulties) will be videotaped and attached to the survey or made audible on phone calls. In a pilot study including 10-20 children with respiratory symptoms we will test alternative ways of assessment of frequency, type, pattern and severity of symptoms.

Table 1 Scoring system for respiratory symptoms

Symptom Score		Symptoms during day	Symptoms during night
0	None	None	None
1	Mild	No treatment given	Sleep not disturbed
2	Moderate	Required treatment, but no outside help	Sleep disturbed once; no help required
3	Severe	Required help from general practitioner	Sleep disturbed >once, needed help
4	Very severe	Admitted to hospital	Sleep very disturbed or general practitioner called

Secondary endpoints are:

- Treatment and treatment burden of children and parents for respiratory symptoms. Exact treatment including oral/inhaled steroids, diuretics, oxygen, spray/powders for breathing difficulties, nasal sprays and other modalities will be assessed with initiation, dosage, change over time. We will ask whether treatment had any effect on respiratory symptoms.

- Neonatal and sociodemographic predictors of respiratory symptoms. We will retrieve all potential perinatal risk factors that are known to affect long-term outcome and/or having an influence on the occurrence of BPD from the SwissNeoNet registry. These include gestational age, birthweight, gender, maternal infections (e.g., chorioamnionitis), patent ductus arteriosus, days of mechanical ventilation, nasal continuous positive airway pressure (CPAP) ventilation, oxygen support and pre- and postnatal steroid application. Further, we will record factors of postnatal adaptation with Apgar score, and acidosis in the cord blood. Further, sociodemographic and environmental factors will include number and age of siblings, breastfeeding, socio-economic status, smoking of parents, pets in the household, exposure to daycare, familial atopic symptoms and constellation as well as child's physical activity and time in sedentary activities.

  Children will be categorized based on their neonatal records into those with and without BPD. Based on the standard definition of BPD, we will categorize preterm infants into healthy, mild, moderate and severe BPD, respectively [32]. BPD will be defined as supplemental oxygen requirement for at least 28 days. The time point of assessment for BPD severity shall be at 36 weeks post-menstrual age or at discharge, whichever came first. Mild BPD is defined as breathing room air, moderate BPD as requiring less than 30% supplemental oxygen and severe BPD as requiring more than 30% of oxygen or positive pressure ventilation (PPV).

2.3 Project design

This is a cross-sectional observational study of children born prematurely using an electronic survey. We aim to assess participation rate, accuracy of answers, the burden of respiratory disease and its treatment in prematurely born children in the Zurich area. The primary project will use data from the Swiss national cohort of preterm children which is coordinated by the Swiss Neonatal Network & Follow-Up Group (SwissNeoNet), a national registry containing information about all children born since 2000 and below 32 weeks of gestation [6]. Specifically, our project involves patients from the University Hospital Zurich and the University Children's Hospital of Zurich.

The present project will be carried out in collaboration with the SwissNeoNet, the Department of Neonatology from the University Hospital Zurich and the Child Development Center and the

Division of Respiratory Medicine from University Children's Hospital Zurich. Mark Adams will lead the connection with the SwissNeoNet and will provide technical and methodological support to the project. Dirk Bassler is responsible for the administration of the addresses of study participants and will supervise the person in charge of contacting families. Giancarlo Natalucci is responsible for the recruitment and follow-up of neonates included in the SwissNeoNet and will provide his expertise in working with data from this registry. In addition, Dr. Bassler and Dr. Natalucci will provide their neonatology expertise on, for instance, how preterm history is entered in the database, or in selecting and categorizing the perinatal and postnatal predictor variables for later respiratory symptoms. Finally, Alex Möller will provide his expertise in developing the respiratory questionnaire and will support the project team with producing the videoclips showing the respiratory symptoms. As a proof of this agreement, all collaborators have signed the protocol form.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

The study population will be restricted to children born < 32 weeks of gestation in the Zurich area born between 2006 and 2019 (n≈1720). Thus, participants will be between 1 and 14 years of age. This subsample of the SwissNeoNet corresponds to 20% of the whole registry population, including 12.2% with moderate to severe BPD. Inclusion criteria for participants are: 1) born < 32 weeks of gestation and currently alive, 2) born between 2006 and 2019 and included in the SwissNeoNet registry, 3) perinatally treated at the neonatology ward of the University Hospital of Zurich and/or at the Children's University Hospital of Zurich. Exclusion criteria for participants include any significant lung condition apart from asthma. Inclusion criteria for the term-born siblings are: 1) they have to be born between 37 and 42 weeks of gestation and should not have overt chronic disease. One to two siblings of similar age than the preterm children are selected as control population as they share the same environment and the atopic family constellation that potentially affect and confound respiratory symptoms. Each preterm child even without siblings can participate. These missing siblings will be selected among additional siblings from other preterm children, matched for socio-economic state and age (± 2 years).

3.2 Recruitment, screening and informed consent procedure

Upon the approval of the protocol by the ethics committee, eligible children and parents will be contacted through the Department of Neonatology from the University Hospital Zurich (see Figure 1). We will hire and train a student to retrieve the addresses from the neonatology ward of the University Hospital of Zurich and the Children's University Hospital of Zurich and to update them. He/she will work at the Department of Neonatology and will be required to maintain full professional confidentiality. The student will be introduced and supervised by Prof. Bassler. If eligible families do not respond to the invitation, a second and third invitation will be sent. A special effort will be taken to include all children with a history of BPD and those <30wk of gestation. In this population, further steps will be taken, and three phone calls will be done at different times of the day to invite them again or ask about reasons for denial. For those not knowledgeable enough to use the web-based survey, a structured interview will be done by phone. Those from foreign countries not knowledgeable enough in German, English French or Italian will be offered to fill out the survey by phone with the help of research staff fluent in their mother language.

The invitation letter will describe the study in plain language and will include contact information of the project leader/study team so that participants can contact us if they have any questions. The invitation letter will include a link and a Quick Response (QR) code to the survey. Filling out the electronic survey is considered as providing consent which enables us to claim an exception

from written consent form (in accordance with Article 9 of the HRO). Each parent and participant will be informed that participation in the study is voluntary and that s/he is free to withdraw, without justification, from the investigation at any time without consequences. Participants will be requested to fill out the electronic consent and the survey in 2 weeks (excluding school holidays). Study participants will not receive any financial compensation for their participation but will get a voucher for a sport shop of about 15 CHF per child. In addition, parents will be offered to receive individual feedback about their child's health.

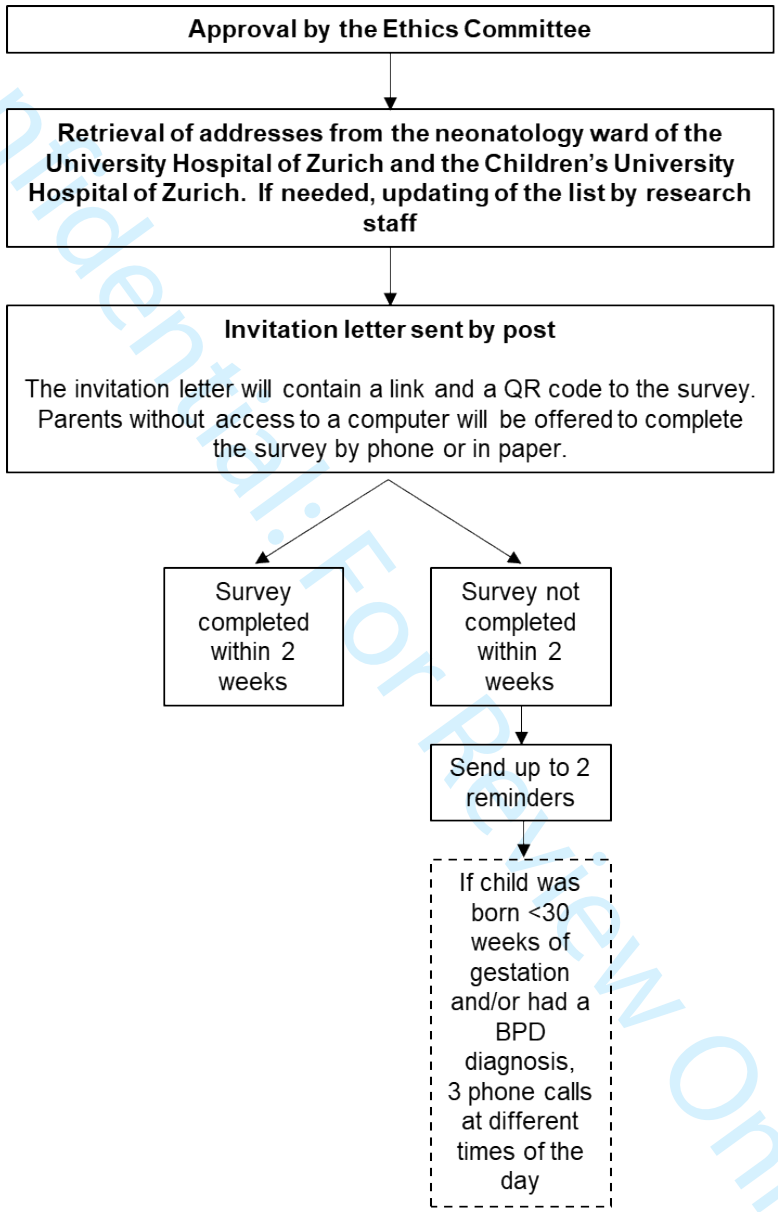

Figure 1. Recruitment of study participants

3.3 Study procedures

Study assessments and data collection

The online survey will last at maximum 30-45 minutes per child. The survey will contain questions about demographic background, the start, type, pattern, and severity of respiratory symptoms at rest and during exercise, and about their treatment. It will be sent out to a third of the families during the winter months, a third during spring, and a third during the summer months to cover the variability of respiratory symptoms by season. We will also ask whether respiratory symptoms are causing functional and/or psychological limitations in daily life, when they did start to occur, as well as where, when and how a diagnosis was established. Further, we aim to assess what kind of therapy was and is performed (e.g., medication, dosage, other procedures). The survey will contain questions from a validated respiratory questionnaire from the Swiss Paediatric Airway Cohort (SPAC) [31] and newly developed questions. The survey will also include the KINDL^{R} questionnaire [32] to measure quality of life of children and adolescents and the PedsQL™ Family Impact Module [33] to measure family functioning as a result of child's health. The respiratory questionnaire and a sample version of the KINDL^{R} and the PedsQL™ Family Impact Module questionnaires are attached to the present proposal. In the electronic survey, we will include the validated translation of these questionnaires into German, English, French and Italian. The online survey will also include short informative videoclips to describe respiratory symptoms like wheezing that may be difficult to explain only in text form. The survey will be prepared in close collaboration with important stakeholders (e.g., neonatologists, paediatric pulmonologists, experts from SwissNeoNet, Swiss and immigrant family participants) to ensure adequacy and accuracy of all included questions. Pilot testing will be performed prior to the start of the study.

The survey will be run using the electronic database from SwissNeoNet, a secure web application that has been used previously to run similar online surveys. Collected data will be saved on a server of the SwissNeoNet registry and managed only by authorized research staff.

Study duration

The proposed project will be completed within a 17-months period (Table 2).

Table 2. Workplan for the proposed project

	2020			2021											2022				
	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
Search addresses				■	■	■	■	■	■											
Pilot survey				■	■															
Run survey					■	■	■	■	■	■	■	■	■	■	■	■				
Data entry/cleaning									■	■	■	■	■	■	■	■				
Data analysis													■	■	■	■				
Writing manuscripts															■	■	■	■	■	■

Potential biases

Potential biases of this project are:

- Selection bias: lack of representativeness of the study population for the Zurich area because eligible families are not willing to participate. If eligible families do not respond to the invitation, a second and third invitation will be sent. A special effort will be taken to include all children with a history of BPD and those <30wk of gestation. In this population, further steps will be taken, and three phone calls will be done at different times of the day to invite them again or ask about reasons for denial. For those not knowledgeable enough to use the web-based survey, a structured interview will be done by phone. In addition, those from foreign countries not knowledgeable enough in German, English, French or Italian will be offered to fill out the survey by phone with the help of research staff fluent in their native language.

- Recall bias: participants do not recall accurately respiratory symptoms/treatment in the past. To try to minimize this bias, we will pilot the survey in a subgroup to test alternative ways of assessment. We will also include questions about symptoms/treatment in the last 12 months, a period that may be easy to recall to participants.

3.4 Withdrawal and discontinuation

Participation is voluntary and participants have the right to discontinue and withdraw their consent at any time during and after the study without any explanation. Neither disadvantages nor adverse consequences will arise. If a participant withdraws consent, already collected data will no longer be used for further analyses except for already processed samples and published or processed data. Already processed data and samples will be anonymized. Unprocessed data will be destroyed.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

A detailed statistical analysis plan will be provided in collaboration with experienced biostatisticians. Data will be described using appropriate summary statistics according to the type and distribution of each variable. The distribution of all variables will be reviewed and checked for inconsistencies or outliers. Categorical variables will be described using frequencies and percentages and continuous variables using mean and standard deviations (for variables normally distributed) or median and interquartile ranges (for variables non-normally distributed) as appropriate. To compensate for the differences between the two samples of siblings and preterm children, we will use a weighing factor based on age and sex. As such, we can match the siblings to the distribution of preterm children. We will also control for family clustering using a logistic regression [34]. Differences in predictors of respiratory symptoms among groups of children (e.g., younger – older age groups, preterm–term, BPD–no BPD, treatment–no treatment, within–between families, with–without atopic constellations) will be analyzed by logistic regression analysis. The association of predictor variables (e.g., sociodemographic or neonatal characteristics) with onset, type, pattern, severity and treatment of respiratory symptoms will be assessed using appropriate multivariate statistical models depending on the type and distribution of predictor and outcome variables.

For comparisons, a level of significance of alpha = 0.05 will be used. Analyses will be conducted using various packages for R or other standard statistical software (e.g. Stata).

4.2. Handling of missing data

We will analyze the distribution of missing data and we will clarify whether there are significant differences between individuals with complete and incomplete data. According the percentage and the type of missing data we will consider the most suitable imputation model, if any.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [4], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges her responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader will be promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.5 End of project

Upon project completion or discontinuation, the Ethics Committee will be notified within 90 days. Data collected by questionnaire assessments will be stored in pseudonymized form in a password-protected file on a secure server at the University of Zurich (UZH) and retained for 10 years. The participant identification list will remain accessible only to the Project Leader and will separately be stored in a password-protected file on a secure server at the UZH.

5.6 Insurance

In the event of project-related damage or injuries, the liability of the UZH provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

This cross-sectional study has been deemed a “Category A” research project according to HRO Art. 7, as the planned data collection entails only minimal risks and burden to participants. Inclusion of participants will be done after obtaining written informed consent. The project leader or his/her representative from the research team ensures an appropriate informed consent process so that all participants are fully aware of the nature and objectives as well as risks and benefits of the study. Participants can withdraw consent at any time during the study. The project leader will retain the original version of the consent form and provide a copy to the participant upon request.

An important aspect to consider within this study is whether some eligible families may not have the ability to access and use a computer to fill out the electronic survey, specially families from low socioeconomic status. Taking this into consideration, we will offer a structured interview by phone to those not knowledgeable enough to use the web-based survey or that do not have access to a computer.

6.2 Risk-Benefit Assessment

The primary benefit of the study is indirect. The global burden of lung disease following preterm birth is rising, and this early life event will increase morbidity throughout life, and ultimately result in the premature development of chronic obstructive pulmonary disease. A complete characterization of the respiratory symptoms, their treatment and burden of disease in childhood will be most useful to create primary prevention strategies for chronic pulmonary morbidity resulting from prematurity. The study thus aims at providing better clinical care to survivors of very preterm birth and their families living in the Zurich area. In addition, identifying the sociodemographic and neonatal predictors that influence the long-term consequences of pulmonary sequelae is of utmost importance as these factors can be targeted by specific intervention programs. Also, it is possible that the comprehensive assessment of preterm children born in the Zurich area will improve treatment and nurture further studies to better understand long-term outcomes and their predictors and provide better clinical care to this growing population at risk for long-term respiratory sequelae. The inclusion of siblings will allow to compare respiratory disease burden to a term-born control population and also tease out whether the burden of respiratory disease is higher within than between families. Finally, the multidisciplinary approach of this project combining knowledge of neonatologists, pediatric pulmonologists, and epidemiologists from the University and University Hospitals of Zurich provides an optimal basis for bringing the best of knowledge together, educate early career scientists, and make it a successful project with relevant outcomes that has high potential to improve the health and quality of life of children and families after preterm birth in Zurich.

We do not foresee any risk associated with the completion of the online survey.

6.3 Rationale for the inclusion of vulnerable participants

Children are per se a vulnerable population but the completion of the online survey do not expose them at any risk. In addition, the completion of an online survey seems a reasonable study burden in view of the benefits that the study may have for survivors of premature birth and their families.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

Resource management system

We will implement and maintain quality assurance and quality control with written standard operating procedures (SOPs) to ensure that the data is generated, documented, and reported in

compliance with the protocol. Specific quality checks and measures will be conducted throughout the study.

The documents that are necessary for data collection will be stored on local servers as well as on paper for specific tasks (staff training, logbooks if necessary) defined in the SOPs. Participants' data will be managed and securely recorded by SwissNeoNet customized interface. Data collected by phone interview will be entered into SwissNeoNet interface and checked by two independent researchers.

Project personnel

Study staff will receive the relevant SOPs and be trained on their respective tasks in the research project. The study coordinator will document the staff training and ensure that the staff has a precise definition of their roles and responsibilities.

Ethics Community

The study protocol and accompanying documents need approval by the Cantonal ethics committee of Zurich. After approval, any deviation from the study protocol or significant changes in the study documents will be amended and submitted to the responsible committee. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Source data

Study-related source data comprise:

- Addresses of eligible families. Addresses will be retrieved from the neonatology ward of the University Hospital of Zurich and at the Children's University Hospital of Zurich and, if necessary, updated by research staff.
- Neonatal and sociodemographic information retrieved from the SwissNeoNet registry.
- Data collected using the online survey.

Data recording

The data will be collected using the SwissNeoNet electronic database. Collected data will be hosted on a safe server on the SwissNeoNet registry facilities and managed by authorized research staff only. Regular scheduled backups of the database will be performed. Password-protected accounts will be created for authorized research group members and the degree of database access granted to each member will depend on their respective roles within the study. For each participant, a specific random identifier code (ID) will be generated automatically by the electronic database.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and will only be accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants will only be identified by a unique participant number.

Person identifying data and the unique participant number are linked at two sources:

1) Address lists of eligible families: This list will be stored and password protected on a secure server at the SwissNeoNet registry facilities. This list will be only accessible by authorized and trained research team members that need participant contact information to conduct and organize the mailings. After finalization of data collection, the password will be changed by the Project Leader and this file, which serves as the participant identifier list, will remain accessible to the Project Leader only.

2) Variables with person-identifying information retrieved from the SwissNeoNet registry: Variables containing person-identifying data which is needed for administrative purposes (email address, phone number, name) will be declared with an identifying flag, which restricts the possibility of export and which are accessible by trained and authorized staff members only. After finalization of data collection, the person-identifying variables will be deleted (pseudonymization).

7.4 Retention and destruction of study data and biological material

Survey data obtained in this study will be stored on a secure server at the UZH at least for 10 years after publication of the research project.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The present project is mainly funded by Lunge Zürich. In addition, the postdoctoral researcher involved in the project is recipient of a European Respiratory Society Fellowship (ERS Long-Term Research Fellowship 2020). Ethical guidelines for funding stated by Lunge Zürich and ERS will be respected.

Results of the study will be published in scientific journals. International guidelines for scientific publication of results and co-authorship will be respected.

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Seroprevalence of SARS-CoV-2 antibodies and development of immunity in a public school population – a population-based observational study to inform policy making (CORONA IMMUNITAS SCHOOLS – Ciao Corona)

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) (1).
Type of Research Project:	Research project involving human subjects
Risk Categorization:	A

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PROTOCOL SIGNATURE FORM

Study Title	Seroprevalence of SARS-CoV-2 antibodies and development of immunity in a Swiss school population – a population-based observational study to inform policy making **(CORONA IMMUNITAS SCHOOLS)**

The sponsor and the project leaders have approved the protocol version 8.0, 16 September 2021, and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements (2,3), current version of the World Medical Association Declaration of Helsinki (4) and the principles and procedures for integrity in scientific research involving human beings.

Sponsor: Prof. Dr. med. Milo Puhan

Site: Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich. Hirschengraben 84, 8001 Zürich

Date: 01.04. 2022 _____ Signature:

Project leader: Prof. Dr. med. Susi Kriemler

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Date: 01.04. 2022 _____ Signature:

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
BMI	*Body Mass Index*
CFR	*Case Fatality Rate*
CRF	*Case Report form*
CER-VD	*Ethics Committee of the Canton of Vaud*
CLIA	*Chemiluminescence Immunoassay*
COPD	*Chronic Obstructive Pulmonary Disease*
COVID-19	*Coronavirus disease 2019*
ELISA	*Enzyme-Linked Immunosorbent Assay*
FOPH	*Federal Office of Public Health*
FSO	*Federal Statistical Office*
GP	*General Practitioner*
HRA	*Human Research Act*
HRO	*Ordinance on Human Research*
ID	*Identifier Code (here: unique participant number randomly generated by REDCap)*
IgG	*Immunoglobulin G*
IgA	*Immunoglobulin A*
MERS	*Middle East Respiratory Syndrome*
PCR	*Polymerase Chain Reaction*
R0	*Basic Reproduction Number*
RNA	*Ribonucleic Acid*
RDT	*Rapid diagnostic test*
RT-PCR	*Real time polymerase chain reaction*
SARS	*Severe Acute Respiratory Syndrome*
SARS-CoV-2	*Severe acute respiratory syndrome coronavirus 2*
SOP	*Standard Operating Procedure*
SSPH+	*Swiss School of Public Health*
UZH	*University of Zurich*

1 BACKGROUND AND PROJECT RATIONALE

Setting the scope The coronavirus (SARS-CoV-2) pandemic has resulted in close to 3 million deaths worldwide to date. In Switzerland, over 700'000 persons were diagnosed with a SARS-CoV-2 infection, roughly 30'000 resulted in hospitalization and 10'000 in death by August 2021. In children, SARS-CoV-2 infections are generally asymptomatic or mild and do not result in hospitalizations nor death although incidence has increased since the delta variant is predominant.[1] This picture of SARS-CoV-2 infections is unusual for respiratory viruses for which children are usually main drivers of infection and transmission. The relatively mild disease in children may have contributed to the political decision in Switzerland to keep schools open since May 18, 2020. They were, unlike many other school systems worldwide only temporarily closed, and remained open with hygiene and distancing measures in place. It is crucial that these and future policy decisions on how to minimize societal burden - while keeping the spread of SARS-COV-2 under control - are constantly evaluated and informed by reliable and accurate data. This in turn requires knowledge of the nation-wide prevalence of SARS-CoV-2 infection at the level of the population and of specific groups as for instance children and adolescents in and outside schools. This study initially aimed at measuring the evolution of SARS-CoV-2 seroprevalence in schoolchildren and clustering of seropositive children on the class and school level from June 2020 to April 2021. As the pandemic is ongoing, many questions around the evolution of the immunity in children remain and the delta and omicron variants seem to affect children and adolescents more than before, this study will be ongoing until 2022 and possibly even longer (the timing depends on the evolution of the pandemic). The main questions will remain and appended by looking in more depths at cellular immunity in a subsample of children. As consent was given by schools, parents and children for 3 measures from June 2020 to April 2021, a new consent is needed for the follow ups. As about 30% of children changed or quit schools, we will recruit new children and classes within schools that already participated.

Ciao Corona is a population-based evaluation of seroprevalence in school children in the canton of Zurich. The evolution of seroprevalence was measured starting in June-July 2020 (R1), then in October-November 2020 (R2), in March-April 2021 (R3), and in November-December 2021 (R4). The design paper,[2] baseline R1 results,[3] findings in R2 and R3 were published in peer-reviewed journals[4-7]. In brief, around 2500 children from 275 classes and 55 took part in the study. Participation of eligible schools was, on average, 30%, among eligible children within classes about 50%, with less children participating from lower school level (37%). Retention of children and adolescents was high with 84% from R1 to R2, and 88% from R1 to R3, and lower from R1 to R4 (50%). Main findings were increasing SARS-CoV-2 seroprevalence from 1.6 to 6.5 to 16 to 25% in R1, R2,R3 and R4, respectively. If the 50% of vaccinated adolescents 12 years and older were also counted, seroprevalence at R4 of vaccinated and recovered youth was 42%. Symptoms occurred in 28% and 37% of seropositive children, and in 22% and 16% of seronegative children at R2 and R3, respectively. Clustering of SARS-CoV-2 in schools, (i.e. 3 or more seropositive children within classes with at least 50% of children tested) occurred in a minority of classes but increased over time along with the overall seroprevalence of children in the community. Clustering in R2 and R3 was predominantly explained by chance distribution of infections and was highest in lower school level (in around 20% of classes).[7] At R4, 15-40% of children in primary schools, and 60-98% of secondary school children showed evidence of a previous SARS-CoV-2 infection or were vaccinated. Symptoms compatible with long COVID under the wildtype virus variant occurred in 4% of seropositive and 2% of seronegative children from fall 2020 to spring 2021.[5] Preliminary data show that prevalence of long COVID covering the alpha VOC from spring to autumn 2021 (from R3 to R4) was identical to the previous assessment from R2 to R3. All research findings were communicated by media and press releases, documented on our website (www.ciao-corona.ch), and sent to the participating schools. Individual results of participating children were sent to all parents, and parents and school personnel also received individual results if they took part.

Relatively mild disease in children We still do not know the reason of the generally lower percentage of symptomatic SARS-CoV-2 infected children. Children seem to have a lower amount

and function of angiotensin converting enzyme II (ACE2) cell receptor where SARS-CoV-2 binds to the cell and enables the virus to invade and infect the host cells.[8] It is also possible that the mild symptomatology is related to a reduced inflammatory response of the immature immune system of children and adolescents or that immune response to other respiratory viruses (e.g. influenza, parainfluenza, adeno, rhino or respiratory syncytial viruses) that affect many children may protect them through cross-reactivity to the SARS-CoV-2.[9]

Despite the long journey of the pandemic, the correlates of protection against SARS-CoV-2 infections are not yet fully understood, especially not in children. What we know is that antibodies, and neutralizing antibodies in particular,[10] are important markers of immunity against re-infection. Recent longitudinal studies in adults have shown that SARS-CoV-2 antibodies following SARS-CoV-2 infection last for at least 6-8 months[11] and are associated with up to 90% protection against re-infection.[12] Evidence to date, including our own study, has demonstrated antibody persistence in children up to 2-6 months after SARS-CoV-2 infection.[13] [14] In a school-children cohort, most seropositive students and staff retained RBD antibodies for >6 months after SARS-CoV-2 infection which were highly correlated with neutralizing antibodies.[15]

There is currently very little information regarding the cellular immune response to SARS-CoV-2 in children. T cell responses against the SARS-CoV-2 spike protein seem to be higher in children compared to adults.[16] In this study, all children retained high antibody titers and cellular responses for more than 6 months after infection whilst relative antibody waning was seen in adults. Interestingly, SARS-CoV-2 spike-reactive cellular responses were also present in more than half of the seronegative children, indicating pre-existing cross-reactive responses or prior sensitization against SARS-CoV-2, as documented before in adults.[17] [18] Alternatively, it is possible that these responses represented genuine SARS-CoV-2-specific T cells generated following virus exposure in the absence of antibody sero-conversion as reported in health care workers with high levels of viral exposure.[19] It is well possible that unrecognized high viral exposure also happens in primary schools where enforcement of social distancing is challenging. Children thus seem to generate robust, cross-reactive and sustained immune responses after SARS-CoV-2 infection which provides insight into their higher protection (i.e., less severe disease) compared to adults, but this is by no means clear.

SARS-CoV-2 transmission in children The role of children and adolescents in the transmission of SARS-CoV-2 remains unclear and has been a key question since the early days of the pandemic.[20] This has important consequences for policy decisions, especially concerning the maintenance of open schools, sport facilities and intergenerational contacts. Over the course of the pandemic, school closures have become a less and less an acceptable option due to its striking burden on the physical and psychological health of children, and its adverse impact on education and social functioning of youth, especially penalizing those children and families that are already vulnerable.[21] [22] The knowledge about the spread of the virus within schools and between children has therefore become a critical political and Public Health issue. Several studies showed that the spread of SARS-CoV-2 infection within schools was not larger than in the surrounding community in 2020, when virus mutations of concern (VOC) such as alpha (B.1.1.7) and delta (B.1.617.2) were not prevalent in most of the countries, and the rates of secondary attack and outbreaks low.[23-26] Less evidence exists about how SARS-CoV-2 spreads within schools that might change due to vaccination of children and adults and the occurrence of VOC with higher infectiousness.It may perhaps be only our public awareness of much higher numbers of infected children and upstream outbreaks in school. The role of children and schools in explaining transmission chains has become more important than ever since the emergence of new SARS-CoV-2 variants, the relatively rare, but significant existence of long COVID[5] [27] and pediatric multisystemic inflammatory syndrome in children (PIMS),[28] and the evolution of vaccination in adults and youth.

Aims of the study are therefore

1. to measure the evolution of the population-based (sero)prevalence of SARS-CoV-2 and long COVID in youth

2. to detect ways of transmission from and among children and adolescents in Switzerland and worldwide, especially with the emerge of VOC
3. to determine the evolution of asymptomatic infection rates among youth,
4. to evaluate long-lasting humoral (all) and cellular (subsample) immunity in children
5. to assess the effect of open schools with preventive measures in place (including repetitive testing and facemasks) on the spread of the virus among children over time.
6. To assess the evolution of lifestyle and mental health in children and adolescents

Knowledge from ongoing population-based cohorts of children and adolescents over time will help to answer these critical questions. Results will inform policy, what preventive measures should be applied for youth during the pandemic – primarily in schools, but also in the strictness of social distancing measures towards (un)vaccinated adults. This approach is needed, to protect our children and adolescents from SARS-CoV-2 infections.

With this study, we intend to build up a Sentinella monitoring system to detect and monitor the immunity against SARS-CoV-2 in children and adolescents who attend school in the canton of Zürich. We aim to assess children of randomly selected schools during the first weeks of re-entering school after May 2020 from all districts of the canton of Zurich and at several later time points, which allows measuring how seroprevalence of SARS-CoV-2 of school children evolves. We will also test the school personnel and parents of participating children until the majority is vaccinated and evaluate possible transmission routes. Repeated follow-ups capturing the immune and health status, symptoms and behaviors over time will determine prevalence of SARS-CoV-2 infections and symptomatology in youth, the occurrence of long-term sequelae (Long COVID), the extent and duration of immunity, and the spread of the virus in schools under ever changing conditions.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Objectives

The overall aim of this school- and population-based study is to determine the extent and nature of infection with SARS-CoV-2 in children and adolescents in the canton of Zurich shortly after re-opening of the school system and thereafter, and thus, to contribute to consistent estimates in the Swiss population. Results will help schools, national and cantonal policy makers to plan and time the maintaining or lifting of the current and future public health measures that are related to children. They will allow timely planning of the way forward after the first major wave and the further epidemic phases of SARS-CoV-2 and will also inform the needs and planning of a vaccination program in Switzerland.

The main objectives addressed in this Sentinella monitoring are:

1. To repeatedly determine the seroprevalence of SARS-CoV-2 antibodies in school-aged children covering grades one to eight (approximately 6-17 years old) after the lockdown and the subsequent reopening of schools (R1, June/July 2020), three months after the start of the next school year (R2, October/November 2020), after the winter (R3, March/April 2021), in fall (R4, November/December 2021), in 2022 (R5, June 2022) and optionally in 2023 (R6) according to the evolution of the pandemic.
2. To examine clustering of seropositive cases within classes, schools and districts, and temporal evolution of the clusters;
3. To determine the proportion of asymptomatic children and adolescents with SARS-CoV-2 antibodies;
4. To determine the duration of the acquired immunity by examining new infections and vaccination status in children with positive serology, B- and T-cell function (subsample) and temporal persistence of SARS-CoV-2 immune responses;

5. To identify sociodemographic, exposure, hygiene, school- and family-based behavioral and environmental risk factors for SARS-CoV-2 infection;
6. To assess how school-children and their families adjust their lives and adopt preventive measures for SARS-CoV-2 over extended periods of time, and how quality of life is affected by the epidemic and preventive measures imposed or recommended by health authorities;
7. To assess how schools adopt preventive measures for SARS-CoV-2 infection over extended periods of time, and how they influence the infection rate;
8. To assess seroprevalence, clustering, and possible routes of transmission to and from children, school personnel and parents.
9. To assess how quality of life and lifestyle of schoolchildren was and is affected by the threat of the SARS-CoV-2 epidemic and by preventive measures imposed or strongly recommended by health authorities.
10. To assess whether and by how much seropositive children develop symptoms compatible with long-COVID
11. To assess why children and parents participate in Ciao Corona and what reasons prevent participation

Substudy addressing school personnel (R1b and R3)

1. To repeatedly evaluate the seroprevalence of school personnel and to compare the seroprevalence in the general population;
2. To determine whether seropositivity of children is linked to seropositivity of their school personnel.

Rationale: It is of great interest to know the seroprevalence of school directors, teachers, special teachers (HandarbeitslehrerInnen), Logopedists, housekeeping and “Mittagstisch” personnel, to weigh the risk of transmission to the children. Clustering of seropositivity within schools (e.g. seropositive children/adolescents and teachers) would suggest transmission within schools.

Substudy addressing parents of children and adolescents (R1b and R3)

1. To evaluate the seroprevalence in family clusters of seropositive children and adolescents.

Rationale: It is of great interest to understand transmission to and from children to parents (and through children to other parents) to better plan and implement appropriate school-based measures of social distancing also for parents (events for parents, discussion groups, parental presence at school). Currently inconclusive evidence suggested a potential spread of SARS-CoV-2 through schools to different families with community nuclei (37) and study of individual family clusters suggested that children get infected from their parents, but not the other way around (17). Thus, understanding of transmission routes affecting children within families is lacking.

Substudy of point prevalence of SARS-CoV-2 infection in children in school (additionally after R2)

1. To determine the point prevalence of SARS-CoV-2 infection in children and their classroom teachers attending randomly selected school in the canton of Zurich (as a pilot study for a potential Sentinella network to monitor infection in school children) during the peak time period of the second wave of the SARS-CoV-2 pandemic.
2. To determine the spread of SARS-CoV-2 infection within classes
3. To evaluate whether a RDT can be used at school in children, adolescents that are asymptomatic or mildly symptomatic to differentiate between the infectious and postinfectious PCR+ state

2.2 Primary and secondary endpoints

Primary endpoint is the seroprevalence of SARS-CoV-2 in randomly selected 5- to 17-year-old population of school-children after the peak phase of the first major wave shortly after re-opening of schools and at repeated time points during the epidemic in the canton of Zürich.

Secondary endpoints are:

On the level of the child

- Presence of symptoms (from January 2020) suggestive of a common cold, influenza and similar upper respiratory tract infections prior to the first study visit;
- Presence of symptoms suggestive of long COVID since fall 2020 (R2 onwards)
- Incidence of self-reported symptoms and SARS-CoV-2 infections in seropositive individuals (to determine the extent and duration of immunity after infection with SARS-CoV-2);
- Proportion of seronegative individuals who will self-report symptoms and infection with SARS-CoV-2;
- Proportion of children and adolescents that keep their positive antibodies against SARS-CoV-2 over time also considering their vaccination status
- Presence and agreement of antibody, T- and B-cell responses against SARS-CoV-2 over time in a subpopulation of seropositive children and adolescents
- Potential risk factors and preventive measures for SARS-CoV-2 infection (exposure, family constellation, socio-economic factors, adherence to general hygiene and physical distancing rules within families, utilization of mask and gloves and testing) prior and during the study;
- Changes in lifestyle and markers of lifestyle over the study time: going outside (frequency, reason), physical activity, sleep, media-use, substance abuse during and after the lock-down;
- Changes over the study time in mental well-being and quality of life during and after the lock-down.
- Predictors of participation and non-participation in the study by children and adolescents
- For point prevalence sub-study: identification of SARS-CoV-2 infection and the associated point prevalence in November/December 2020 and the spread within classes;
- Agreement of PCR-testing and RDT in saliva of mildly or asymptomatic children and youth.

On the level of schools

- Incidence of clusters of seropositive children and adolescents and adults within schools and classes at baseline and over time.
- Incidence of clusters of seropositive families within and among schools at baseline and over time
- Proportion of seropositive and seronegative school personnel at baseline and over time
- Impact of the number of children/adolescents at a specific period (baseline, follow-up periods) within a school or class changes in seropositivity within the same group.
- Incidence of seropositive children according to potential risk factors and preventive measures for SARS-CoV-2 infection within schools (size of school, number of adult school personnel, school hours and timing, tapering of children for reaching and leaving schools and for breaks, adherence to general hygiene and physical distancing rules within classes and school, use of public transport);
- Incidence of seropositivity of school-aged children according to changes in potential risk factors and preventive measures for SARS-CoV-2 infection within schools (number of adult school personnel with or without seropositivity or vaccination status), change in school hours and timing, changes in tapering of children for reaching and leaving schools and for breaks, adherence to general hygiene and physical distancing rules within classes and school, change in use of public transport, change in rules for group events, (e.g. Camps, choir, physical education classes); correlates of and impact of repetitive testing at school

- Perception of the school authorities, teachers, children and their families toward this study (e.g. acceptance, burden, reach of children, parents, teachers and the schools, approach with the help of media for study information, parental information meetings, electronic questionnaires) to better understand and implement similar studies (specific interviews and questionnaires will be defined after the first baseline assessment)
- Substudy (R2+): Point-prevalence of clusters of PCR or RDT positive pupils and classroom teachers

2.3 Project design

This is a canton-wide, population-based observational study in a randomly selected population of school-children including a longitudinal assessment of serological SARS-CoV-2 infections and their symptomatology combined with a baseline and a digital follow-up questionnaire to track flu-like symptoms, possible risk factors, preventive measures, quality of life and lifestyle.

The longitudinal design allows for monitoring the evolution of the epidemic in Switzerland, as well as the impact of school-based and other control measures enforced by the federal council and cantonal authorities. Different phases are defined and subject to change according to the highly dynamic pandemic and additional needs that may emerge:

- **Phase R1a** (June 2020): **Early estimates of seroprevalence in school-children** in the canton of ZH **shortly after the re-opening of schools**
- **Phase R1b** (August/September 2020): Early estimates of seroprevalence in school personnel and parents of participating children.
- **Phase R2 (**October/November 2020): **Estimates of seroprevalence of SARS-COV-2 in school-children after four months of regular school**. There may be further centers in close future that perform population-based seroprevalence surveys providing data for this phase (currently planned is Liechtenstein). The protocol for this phase will be refined based on phase I experiences
- **Phase R2+** (end of November/beginning of December 2020): **Estimates of point prevalence of SARS-CoV-2 infection in children and their classroom teachers in schools** during a period of high regional incidence of the infection and preventive measures implemented in schools, and estimates if infected children infect other children of the same class (subsample).
- **Phase R3** (March/April 2021): **Estimates of seroprevalence in schoolchildren (canton ZH), school personnel and parents of participating children by the end of the school year and potentially after lifting some measures** (e.g. normal class sizes, etc. opening sport facilities, small business, re-opening normal public transport). This phase will help to evaluate the lifting and monitoring (and potential re-introduction of more strict measures), prepare for the fall and determine the needs for a vaccination program.
- **Phase R4** (November/December 2021) **Estimates of point prevalence of SARS-CoV-2 infection in children in schools** during a period where more than a half of adults (and also a certain proportion of adolescents) are vaccinated and new variants evolve, and to estimate if infected children infect other children of the same class.
- **Phase R5**: (in June 2022) **Estimates of point prevalence of SARS-CoV-2 infection in children in schools** during a period where possibly a larger percentage of children, adolescents and adults are vaccinated, omicron was the predominant VOC, and to estimate if infected children infect other children of the same class.
- **A Phase R6** round in 2023 may be added depending on the evolution of the pandemic

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

3.1.1. Study population

For each phase and district of the canton of Zurich, we aimed to include a random sample of public schools that teach children aged 6- to 17-years of age from the general population of Switzerland. An independent team of biostatisticians randomly selected schools fulfilling the inclusion criteria from a list of schools per district that is provided by the statistical department of the educational directorate of the canton of Zürich. The sampling within schools was stratified for "Unter- (6-9 years), Mittel- (10-12 years) and Oberstufe (13-16 years)". As a third of children and adolescents will have left school or the selected classes (mainly 6th and 9th grade students) by summer 2021, more classes within the already participating schools were invited to participate from R4 on. The aim of each future round will be to maintain the number of children and adolescents participating in the study (e.g., around 2500 children) and within each participating school. If needed, new classes within schools will still be selected randomly according to the list provided by the educational department of the canton of Zurich.

3.1.2 Eligibility criteria

Eligibility criteria are as follows:

Inclusion criteria for schools and classes:

- Any public and private primary or secondary school (ie Unter-, Mittel- and Oberstufe) in the canton of Zurich
- Any randomly chosen and consenting school

Inclusion criteria for the seroprevalence study in children (R1-R5):

- Any school child residing in Switzerland aged 6 years or older and attending a public school that hosts classes of interest (grade 1 through 9) in the canton of Zürich, the school personnel of the participating schools and their parents living at least part time with the child;
- All children and adolescents that have participated in the past, but do not anymore belong to the schools will be kept in the study if they want to;
- No acute respiratory and SARS-CoV-2 infection:
    - In case of unknown respiratory infection, no presence of symptoms for at least 48 hours.
    - In case of confirmed SARS-CoV-2 infection: inclusion at the earliest 21 days from PCR-positive diagnosis after the onset of potential symptoms and no presence of symptoms for at least 48 hours (according to Standard of Care).
- Informed consent of parents or legal guardians and children

Inclusion criteria for the point prevalence study in children and classroom teachers (R2+):

- Any school child (irrespective of their vaccination status against SARS-CoV-2) residing in Switzerland aged 5 years or older and attending a public school that hosts classes of interest (grade 1 through 9) in the canton of Zürich;
- Any (un)vaccinated (against SARS-CoV-2) classroom teacher that teaches several hours per day in the selected classes
- No severe acute respiratory and SARS-CoV-2 symptoms including recurrent coughing, fever of 38.5° or more, or lack of smell/taste;

- In case of confirmed SARS-CoV-2 infection: inclusion at the earliest 10 days from PCR-positive diagnosis or after the onset of potential symptoms and no presence of symptoms for at least 48 hours (according to Standard of Care).
- Informed consent of parents or legal guardians and children

Inclusion criteria to determine the B-cell and T-cell function (R4-R5):

- Any school child residing in Switzerland aged 6 years or older, among randomly selected schools and classes (grades 2 through 9) in the canton of Zurich, having participated in R2/R3 rounds, and willing to participate in R4 and R5.

Exclusion criteria for schools, school personnel, parents and children:

- No informed consent by schools, school personnel, children and/or their parents;
- Schools with <40 students in one of the sampled grades (1, 2, 4, 5, 7, or 8);
- Children of Kindergarten age and younger: We decided to abstain from including smaller children due to the difficulty of the technical procedure involved in collecting samples from them in a "school-setting" and the associated risk of complications. If valid tests based on sputum or capillary blood become available this criterion may be reconsidered;
- Diagnosis of acute COVID-19 infection;
- Special need schools.

Sampling and sample size calculation

The canton of Zurich has a surface area of 1729 km^2, is divided into 12 districts and has 1.5 Mio inhabitants. The population size within districts is very heterogeneous and ranges from 32'000 in Andelfingen (smallest) to 423'000 in Zürich (largest). There are more than 500 school communities in the canton of Zürich, many of them with several schools per community. 25% of the cantonal population (e.g. about 400'000) of Zürich is 0 to 18 years old. 160'000 children go to primary or secondary schools covering ages from 5 to 16 years of age.

A random selection of schools is stratified within districts of the canton, and random selection of classes is initially stratified within lower, middle and upper levels of schools. All children attending the selected classes are invited, except in mixed-age classes (only students from the eligible grades invited). Primary schools are randomly selected and the closest secondary school geographically is matched. The targeted number of schools to enroll per district ranges from 2 to 10 depending on the district population size. After initial invitation round, school participation rate is assessed and additional schools are selected within required districts, until the aimed number is reached or further recruitment would not be feasible. Population sizes and targeted number of enrolled schools within districts is depicted in **Figure 1**.

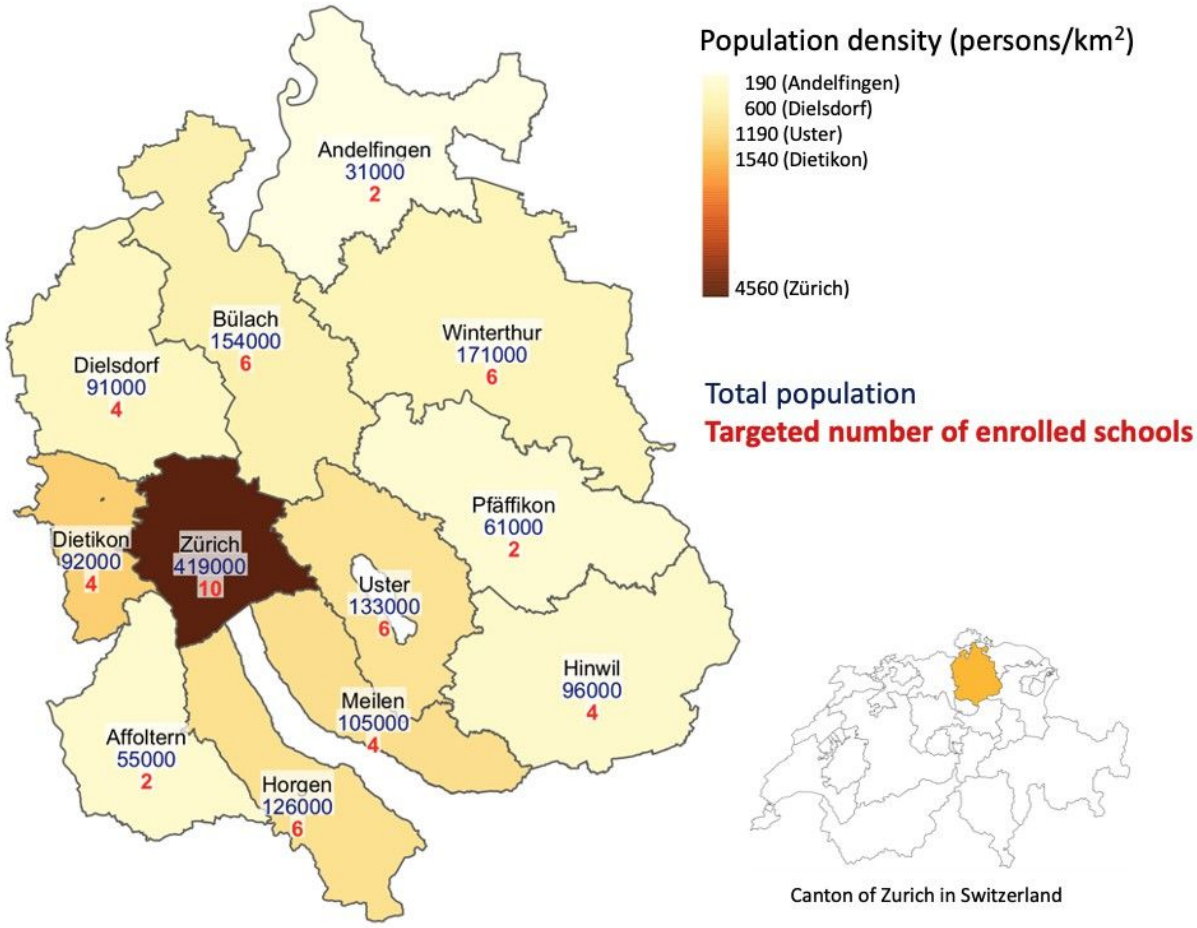

Figure 1 Districts of canton of Zurich: population density, count, and targeted number of enrolled schools.

The overall targeted number of schools is 58 (29 primary and 29 secondary schools). We aim to invite at least 3 classes and at least 40 children per school level. The number of classes and children to invite will be reassessed after calculating the average children participation rate in the first week of enrollment. If needed, additional classes will be invited, aiming to enroll at least 40 children per school level. At baseline, children/adolescents of level 3 and 6 and 9 will not participate and be randomly selected as they change their class levels and possibly classes after the summer break.

Assuming a participation rate of 60-80% per class, we would enroll 2100-2800 children in June/July 2020. We expect a seroprevalence rate of 1 to 5% based on the existing research. Depending on the specificity and sensitivity parameters of the test, we expect a precision of about ±2%.

New classes from R4 on will be enrolled assuming a participation rate of children of 50% within classes. Grades will be selected to ascertain, that children remain in these schools for at least 2 more years.

Cellular immunity will be assessed in a subsample of children. For the T-cell sequencing study, a sample of 300 children including 200 seropositive children and 100 seronegative children from R2-R3 will be included in this explorative study. For the B-cell and T-cell function in R4 and R5, previously participating children and adolescents from R2-R3 will be invited to participate (n=200). Among children and adolescents willing to participate we will select the subsample according to the laboratory capacity. If more children than needed want to participate we will select the children alphabetically and evenly distributed among school levels until we have the sample size reached.

Aiming at a subsample of 50 seropositive children and 150 seronegative children to assess B-cell and T-cell function in R4 (and possibly R5) would require a participation rate of 30% for the previously (at R2/R3) seropositive children. As retention rates in previous rounds were 85-90%, this scenario should be realistic.

For the sub-study of point prevalence, the enrolled schools within the city of Zürich will be invited, and additional schools from high-incidence districts as necessary so that 6 primary and 6 secondary schools are invited in total. The target sample size depends on a number of assumptions that are currently unclear (e.g., proportion of asymptomatic children tested with diagnostic RT-PCR, proportion of asymptomatic children not attending school due to quarantine, proportion of not diagnosed symptomatic children, etc). It also depends on the projected weekly incidence at the time of invitation to the sub-study (November/December 2020). Given the weekly incidence of 80 RT-PCR (real-time polymerase chain reaction) diagnosed cases in 44th week of 2020 in 0-9 year-old children and 661 diagnosed cases in 10-19 year old adolescents, assuming that an infected child is RT-PCR positive for 3-4 days, that only 1 in 10 cases are diagnosed, that 30% of undiagnosed cases are quarantined and thus do not attend school, given that the population of 0-9 and 10-19 year-olds in the canton of Zürich is 161613 and 141482 respectively, we expect 1 RT-PCR positive case in 570 children 0-9 years old and 1 in 58 children 10-19 year-old. However, the estimate is imprecise due to uncertain assumptions.

Due to pilot character of the PCR substudy (R2+) with much uncertainty of the power calculation that is full of assumptions, the urge to proceed during the period of high incidence of SARS-CoV-2 infections and the available testing capacity and funding, we aim to enroll 700-1000 children in total in this substudy. We will invite all children from already enrolled classes. With predicted participation rate similar to the other rounds of testing (50-60%), we expect to enroll 750-850 children in this sub-study.

3.2 Recruitment, screening and informed consent procedure

Upon the approval of the protocol by the ethics committee, the following procedures take place:

1. Written pre-information of all school authorities about the plan and aims of the study
2. Random selection of participating schools and classes according to protocol
3. Written information of the school authorities (“Schulgemeinde mit Schulleiter und Schulpflege”) about their selection in the sampling process
4. At least one zoom session for school heads and “Schulpflege” to explain the study and answer questions
5. Request to respond within 3-5 working days about their willingness to participate
    - A written consent sent back electronically will be asked for (Information – Consent to schools and classes)
    - Schools not participating will be asked about reasons why they do not participate, e.g. no priority, no time, not interested in research projects at schools, no necessity, too much work by an electronic survey through REDCap
6. Participating schools’ heads, about their written and signed consent, will get a study package on paper (invitation letter, information and consent sheet including a link to the videoclip about testing procedures) that will be forward to the selected teachers and classes for all children and adolescents potentially participating. A short videoclip will give a brief summary of the study aim, will explain the timing of a corona infection by an infographics, and will show study procedures with some children that had agreed to participate in the videoclip (oral consent was given by children, written consent by parents). The videoclip will be available on a public platform Youtube (https://youtu.be/4KWwwP4RUUk) and have subtitles in the 8 most

commonly spoken languages in Switzerland. Consent was given by the children and their parents to use the videoclip for the study and put it on Youtube.

7. Right after sending this package to the potentially participating children and adolescents, at least one informational parent evening session will be scheduled on Zoom to inform parents about the study and answer questions. Questions will be answered orally during the online session or by chat/email if time does not allow to answer all questions.
8. In parallel, consenting schools will be scheduled and will be informed when the testing at their school takes place.
9. Written consent of the children/adolescents and their parents will be collected by the teachers in closed sealed envelopes in a box that is in the corner of the classroom. The teacher will only inform about the deadline and will be instructed by us not to influence participation of the children in the class. It will include an email address and phone numbers of the parents (for children up to 14 years of age) and emails and phone numbers of the adolescent and parents for those 14 years and older.
10. An electronic version of a new second consent for the fall 2021, consecutive measures and the substudies will be collected electronically through REDCap Database.
11. A copy of the consent is provided to participants if this is asked for actively based on an informative letter to the participants. It will give them the choice between storing the consent as password protected files in a study folder on the University of Zurich server, or providing the participants and/or the parents of the child participant with an additional copy of the consent (Handhabung der Einverständniserklärung Version 1.0, 9.9.2020).
    Parents/caregivers and teachers signing the electronic consent via online REDCap platform have the opportunity to download and save the signed document.
12. The confirmation of the test personnel that various means of information about content, significance and consequences of the study were provided to the participants is considered as given (even without explicit signature on the consent). If the participants at any time after consenting ask proactively for a copy of his/her consent, the study principle will sign this confirmation of providing sufficient study information prior to sending out the consent. This was agreed upon in writing between the KEK and the study PI according the written agreement (Handhabung der Einverständniserklärung Version 1.0, 9.9.2020).
13. Those consenting will get an electronic invitation with the date of testing and the request to fill out the online or paper-and-pencil questionnaires until the date of testing.
14. Testing of children and adolescents in schools will start as soon as we have received consents from schools and individual children and adolescents. Testing will be performed in gym halls or, if not available, sufficiently large school halls of the respective schools, ensuring social distancing and proper hygiene during the testing. Hence, we will inform participants on the protective measures they should take, in accordance to the Federal Office of Public Health instructions at the time.
15. Testing of school personnel and parents will also take place in schools right after the summer break 2020 (R1b) and in March/April 2021 (R3). Classroom teachers of the participating classes will be asked to take part in all measurements of the R4 and R5. This is done primarily for motivational reasons to increase participation of children within classes. Teachers will receive their individual result, but their data will not be used for further analysis. Large rooms will be used ensuring social distancing and proper hygiene during the testing. All adults will wear a face mask.
16. The point prevalence sub-study will be conducted in a sub-sample of enrolled schools from the city of Zürich and other districts of high incidence (see above). Additional electronic consent will be requested for participation in this sub-study. Parents/caregivers and teachers

signing the electronic consent via REDCap have the opportunity to save the signed consent for their own documentation.

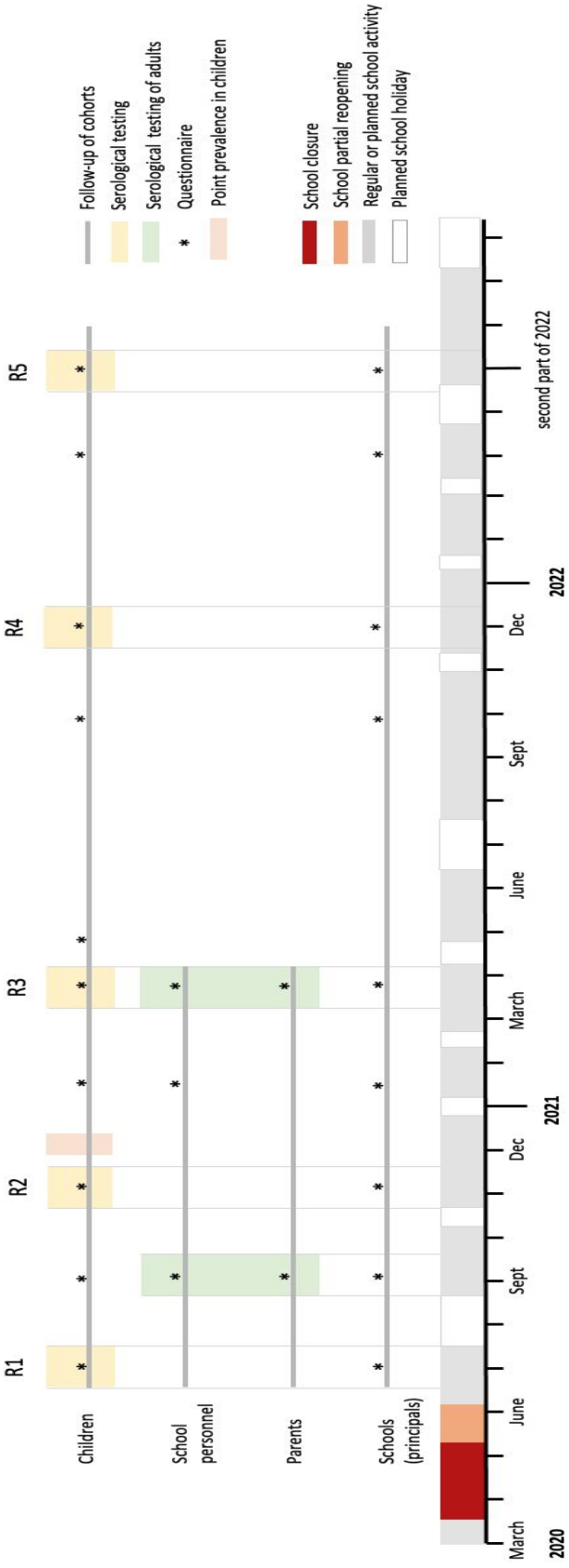

Figure 3: Testing procedures in the schools.

Once the appointments of the schools have been scheduled, each participating child and adolescent, parent and school personnel will receive an electronic confirmation to participate in the study, and the request to complete an online or paper-pencil questionnaire with a personal ID. We will have students fluent in the 8 mostly spoken languages in Switzerland (French, English, Italian, Spanish, Portuguese, Albanian, Turkish, Tamil) available to help school personnel and parents that speak a foreign language with filling out the questionnaires. This will be done by phone. Questionnaires will contain questions about the past or present symptoms, individual behavior of school personnel, the family and the child or adolescent in the context of the COVID-19 pandemic and about socio-demographic and co-morbidity data of the child. They will also include questions that focus on the aspects of life particularly influenced by attending school or conversely spending time at home without usual social interactions (e.g., physical activity; sleep; media use; level of stress; well-being).

On the day of the first study visit, a study staff member will greet the participant, check the completion of the consent and the questionnaire in REDCap, and if necessary, offer to complete the documents on site or upon a scheduled time (face-to-face in school or by phone) if there are time constraints or the parents/guardians are absent. Beside usual hand washing and disinfection procedures, study team members will wear masks, during all their interactions with participants.

In schools, the study team taking blood (and saliva for children) will wear gloves and masks. For the R4 and R5 testing, only personnel that is fully vaccinated (i.e., 2 doses of a two-dose vaccination regimen confirmed by certificate), at least 2 weeks prior to testing at schools, will support this study. The gloves and masks will be disposed on the spot just before leaving the schools (or in a special bin) and put in a special bag for that purpose, which will be taken out with the study team after leaving the school. We will wear T-Shirts and jeans attractive to the children/adolescence and wash them every day in the evening in a usual washing machine. Surfaces within a perimeter of 2 meters from where the participating child/adolescent or adult sat or lied down will be disinfected after the participant has left.

Prior to testing, we will make sure that the purpose of the study visit and exact procedures are clear to the children, the parents and the school personnel. Consent for children under 10 years old will be obtained from a parent or legal guardian and in the absence of evident refusal of the child. Consent for children aged between 10 and 15 years old will be obtained from both the child and a parent or legal guardian. Each participant will be informed that participation in the investigation is voluntary and that s/he is free to withdraw, without justification, from the investigation at any time without consequences and without affecting professional responsibilities. Informed consent will seek approval to collect blood and epidemiological data for the intended purpose of this investigation, and that samples of children may be shipped outside of the country for additional testing and that samples may be used for future research purposes. Blood of school personnel and parents will not be bio-banked. Study participants will not receive any financial compensation for their participation in the study but will get a present that is attractive to them. These will be adapted to the age group of the child and have a value around 10-20 CHF for children of grade 1 through 6 and 30 CHF for the older children of grade 7 to 9.

3.3 Study procedures

3.3.1 Study duration

At this point, we expect four to five main phases of testing the same children/adolescents, classroom teachers between May 2020 and in 2022 and according to the evolution of the pandemic perhaps 2023 (further specified according to the evolution of the pandemic). As for now, children will be tested up to 5 times, school personnel and parents twice, and classroom teachers of Ciao classes 3 to 4 times.

3.3.2 Study assessments and data collection

Baseline study visit R1 or R4

After obtaining the written informed consent of the participants, their parents and the school personnel, the study visit will take place at the school with an expected duration of 20-30 minutes on average per participant:

1) Study staff checks the completeness of the questionnaire and/or advises the participating child and present parent to complete the questionnaire in case it was incomplete. If the parent/guardian is not present, but consent given, the questionnaires will be filled out during the next days through telephone
2) A trained study staff applies an EMLA patch to both crooks of the arm in children and adolescents to make the skin insensible for the planned venipuncture. The patch will remain in place 30 to 60 min prior to the procedures. We will not put the EMLA patches if the child/adolescent do not wish to get it. Venipuncture for adults will take place without EMLA patches in sitting position.
3) A registered nurse or medical doctor collects a peripheral blood sample by venipuncture for the determination of SARS-CoV-2 antibodies.
4) A trained helper collects saliva (at R1 only) of the children by letting them spitting twice into a tube for the determination of SARS-CoV-2 IgA/G antibodies in June/July 20 and Oct/Nov 20 only. Prior to the procedure, the child will not drink or eat for an hour. The child will be asked to produce saliva in the mouth, if needed through intensive hurrumping (=räuspern), and spits it then out. Thereafter, a humidifying transport medium is poured into the tube before it will be closed and stored until transported to the lab.
5) All participants will be asked and invited to participate in the bi- to four-monthly digital follow-up in order to track their health status over time.
6) During the RT-PCR sub-study (between R1 and R2), buccal swabs will be collected, thus shortening the duration to 10 min per child. Whenever possible (e.g., by appropriate weather), collection of saliva will be performed outside.

The single stages and elements of the visits (at the study centers and at home) as well as the roles and activities of the study staff are determined in SOPs.

A) Data collection

Baseline questionnaire to children and parents

The following information will be collected by a questionnaire using paper/pencil at baseline, or REDCap on tablets or computers or, if the participant, his/her parents prefer, by paper/pencil again. ID1 that was given to each child for the baseline assessment will be linked to the automatically created ID2 and ID3 through REDCap. We will double check all IDs (ID1, ID2 and ID3) for children/adolescents and parents to make sure that no mix-up will occur. The codes will appear on the CRF handed out to each participating child. During the baseline parental testing, only some few questions will be added to a baseline parental questionnaire that were missing in the children's questionnaire (e.g. use and SwissCovid App).

The following information is assessed:

- Date and personal information: Sex, date of birth, age, email, phone number, school, grade, class
- Family information: name, age, phone number, email of parents, number and age of siblings that live in the same household as the child/adolescent
- Health data: Chronic conditions, height, weight, influenza and if adequate SARS-CoV-2 vaccination
- COVID-19 specific information of the child/adolescent, their parents and siblings in the same household: Acute and prolonged flu-like symptoms, number and time of episodes, drugs taken during last episode, hospitalizations, COVID-19 tests performed and results, SARS-CoV-2

antibody tests in the past, positive tested persons in environment (date, age, sex, same household), close persons, who developed symptoms but were not tested (date, age, sex, same household)

- Socio-demographic data of the parents: nationality, mother tongue, number of persons in same household (age, sex), status of employment, highest education, professional activity, place of work, change of work since outbreak
- Risk behavior, exposure and level of concern within the family (since January 2020): Adherence to general hygiene and physical distancing rules, number of people met, reduction of people met since outbreak, use of public transport, use of SwissCovid App.
- A few questions about the lifestyle behavior and well-being of the child/adolescent: hours spent in physical activities, sleep, media use (lifestyle), level of stress, short quality of life questionnaire (well-being)
- For the point prevalence sub-study, only minimal sociodemographic information and information on recent SARS-CoV-2 test results and acute symptoms in children, teachers and their household members will be collected.

Baseline questionnaire to school personnel (R1b and R3)

Baseline information will be collected by a questionnaire using REDCap on tablets or computers, or, if the participant prefers, by paper/pencil. This questionnaire is a shortened version of the baseline questionnaire of Corona Immunitas adults. It will include demographic information, COVID-19 specific information including adherence to general hygiene and physical distancing rules. It will also assess their function in school and frequency of exposure with children and adolescents of the same school.

Baseline and follow-up questionnaire to school principals (R1 to R5)

The following information will be collected from participating schools from their school principals using REDCap on computers:

Social distancing measures such as number of children per class in schools (e.g. max 15), the number of teachers per class, the reduction in school hours and number of days at school, the prevention of mixing of classes (eg timing of recess, lunch time), policy about cancelling high-contact activities (e.g. team sports, choir), reduction of participation of children in after-school settings (e.g. 'Hort'), hygiene measures at school, wearing of face-masks by school personnel, repetitive testing taken up since the summer break 2021, vaccination status of school personnel etc. The follow up questionnaire will assess social distancing and hygiene measure changes since baseline or in comparison to the last assessment.

Follow-up questionnaires to children, parents and school personnel

The participants are asked to take part in the digital follow-up of the study where they fill-in short online-questionnaires bi- to 4-monthly until at least 1 year after the last assessment over a secure online platform (REDCap). The following data will be assessed *(about 15 minutes to complete):*

- Questions regarding acute and prolonged flu-like symptoms (onset, type, duration);
- Health-care professional contacts, hospitalizations;
- Test results (COVID-19, SARS-CoV-2 antibodies);
- Vaccination status and side effects of vaccination
- Questions regarding preventive measures (adherence to general hygiene and physical distancing rules, utilization of mask and gloves, use of SwissCovid App);
- Possible risk exposures (travels abroad, contact with confirmed SARS-Cov-2 cases, etc.);
- Questions regarding mental health, general well-being and lifestyle

Telephone interview for children with symptoms beyond 3 months

Parents for their children and adolescents themselves are asked about any symptoms lasting more than 3 months in the period between R3 (March/April 2021) and R4 (Nov/Dec 2021) and possibly in future rounds. There were 16 children and adolescents overall who reported long COVID compatible symptoms (n=7 seropositive and n=6 seronegative children, n=3 with symptoms beyond 12 months) after excluding those that had seroconverted by R4. In order to better understand the characteristics of their symptomatology and burden of disease for their daily life, we intend to perform a zoom interview for 30-45 min with those who are willing to participate. We will send the parents (for children below 14 years) and adolescents above 14 years an individual information by email about our plan, and then call them to fix a date if agreed. Parents and children, and adolescents alone or with their parents, according to their preference, will participate. We will lead to interview with the parents in case the child is below 14 years of age, and with the adolescents for the older population according to a predefined interview protocol. Children will be verbally involved as much as possible, but especially when they do not agree with the answer of the parent. At the beginning of the interview the interviewer will explain the content of our questions and ask the interview partners whether 1. They are willing to participate, 2. whether we can audio-tape the interview for some time, e.g. until we have analysed and categorized the answers. This will take about 1-2 months. As soon as this is done, the audio-tape will be erased. If the participant does not want us to record the interview, an extra person beside the interviewer will participate and write down the answers of the participants. This interview will help to understand how seriously affected these children and adolescents were/are, how much these symptoms influenced their lives, and how their environment (family, teachers, friends) responded to their situation.

Biological samples *(sample collection, transport, analyses, preservation)*

For each child and adult participant, 1-2 samples (total 10.2 mL for children and 4.9 mL for adults) of venous blood will be collected for the assessment of SARS-CoV-2 antibodies. Children's and adults' EDTA blood will be sent directly to the Centre Hospitalier Universitaire Vaudois (CHUV) where it will be processed immediately. Of children, the remaining serum after analyses of antibodies will be biobanked at -80°C and 1 aliquot sent to the Institute of Medical Virology of the University of Zurich to run serological analyses (R1-R3). From R4 on, serological testing will be done at CHUV only.

For T- and B-cell function analyses we will draw 2 extra tubes of 9 ml blood each in a subsample of children (n=50 seropositive at R2/R3, n=150 seronegative at R1/R2/R3/R4). The T-cell receptor sequencing (TCRseq) can be made from the same blood. These analyses will be continued in next rounds if our main question, whether activated T-cells are found in previously seropositive child and whether they correlate with antibody titers or rather "replace" the antibody function, requests further testing. The amount of blood drawn (28ml) is acceptable even for the lightest 8-year-old girl that would be 18 kg (3rd percentile for weight). The overall quantity would thus be roughly 2% of her total blood volume, considering that a child of this age has 80ml blood per kg bodyweight. For taller and heavier children this percentage will be smaller. Parents and children will be given the explicit option to participate or not in this add-on substudy.

Saliva samples were collected in R1a and R2 in clean tubes and enriched with virus transport medium (R1a-R2). Saliva will first be validated for serological testing. If serological testing in saliva is deemed sufficiently accurate, venous blood sampling might not be necessary in further testing phases. Conversely, if serological testing in saliva is deemed not accurate enough, saliva sample collection will not be continued.

For serological analysis, a bead-based binding assay based on the Luminex technology will be used for children. The ABCORA test (version 2.3, this updated version has been used since R3) provides a highly differentiated picture of the immune response: immunoglobulins G (IgG), M (IgM) and A (IgA) antibodies against four SARS-CoV-2 targets (receptor binding domain (RBD), spike proteins S1 and S2), and the nucleocapsid protein (N) of SARS-CoV-2) are analyzed, resulting in twelve analyzed parameters. Owing to the broad assessment of serological parameters, the ABCORA 2.3 test provides an estimate of infection recency. Based on the ABCORA 2.3 results the seroconversion status of a sample will be classified as positive, weakly reactive, indeterminate, or negative, based on pre-specified threshold values of detected antibody reactivities. In a validation study a sample of

SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) positive children and a sample of pre-pandemic, healthy blood donors, Accuracy parameters of ABCORA 2.3 are 98.2% sensitivity and 99.4% specificity (the latter established against children pre-pandemic plasma values).[29] For children and adults, the SenASTrIS (Sensitive Anti-SARS-CoV-2 Spike Trimer Immunoglobulin Serological) assay developed by the Centre Hospitalier Universitaire Vaudois (CHUV), the Swiss Federal Institute of Technology in Lausanne (EPFL) and the Swiss Vaccine Center that has been validated will be used.[30] The test is also used by all study sites of the nationally coordinated research program *Corona Immunitas*. This test achieves a sensitivity of 96.6% and a specificity of 99.2% to detect SARS-CoV-2 infection by immunoglobulin IgG. If IgG and immunoglobulin IgA are analyzed in combination, the sensitivity is almost 100% and the specificity is 98.4%.

In a subsample of children (R4,R5, and R6 on demand), we aim to analyze their B-cell and T-cell function and evaluate whether these cells are activated after contact with the SARS-CoV-2 virus. To evaluate **T cell immune responses**, peripheral blood mononuclear cells (PBMCs) from participants will be purified and examined using various techniques. The frequency of S, M and N-reactive SARS-CoV-2 specific T cells will be examined by interferon (IFN)-gamma ELISpot assay using peptide libraries of the respective viral antigens. $CD4^+$ and $CD8^+$ T cell subsets and expression of markers of recent antigen-specific activation (CD137 for $CD8^+$ and CD40L for $CD4^+$ T cells) will be quantified using flow cytometry. In a subset of participants, immunodominant SARS-CoV-2 proteins/epitopes which could be used as vaccine targets will be evaluated by incubating cells with peptides from all SARS-CoV-2 proteins and phenotype and functionality of responding T cells will be characterized by flow cytometry with intracellular cytokine staining of IFN-gamma IL-2, TNF-α, degranulation by CD107a surface expression and expression of co-stimulatory and co-inhibitory molecules, such as PD-1, TIM-3 and 2B4. We will further analyze circulating **Antibody-Secreting B cells.** We will conduct a B cell ELISpot assay to evaluate frequencies of IgM/IgG-producing, virus-specific B cells following incubation with SARS-CoV-2 S or N proteins. We will additionally perform a phenotypic evaluation using flow cytometry, assessing the expression of markers CD20, CD27, CD38, CD138, IgM and IgD. To identify virus-specific B cells we will utilize a flow cytometry-based assay with biotin-conjugated spike protein, which can be bound by spike-specific B cells and detected by streptavidin-PE complexes. For all analyses, we will compare the frequencies of activated T cells and/or B cells, and anti-SARS-CoV-2 antibody titers between age groups.

T cell receptor variable beta chain immune-sequencing of the CDR3 regions of human TCRβ chains will be performed using the immunoSEQ Assay (Adaptive Biotechnologies) (R2 and R3, possibly R4 and R5). Extracted genomic DNA will be amplified in a bias-controlled multiplex PCR, followed by high-throughput sequencing. Sequences will be collapsed and filtered to identify and quantitate the absolute abundance of each unique TCRβ CDR3 region for further analysis as previously described.[31] The fraction of T cells will be calculated by normalizing TCRβ template counts to the total amount of DNA usable for TCR sequencing, where the amount of usable DNA will be determined by PCR amplification and sequencing of several reference genes that are expected to be present in all nucleated cells. TCR sequences from repertoires will be mapped against a set of TCR sequences that are known to react to SARS-CoV-2 by matching on V gene, amino acid sequence and J gene. In brief, these sequences will be first identified by Multiplex Identification of T-cell Receptor Antigen Specificity (MIRA).[32] TCRs that react will further be screened for enrichment in SARS-CoV-2 positive repertoires collected as part of ImmuneCODE compared to SARS-CoV-2-negative repertoires to remove TCRs that may be highly public or cross-reactive to common antigens. Individual response can be quantified by the number and/or frequency of SARS-CoV-2 TCRs seen post-infection. TCRs will be further analysed at the level specific ORF or position within ORF based on the MIRA antigens. The breadth summary metric will be calculated as the number of unique annotated rearrangements out of the total number of unique productive rearrangements, while depth summary metric corresponds to the sum frequency of those rearrangements in the repertoire. Sequences of known variants will be obtained from GISAID (www.gisaid.org) and aligned to known MIRA antigen locations. All these substudies will be done in close collaboration with the Institute of Forensic Medicine, the

Functional Genomics Center of University of Zurich and experts in the field (Prof C. Münz, University of Zurich and G. Pantaleo, CHUV)

For the point prevalence sub-study (R2+), two tests for detection of SARS-CoV-2 virus in saliva will be used: standard RT-PCR test and rapid diagnostic point-of-care test of SARS-CoV-2 antigens (RDT). PCR in naso-pharyngeal swabs and in saliva (PCR Cobas) were compared to 3 different rapid diagnostic antigen tests (Standard Q de Biosensor and Roche; PanBio de Abbot, COVID-VIRO de AAZ-LMB) in a validation study including 675 persons with 97% of the cohort experiencing at least 1 major SARS-CoV-2 symptom (e.g. 66% cough, 43% fever, 62% sore throat, 29% lack of taste) and 3% of the cohort experiencing 1 minor symptom but having a direct contact with a positive person (unpublished). 32.2, 32.6, 27.5% were positive in naso-pharyngeal PCR, saliva PCR and rapid tests, respectively. This documents that PCR test in saliva performs as well as the naso-pharyngeal swab, and rapid tests detect slightly lower numbers of positive cases. Rapid antigen tests had sensitivity of 80.7-92% (Roche test performing best) and specificity of 99.8%. These results were confirmed elsewhere (39). Buccal swab samples will be collected in two separate tubes at two time points 7 days apart. RT-PCR tests will be analysed each day. The second tube will be used to perform RDT immediately, at the testing site. The results will be entered into a database by dedicated personnel. After each testing of a complete class, a responsible in each study team will inform parents, teachers and school principals in case of positive RDT results. The school principals will then inform the responsible health authorities to proceed with contract tracing. The rationale for the results communication is explained in section 6.1. These samples will not be stored for further analysis.

Repeated collection of biological samples

For each additional blood collection for serological analysis in participants who are repeatedly tested, the same procedures are used as described above.

3.3.3 Potential biases

Potential biases of this project are:

- Representativeness of study population for Switzerland overall and in each phase (selection bias):
    - Randomly selected schools are not willing to participate
        - We will follow a multicomponent approach to reach the highest possible participation of schools: we send an extended information sheet to the schools explaining the importance of the study for the schools and whole Switzerland; we provide a hotline for school heads; we will organize zoom-based session for schools and teachers to explain the study and give the option to ask questions; we organize all the testing procedures and logistics as carefully as possible with the aim to take off any potential load from the school system
    - Randomly selected children/adolescents are not willing to participate or have parents that are unable to fill out questionnaires despite help.
        - We will follow a multicomponent approach to reach a highest possible participation of children: we append the information sheet of the study with an easily understandable picture that describes the infection process, we provide a videoclip explaining all procedures visually; we organize zoom-based sessions for parents to explain the study and give the option to ask questions; we provide a hotline where children and parents can call to answer all questions; we provide help to fill out the questionnaires face-to-face or by phone the 8 mostly spoken languages in Switzerland; we provide individual results for children and their parents; during the third round of assessment we will through the help of the schools hand out a short questionnaire to all non-

participating children and parents to assess information about reasons of non-participation. Parents are free to respond to the anonymized questionnaire.

- Conduct of the same procedures and measurement strategies across schools (information bias): Development of clear and detailed SOPs, training of study staff, monitoring of study sites.

3.4 Withdrawal and discontinuation

Participation is voluntary and participants have the right to discontinue and withdraw their consent at any time during and after the study without any explanation. Neither disadvantages nor adverse consequences will arise.

The serological survey part of this project involves a longitudinal study, i.e. the assessments are conducted right after the participants provided confirmed, written, informed consent, and during period 2 and 3 spread over the year. If a participant is not willing to conduct the subsequent assessments (e.g. not willing to provide the blood sample or complete the follow-up assessments), he or she will not be further included into the study. If a participant withdraws consent, already collected data and biological material will no longer be used for further analyses except for already processed samples and published or processed data. Already processed data and samples will be anonymized. Unprocessed data and biobank samples will be destroyed. Biological material preserved for potential future research use (biobank samples) will be destroyed if this is requested by the participant. All participating children and adolescents will be asked after their 18th birthday, irrespective whether they themselves have agreed upon the storage of their blood or their parents, whether the biological probes and questionnaire data can be kept for undefined times or not. If they do not agree, all samples and information will be destroyed.

Participants who are not willing to participate in the digital follow-up will remain in the study and re-contacted for the assessment periods 2 and 3. We will then try to get some of the missing information retrospectively. If the child/adolescent withdraws consent or is not showing up for assessments, the data collected during the serological survey so far, and data already collected will be kept.

Children participants who are not willing to provide blood but are willing to be still enrolled in the study will be allowed to provide saliva only.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

Statistical methods

A detailed statistical analysis plan will be provided in collaboration with experienced biostatisticians.

Descriptive analysis of participant sociodemographic, lifestyle, and behavior information will be performed. Total seroprevalence and cumulative incidence will be calculated, as well as age-, time- and region-specific estimates. In order to include also the sensitivity and specificity of the serological test in the analyses and account for the complex sampling structure (clustering within classes, grades and schools), hierarchical Bayesian logistic regression models will be used. The total numbers of school children in the respective grades per district will be used for post-stratification, so that the estimates are representative for the demographics of the canton of Zurich.
Associations with health and quality of life outcomes will be assessed with multiple regression models. Other planned estimates include proportion of seropositive individuals who have been asymptomatic, risk factors for infection at individual and school level. Associations of levels of IgG, IgM and IgA antibodies with symptoms and risk factors will be assessed.

For comparisons, a level of significance of alpha = 0.05 will be used. Analyses will be conducted using various packages for R or other standard statistical software (e.g. Stata).

4.2. Handling of missing data

We do not expect much missing data for the serological survey. The majority of the participants will bring the filled out questionnaire to the measuring days at school which provides us with the option to check and ensure their completeness (paper/pencil and electronic). If incomplete, study staff will help children and parents in completing the paper/pencil questionnaires. Participants, who have not completed the questionnaire within a few days after the testing, will be contacted individually to offer the option of providing the paper version of the questionnaire or translation support (direct support by a translator on a phone). Each research question will handle missing data on covariates based on their specific needs and possibilities (with or without imputation).

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki (4), the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) (1) as well as other locally relevant regulations.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader and the sponsor are promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.5 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days. Data collected by questionnaire assessments will be stored in pseudonymized form in a password-protected file on a secure server at the University of Zurich (UZH) and retained for 10 years. The participant identification list will remain accessible only to the Sponsor and project leader and will separately be stored in a password-protected file on a secure server at the UZH.

The collected biological samples will be labeled with an unique identifier and securely stored for potential future research use in the biobank facility of the EBPI for an unlimited amount of time. In case of withdrawal by the participant, the biological sample will be fully anonymized. In case the participant specifically requests to have the biological sample destroyed, this will be done after completion of the seroprevalence study at the national level.

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

In case the participant does not separately consent to future research use of data and biological sample, they will be fully anonymized at the end of the project (by December 2021).

5.6 Insurance

In the event of project-related damage or injuries, the liability of the UZH provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

This cohort study has been deemed a “Category A” research project according to HRO Art. 7, as the planned data collection entails only minimal risks and burden to participants. Other seroprevalence studies of SARS-COV-2-antibodies under the umbrella of CORONA IMMUNITAS by SSPH+, following mainly the same protocol, have already been approved by the local ethics commissions and already started in the Canons of Geneva (SEROCoV-POP study; Project Leader Dr. Silvia Stringhini) and Vaud (UnderCOVer study; Project Leader Prof. Valérie D’Acremont). In the Cantons Basel Landschaft and Basel Stadt, the project has been submitted to the local ethics commission (CoV-Co-Basel, Project Leader Prof. Dr. Nicole Probst-Hensch) and in the canton of Fribourg (Project Leader Prof. Dr. Arnaud Chiolero).

Inclusion of participants will be done after obtaining written informed consent. The project leader or his/her representative from the research team ensures an appropriate informed consent process so that all participants are fully aware of the nature and objectives as well as risks and benefits of the study. Participants can withdraw consent at any time during the study. The project leader will retain the original version of the consent form and provide a copy to the participant upon request.

An important aspect to consider within this study is whether or not and how the serological status result (SARS-CoV-2 antibodies have been detected in the blood or not) is communicated to the participant. Although sensitivity and specificity of currently available diagnostic tests are already high and will improve even more in the future, they are not 100% accurate. Due to the expected low prevalence of SARS-CoV-2 antibodies in the general population, a relatively high number of participants who will receive a positive test result will truly be seronegative (i.e. false positive). Furthermore, the extent of protection from a seropositive test result against reinfection remains uncertain, although it is expected to be high at least for a few months. On the other hand, test results will be of great interest for participants and schools.

We will inform the parents and children about the individual test result regarding B- and T-cell function by a simplified version and test results on the level of the whole group to everybody participating in this substudy. Each child and their parent will however be given the option to get their individual results, if wanted.

Taking these considerations into account, we will explain to the children and their parents during the study visit how they correctly can interpret an antibody test result on the individual level. We will hand them out a leaflet with the information what it actually means if they will get a positive serological test result (probability is high that it is falsely positive) and instruct them, whatever their test result will be, that they should keep on following the recommendations of the public health authorities.

We will inform the participants on test results by e-mail. We have made videoclips with links embedded into the email for adequate interpretation of serological test result and of the importance that they follow the recommendations of the public health authorities.

Irrespective of the result, teachers, pupils and their parents have the right to know their results based on the Humanforschungsgesetz Art. 8. Each positive results of the rapid diagnostic test (RDT) from the point prevalence sub-study will be communicated to study participants and schools after results have been obtained, eg after testing of each participating class. Parents will be informed by email, school and teachers directly after the testing at school. Negative results will not be communicated. Participants with a positive RDT are infectious and need to be isolated even though they may be

asymptomatic. Furthermore, it is important to let all participants know their positive results to induce isolation and quarantine measures of even asymptomatic potential spreaders. This is to protect their environment which may very well include persons at risk like grandparents. We will, however, not report the results of the PCR tests due to its uncertain clinical relevance in asymptomatic youth. While the concordance of the PCR and RDT is good in early infectious stages of symptomatic adults, many asymptomatic pupils or teachers may demonstrate a positive PCR due to postinfectious viral shedding that can last for months (41). We will also prepare and send a report with the overall results to all children, parents and schools. If the participating children experience more severe SARS-CoV-2 related symptoms or become aware of an exposure, they need to get tested and diagnosed outside of the study, according to the standard FOPH and cantonal regulations.

6.2 Risk-Benefit Assessment

The primary benefit of the study is indirect. The evaluation of the SARS-Cov-2 seroprevalence in the population is essential to understand what phase of the epidemic we are currently in, to be able to make predictions for the continuation of the epidemic and to put in place adequate public health measures. It will also provide information on the proportion of pauci- and asymptomatic school children. The publication of these results as open access will be useful to the entire international scientific community as well as other stakeholders including guideline developers, policy makers and physicians.

The risk associated with the collection of biological samples is very low. Possible complications are minor and include a hematoma at the puncture site, infection, or vagal discomfort during blood collection. All safety measures will be taken to prevent these complications from occurring by adopting standard collection rules and working with registered nurses.

There is also a risk of SARS-CoV-2 infection on the way from participants' homes to the study site. However, the risk is not different from that when children/adolescents going to school anyway. During all interactions, study staff will follow standard hygiene procedures (hand washing and disinfection procedures, wearing masks and gloves) and participants will wear a mask, provided by the study staff.

Prevention of SARS-CoV-2 infection in research personnel

All personnel from R4 on will be fully vaccinated. Additionally, all personnel involved in the study will be trained in infection control procedures (standard contact precautions, droplet or aerosol, as defined by local and national guidelines). These procedures include hand hygiene and proper use of masks (for instance FFP2 masks, in case of particularly high community transmission during the testing phases), not only to minimize their own risk of infection in close contact with people infected with SARS-CoV-2, but also to minimize the risk of infection transmission.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

The general aim of this project is to provide evidence to public health and political decision makers when trying to mitigate the consequences of the SARS-CoV-2 epidemic in Switzerland and to further improve knowledge on how this infectious disease affects people in the community.

Based on the mentioned general aim of the study, quality policy objectives of the study are defined as:

- Providing appropriate measures for the protection of data and samples, which remain at the center of the stakeholders' concerns;
- Providing data of appropriate quality, anticipating the future computational needs and purposes that could emerge from the larger national study;

- Providing samples of appropriate quality, anticipating the future analytical needs and purposes that could emerge from the larger national study.

To follow the implementation of the quality policy objectives, we will implement and maintain quality assurance and quality control with written SOPs to ensure that the data is generated, documented, and reported in compliance with the protocol. Specific quality checks and measures will be conducted throughout the study.

Resource management system

If at a later stage more cantons will follow to participate, a shared folder hosted by protected local servers is in place for the development, management and storage of study documents. The documents that are necessary for data collection in the centers will be stored on local servers as well as on paper for specific tasks (staff training, logbooks if necessary) defined in the SOPs. Study coordinators are responsible for the update on local servers and for the information to the concerned persons in their centers.

Participants' data will be managed and securely recorded by REDCap customized interfaces (see chapter 7.2). It is possible, that the database will not be ready at the beginning of the study. If so, we will have all information, data, and questionnaires on paper. Each paper will have the study ID on it, but no information with which the link to the identity of the child can be made. As soon as REDCap is ready, all information will be entered into REDCap and checked by two independent researchers.

Project personnel

Study staff will receive the relevant SOPs and be trained on their respective tasks in the research project. The study coordinator will document the staff training and ensure that the staff has a precise definition of their roles and responsibilities.

All personnel involved in the investigation will be trained in infection prevention and control procedures (standard contact and droplet precautions, as determined by national or Cantonal guidelines). These procedures should include proper hand hygiene and the correct use of masks, when necessary, not only to minimize their own risk of infection when in close contact with individuals with ongoing SARS-CoV-2 infection (who will be very few in this specific study), but also to minimize the risk of spread among other participants in the investigation.

Ethic Community

The study protocol and accompanying documents need approval by the Cantonal ethics committee of Zurich. After approval, any deviation from the study protocol or significant changes in the study documents will be amended and submitted to the responsible committee. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Source data

Study-related source data comprise:

- Sample of schools and a school population selected from a list received from the educational department (Bildungsdirektion) of the canton Zurich
- Information on the level of schools and on the level of children collected by questionnaires from all assessment periods (online over REDCap e-Case Report Form (eCRF) or by paper/pencil (CRF) or by telephone interview (special interview questionnaire) in a subpopulation with prolonged symptoms;

- Results of the blood and saliva samples SARS-CoV-2 antibody and T- and B-cell activation measurements (received by e-mail as a PDF document or similar or by mail in paper form from the laboratory);
- Results of SARS-CoV-2 infection test in saliva with RT-PCR testing (received by e-mail as a PDF document or similar or by mail in paper from the laboratory);
- Results of SARS-CoV-2 infection in saliva with RDT (recorded in a secure database);
- Information on the level of schools and on the level of children collected by bi-monthly digital follow-up questionnaire (eCRF).

Data recording

The data will be collected using the electronic database REDCap, a secure web application for building and managing online surveys and databases. REDCap will be hosted and saved in the infrastructure and on a save server of the University of Zurich and managed by the EBPI team. Regular scheduled backups of the database will be performed. Password-protected accounts will be created for authorized research group members and the degree of database access granted to each member will depend on their respective roles within the study. For each participant, a specific random identifier code (ID_REDCap) will be generated automatically by REDCap upon completing the entry questionnaire. Another set of IDs (ID_test) will be assigned to the participants at each testing phase. The key to link the IDs will be stored in encrypted and secure database. The IDs will only be merged (automatically and verified by two independent staff members) in order to communicate the results and for data analysis.

Sample from the cantonal school registry

The “Bildungsdirektion”, Department of “Bildungsstatistik” will provide the project leader with a list with all public and private primary and secondary schools of the canton of Zürich by grade and class, including the number of children per grade. This list will be used to organize and conduct the mailing to the schools and for the invitation of the schools and children/adolescents for the study. It will be supplemented with the ID1 for each child/adolescent and their parents that gave written consent. The list will be saved password protected on a secure server at the UZH and will be only accessible to identified and authorized study staff of the study team only.

Information collected by baseline questionnaires

In the invitation letter, children/adolescents, their parents and the school personnel are informed about the study and invited to participate. The initial invitation of the children is sent through schools and the responsible teachers to the children’s homes. If parents and children consent by sending back the filled out and signed consent sheet to the teachers, including the addresses, phone numbers and emails of parents and for the secondary school emails from parents and children, a written confirmation of the appointment and the time of testing at school will be provided electronically to children and parents. Parents will be invited directly through us, as they provide us with their email address when they fill out the children’s questionnaire. Those who do not fill out the children’s questionnaire, or from whom we do not have the email adress, will receive an email from the school principles. They will be invited again to fill out the children’s questionnaire and get the date of testing of the respective school. In case they show up for testing, they have to fill out the children’s and their own questionnaire before their blood is drawn.

For the school personnel a REDCap link is sent to them through the school principles. With the link they register for the testing and provide us with their email. A questionnaire link is then sent to the school personnel. As soon as the participant opens the REDCap questionnaire link, the personal ID will be automatically generated.

The parents questionnaire will be sent to them directly as they provide us with their email address when they fill out the children’s questionnaire. By filling out the parents’ questionnaire a personal ID for each parent will be created that is directly linked to their children’s ID.

In case the participant prefers to fill in the questionnaire in the paper version, he/she is able to do so.

Biological material (results of the blood samples SARS-CoV-2 antibody measurements)

The collection of the blood sample during the study visit will be documented by the study nurse in a paper CRF (date of collection, information whether collection is complete and conducted according to protocol). Results from the laboratory will be sent to the study team by email in PDF format or similar or in paper my mail. Data regarding the biological material will be entered into REDCap. The original PDF or paper document with the results (source data) contains the ID only of the participants and no person-identifying information and will be stored at the EBPI.

Information collected 2-4-monthly digital follow-up questionnaires

To fill in the digital follow-up questionnaires, the participants will receive a link to enter the corresponding REDCap survey. Parents and children will get one follow-up questionnaire together. The scheduling of the mailing is conducted automatically by the REDCap system and, thus, the data will be linked to the participant's ID.

Structured interview with those with longer lasting symptoms

A structured telephone interview also linked to the participant's ID will be done in those with prolonged symptoms that occurred between R3 and R4 to better understand the burden and characteristics of this prolonged symptomatology in these children. The interview is based on the already existing questions from the follow-up questionnaire and will be taken by 2 independent research assistants blinded to the serostatus of the children. If agreed by parents, children or adolescents, the interview will be voice-recorded, but erased, after the results have been stored in REDCap, at the latest 2 months after the interview. This procedure will be again taken up at later rounds. Parents and children can freely decide if they do not want to participate in this interview.

Information collected by 2-4-monthly digital follow-up questionnaire to schools

To fill in the digital follow-up questionnaires, the participating schools will receive a link to enter the corresponding REDCap surveys. The scheduling of the mailing is conducted automatically by the REDCap system and, thus, the data will be linked to the participant's school ID.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified with the ID_test or by a unique participant number generated by REDCap (ID_REDCap). In all paper CRFs and other project specific documents, ID_test is used to identify the participant. All staff members involved in the study will sign confidentiality statements.

Person identifying data and the unique participant number are linked at two sources:

1) Address lists of schools, head of schools, teachers of participating classes, children/adolescents, parents and school personnel: This list will be stored and password protected on a secure server at the UZH. This list is only accessible and can only be printed for temporary purposes (paper copy to be destroyed as soon as not necessary) by authorized and trained research team members that need patient contact information to conduct and organize the mailings and assessments. After finalization of data collection, the password will be changed by the project leader and this file, which serves as the participant identifier list, will remain accessible to the project leaders and the sponsor only.

2) Variables with person-identifying information in REDCap: Variables containing person-identifying data which is needed for administrative purposes (email address, phone number, name) will be declared in REDCap with an identifying flag, which restricts the possibility of export and which is

accessible by trained and authorized staff members only. After finalization of data collection, the person-identifying variables in REDCap will be deleted (pseudonymization).

Biological material which is collected and stored (only the blood tubes and saliva of the children, not of parents and school personnel are stored) within this project will be labelled with the participant' specific ID. The label does not contain any personal information (see chapter 7.2). The results from the laboratory will be sent to the study team by mail or by e-mail (as a PDF), labelled with the ID of the participant only. Biological material will be appropriately stored in the biobank of the EBPI, a restricted area accessible to authorized personnel only.

Biological samples will be appropriately preserved at -80°C to -150°C in order to maintain sample viability. The biological samples will be stored in a physically locked freezer at EBPI (HRS D-03) in a restricted area with access log, which is only accessible to authorized research personnel of the EBPI.

The storage of clinical specimens is a Class 2 activity according to the Einschliessungsverordnung (EVS) outlined by the Federal Office for the Environment. Accordingly, an application for permission for the long-term storage of biological material from this study has been reviewed and approved by the Federal Coordination Center for Biotechnology as required under the Ordinance on Handling Organisms in Contained Systems.

Biological samples will be stored and handled in a certified BSL 2 laboratory environment according to UZH standards for handling biohazardous materials. Samples will be handled by knowledgeable personnel, in a manner consistent with a BSL 2 environment (use of personal protective equipment, sample manipulation within a biological safety cabinet, use of appropriate disinfectants and autoclave for waste disposal).

7.4 Retention and destruction of study data and biological material

Questionnaire data obtained in this study will be stored at least for 10 years after publication of the research project. Biological material collected in this study will be stored up to 10 years for potential future research use. Thereafter, or in case it is no longer needed, the biological material will be destroyed in compliance with the UZH standards for biological waste disposal. The destruction of biological material will include the inactivation of the samples by chemical reagents and autoclavation, and will be documented in a project-specific laboratory journal.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

CORONA IMMUNITAS is funded by several sources: By fundraising of SSPH+ that includes funds of the FOPH and private funders (ethical guidelines for funding stated by SSPH+ will be respected), by funds of the Cantons (Vaud, Zurich and Basel) and by institutional funds of the Universities. For Zurich, funding is provided by SSPH+ funds, the UZH Foundation, Horizon Europe (HORIZON-HLTH-2021-CORONA-01; Project ID 101046041). Ciao Corona got also funding through private foundations including Vontobel Foundation, Blumenau-Léonie Hartmann Foundation, and Gaydoul Foundation. All funding will be declared in the written informed consent form, as well as in the respective research output. Results of the study will be published in scientific journals. International guidelines for scientific publication of results and co-authorship will be respected.

9 REFERENCES

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Health-related quality of life in children and adolescents born very preterm and its correlates: a cross-sectional study

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Data Sharing Statement: Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to Susi Kriemler susi.kriemlerwiget@uzh.ch.

Abbreviations: BPD (Bronchopulmonary dysplasia), FLiP ("Frühgeborenen Lungen Projekt" / Premature Infant Lung Project), HRQOL (health-related quality of life), SES (Socio-economic status)

Contributors Statement:

Sarah R Haile, PhD conceptualized and designed the study, conducted the statistical analysis, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Gabriela P Peralta, PhD acquired funding, collected and cleaned the data and critically reviewed and revised the manuscript.

Mark Adams, PhD, Dirk Bassler, MD, Alexander Moeller, MD, and Giancarlo Natalucci, MD acquired funding, collected data and critically reviewed and revised the manuscript.

Ajay N Bharadwaj, BSc collected data and critically reviewed and revised the manuscript.

Thomas Radtke, PhD acquired funding, conceptualized and designed the study, and critically reviewed and revised the manuscript for important intellectual content.

Susi Kriemler, MD acquired funding, conceptualized and designed the study, coordinated and supervised data collection, critically reviewed and revised the manuscript for important intellectual content, is responsible for the overall content as guarantor.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objective We aimed to assess health-related quality of life (HRQOL) in a cohort of very preterm born children and adolescents (aged 5-16), and to compare it with their fullterm born siblings and the general population. We also explored correlates of HRQOL among the very preterm born.

Design Cross-sectional survey

Patients Children born <32 weeks gestation (N = 442) as well as their fullterm born siblings (N = 145)

Main outcome measures Primary outcome was KINDL total score (0 worst - 100 best), a validated multidimensional measure of HRQOL in children and adolescents.

Methods Linear mixed models accounted for family unit. Secondary analysis compared very preterm born children to another cohort of healthy children from the same time period. A classification tree analysis explored potential correlates of HRQOL.

Results On average, preterm children, both <28 and 28-31 weeks gestational age, had similar KINDL total score to fullterm sibling controls (-2.3, 95% CI -3.6 to -0.6), and to population controls (+1.4, 95% CI 0.2 to 2.5). Chronic non-respiratory health conditions (such as attention deficit hyperactivity disorder (ADHD) or heart conditions, but not including cerebral palsy), age, and respiratory symptoms affecting daily life were key correlates of HRQOL among very preterm born children.

Conclusions Very preterm birth in children and adolescents was not associated with a relevant reduction in HRQOL compared to their fullterm born peers. However, lower HRQOL was explained by other factors, such as older age, and the presence of chronic non-respiratory health conditions, but also by possibly modifiable current respiratory symptoms. The influence of respiratory symptom amelioration and its potential influence on HRQOL needs to be investigated further.

What is already known on this topic As infants born very preterm become more likely to survive, the importance of health-related quality of life (HRQOL) increases. Research on HRQOL in very preterm born children and adolescents often focuses on non-modifiable risk factors without potential interventions.

What this study adds HRQOL in very preterm born children and adolescents is similar to that of their siblings and to the general population. Age, respiratory symptoms, and chronic health conditions were associated with HRQOL. Better control of respiratory symptoms could improve HRQOL in very preterm born children and adolescents.

How this study might affect research, practice or policy A better understanding of the complex picture of pulmonary disease following prematurity throughout life and interventions to treat respiratory symptoms may be leveraged to improve HRQOL as very preterm born children and adolescents grow.

Introduction

Recent decades have seen an increased prevalence of very preterm birth (<32 weeks gestation)[1]. These infants are born more and more premature but also increasingly likely to survive the neonatal period[2]. While much research on school-age children born very preterm has focused on neurodevelopment or somatic disease[3], outcomes such as mental health and health-related quality of life (HRQOL) are of similar importance. It has been suggested that very preterm born children have lower HRQOL than their fullterm counterparts throughout childhood[4,5], but that these differences do not necessarily persist through adolescence or adulthood[4,6,7]. Some research has specifically focused on HRQOL in preterm children with chronic health conditions, where HRQOL was even found to be similar or only slightly lower than that of their fullterm counterparts[8]. Yet, the many systematic reviews[4,5,7,8] on HRQOL in the premature born often cannot account for important potentially modifiable factors, and are likely to suffer from inadequate comparison groups or selection bias, including but not limited to selective dropout.

Identifying modifiable correlates of HRQOL is essential in order to develop targeted interventions for HRQOL in the very preterm born. Studies of such correlates with HRQOL have identified factors as gender, maternal education, socio-economic status, nationality[5,9–11], motor, cognitive or neurodevelopment impairment[6,12,13], and also behavioral or non-adaptive coping difficulties[12,14]. Although a wide range of potential correlates have been explored previously, few of them are modifiable. Accordingly, it has been recommended that studies exploring long-term outcomes in the preterm born examine lifestyle factors, such as physical activity and diet, and other modifiable factors which could be leveraged to improve HRQOL in this population[15]. In this study, we aimed to compare HRQOL in very preterm born school-age children (<32 weeks gestation) to that of control fullterm siblings (37 weeks or longer), as well as to a population-

based cohort from the same time and geographic region. Further, we examined possible correlates, both modifiable and non-modifiable, of HRQOL, using conditional inference trees.

Methods

In the cross-sectional study FLiP ("Frühgeborenen Lungen Projekt" / Premature Infant Lung Project)[16], children born less than 32 weeks gestation between January 2006 and December 2019, in the greater Zurich area, Switzerland were recruited. They were all included in the Swiss Neonatal Network & Follow-Up Group (SwissNeoNet), a nationwide registry of very preterm children[17]. Parents of 1401 of 1720 potentially eligible children with valid postal addresses were invited (May - December 2021) to complete an online survey for their preterm child as well as for a term born (37 weeks gestation or later) sibling aged 1 to 18 years, referred as controls hereafter. Families who did not complete the survey within 2 weeks received a reminder call or a second invitation letter, if the phone number was not available. They could also complete a paper version and the questionnaire was available in German, English, French, and Italian. Our analysis included those participants who were at least 5 years of age or older. The study was approved by the Ethics Committee of the Canton of Zurich, Switzerland (2020–02396). Filling out the online survey was considered as providing consent. The FLiP study was powered to assess the prevalence of respiratory symptoms among children born <32 weeks gestation.

As an additional comparison to schoolchildren from the general population, we used data from the Ciao Corona study, which was part of the Swiss-wide research network Corona Immunitas[18,19]. Ciao Corona was a school-based cohort of randomly selected public and private schools and classes in the canton of Zurich, Switzerland. With 1.5 million inhabitants, the canton of Zurich is largest of 26 cantons in Switzerland by population and is home to a linguistically and ethnically diverse population in both urban and rural settings. While the primary endpoint of Ciao

Corona was seropositivity, questionnaires included a range of other measures, including the KINDL[20], assessed repeatedly between June 2020 and December 2022. For comparison with FLiP, the KINDL total score from September 2021 was used, as this best matched the timeframe of the FLiP assessment period. The Ciao Corona study was approved by the Ethics Committee of the Canton of Zurich, Switzerland (2020-01336). All participants provided written informed consent before being enrolled in the study.

The primary outcome was the KINDL total score[21,22], a validated instrument for assessing HRQOL ranging from 0 (worst) to 100 (best) (for further details, see Supplementary Material and Table S1). Secondary outcomes included all the KINDL subscales (physical, emotional, self-esteem, family, friends, and school). Additional data collected included participants' age and gender, gestational age (in weeks, range 24 - 31), birthweight (in grams), diagnosed bronchopulmonary dysplasia (BPD), socio-economic status (SES), family unit, chronic health conditions, hours of physical activity per week, hours of screen time per week, participation in music lessons, participation in scouts, participation in sports, and need for various types of therapy. Prematurity-related diagnosis of BPD was taken from personal history of the premature born children included in the SwissNeoNet registry (none to mild vs moderate to severe). SES was determined according to each parent's education level (1 university, 2 vocational university, 3 apprenticeship, 4 job requiring minimal training, 5 compulsory education, 6 less than compulsory education), and then summed over both parents (range 2 highest education - 12 lowest education). Chronic health conditions were categorized as respiratory, non-respiratory or cerebral palsy. Respiratory conditions included asthma and cystic fibrosis. Non-respiratory conditions included heart conditions, diabetes, intestinal issues, low/high blood pressure, attention deficit hyperactivity disorder, epilepsy, joint disorders, and depression. Cerebral palsy was reported separately along with its severity (none; mild, no to minimal restriction to daily activities; mild, limitations in daily activities but without the need for aids; moderate, needs

prostheses, medication or technical aids to manage daily activities; severe, requires a wheelchair and has significant difficult in daily activities). Types of therapy included speech, physical, occupational, psychomotor, curative or psychological therapy, as well as early support programs. To assess whether respiratory symptoms affected daily life, parents were asked about several questions related to whether their child had cough or wheezing due to physical exertion in the last 12 months or whether cough, or wheezing restricted their daily activities. Other included variables were: number of siblings, presence of house pets, whether parents smoked (no/outside/in the home), number of therapies used, use of assistive devices (e.g hearing aids, walking aids, wheelchair), hours of physical activity per day, hours of screen time per day, and participation in sports, scouts, or musical activities (see Supplementary Material for wording of selected questions).

Key demographic variables were summarized as median (range), n (%), or in the case of socio-economic status, median [IQR]. Outcomes were compared between FLiP preterm and FLiP control participants using linear mixed models, including family unit as a random effect. Comparisons of FLiP preterm and Ciao Corona control participants were made using linear regression, after 2:1 matching on age in years, sex and nationality. Sensitivity analyses included a) excluding participants with chronic health conditions, b) restricting to preterm born children with control siblings, c) stratification by age, d) adjusting for SES, and e) using fixed effects to account for family unit. Coefficients and corresponding 95% confidence intervals were interpreted according to their possible relevance, rather than with p-values[23,24]. To explore other potential correlates, both modifiable and non-modifiable, of HRQOL among very preterm born children, we used conditional inference trees[25,26] estimated by binary recursive partitioning. To handle missing predictor values, the conditional inference trees used up to 3 surrogate splits[25]. The algorithm stopped if no split with $\alpha < 0.05$ could be constructed or if a subgroup had less than 25 participants. For further details, see Supplementary Material.

The statistical analysis was performed using R (R version 4.4.1 (2024-06-14)). Linear mixed models were fit using the lmerTest package[27], and tables were produced with gtsummary[28]. The classification trees were fit using the ctree function from partykit[29]. Nearest neighbor matching using robust rank-based Mahalanobis distance to the Ciao Corona data was performed using the MatchIt package[30].

Patient and Public Involvement

The FLiP survey used input from parents to optimize content and clarify the questionnaire. A small group of very preterm born children and adolescents as well as members of the public tested the questionnaires in a pilot phase, and were given the opportunity to comment on patient information leaflets.

In the Ciao Corona study, some school principals were consulted during the development of the protocol to ensure feasibility of the planned study procedures. Feedback from invited and enrolled children and parents was continuously collected to adapt the communication strategies and channels. Children and parents always received their individual serological results with interpretation. Regular fact sheets were sent to participants and the public. Online information sessions were organised at the beginning, middle and end of the study to encourage open exchange and feedback for invited and enrolled school principals, staff, and parents of the children.

Results

After inviting 1401 very preterm born children and their parents to participate in FLiP, data from 681 40% preterm children and 205 fullterm control siblings was available. Among the very preterm born, we excluded 199 children that were younger than 5 years of age and 40 had not filled out KINDL, leaving 442 preterm participants. Among their fullterm born siblings, 56 were

younger than 5 years of age and 4 had not filled out KINDL, leaving 145 fullterm siblings (see **Supplementary Figure S1**). We also included 1058 participants from Ciao Corona (total n=4435, 2020 - 2022, of whom 2974 had participated prior to September 2021[31]) with a KINDL total score in September 2021. Characteristics of the included participants are found in **Table 1**, and not included participants were similar regarding most morbidities typical for the very preterm (**Supplementary Table S2**).

Very preterm born children with gestational age 24-27 weeks (n = 130) had an average total KINDL score of 77.3 ± 10.0 points out of 100, while those with gestational age 28-31 weeks (n = 312) had an average total KINDL score of 78.9 ± 10.5, compared to 80.8 ± 8.7 among fullterm born control siblings. On average, preterm children born at 24-27 weeks had a 2.3 point lower KINDL total score than fullterm controls (95% CI -4.4 to -0.2), when accounting for family unit. Similarly, those born at 28 weeks had a 2.3 point lower KINDL total score than fullterm controls (95% CI -3.9 to -0.7) (**Figure 1, Supplementary Table S3**). The pattern was similar for the KINDL subscales (**Supplementary Figure S2**), and when comparing those with birthweight <1000g with those at least 1000g (**Supplementary Figures S3 and S4, Supplementary Table S4**). Results were similar when examining all preterm born children together for both KINDL total score and its subscales (**Supplementary Figures S5 and S6, Table S5**), and did not change in any of the sensitivity analyses.

A number of other potential non-modifiable and modifiable correlates for HRQOL were further considered in a classification tree analysis (**Supplementary Table S6**). It indicated that respiratory symptoms affecting daily activities as well as age and chronic non-respiratory conditions were the primary correlates of HRQOL among very preterm born children and adolescents in our sample (**Figure 2**), with mean KINDL total score ranging from 68.2 ± 13.1 (among those 10 years of age or older with chronic non-respiratory conditions) to 80.5 ± 8.8 (among those with no chronic health conditions and no respiratory symptoms affecting daily

activities). 67% (296 / 442) of the sample was in the latter group that could not be further differentiated with the selected variables. Notably, gestational age, birthweight and BPD were not identified as correlates of HRQOL in our sample.

Discussion

We observed no relevant difference in HRQOL (KINDL total score) when comparing very preterm children to their fullterm siblings, even after accounting for gestational age or birthweight, chronic health conditions, including respiratory conditions or cerebral palsy, and did not change in any of the sensitivity analyses. HRQOL among very preterm children was also similar to that of the general population of schoolchildren. When considering possible variables associated with HRQOL beyond prematurity, respiratory symptoms affecting daily activities, chronic non-respiratory conditions, and age group appeared to play a role and were identified as more important correlates of HRQOL than gestational age. Two points out of 100 difference in the total KINDL score represent a marginal difference in HRQOL that was not clinically relevant. Comparing KINDL in children with and without various chronic health conditions, differences ranging from 1.9 (children with asthma) to 6.2 (cancer survivors) points have been observed[32–34]. The 2 point difference in our study was thus quite small, and based on the variability of the KINDL total score (SD=10.3), likely not meaningful.

In a classification tree analysis the most important factors correlated with HRQOL appeared to be age group, chronic health conditions and the existence of respiratory symptoms affecting daily activities. While age and chronic health conditions are not modifiable, the presence of respiratory symptoms may be modifiable, indicating that improvement of respiratory symptoms may potentially improve HRQOL in the very preterm born.

Children with respiratory symptoms should be investigated for their phenotype profile and potentially treatable traits by a pediatric pulmonologist to understand the complex picture of prematurity associated respiratory symptoms, and whether or not the child may benefit from treatment at all or treatment optimization[35]. This is important as up to 40% of the premature population are prescribed asthma medication during childhood[35], although there is a lack of objective evidence on how to treat these individuals and whether treatment improves symptoms[35–37]. Thus, individual treatment needs to be based on the phenotype or underlying mechanisms of prematurity-associated lung disease as proposed by for instance the wheel-and-spoke model that combines components of a phenotype classification including structural, physiological, inflammatory and clinical traits[35]. Non-pharmaceutical interventions such as exercise to improve cardiopulmonary function might likewise be of benefit[38]. Our finding that respiratory symptoms are correlated with HRQOL could imply that interventions targeting those symptoms may potentially also improve HRQOL in the very preterm born. This hypothesis of course should be tested in future studies.

Our analysis has several strengths. HRQOL was assessed using the validated[22] multidimensional KINDL instrument for children and adolescents. The analysis used a relatively large registry of very preterm born children in Switzerland and included fullterm born siblings as a control group. Family unit was accounted for in the analysis. The Ciao Corona study provided a school-based random sample of school children in the same geographic region and time period. To account for differing severity in terms of prematurity, we stratified the analysis by gestational age and birthweight. We considered a broad range of possible correlates, including respiratory symptoms, of HRQOL in a classification tree analysis, which has to our knowledge not been performed previously in this population, and allowed us to explore a wide range of possible correlates with HRQOL.

A key limitation is that longitudinal data on HRQOL was not available for this sample of children, and not all very preterm born participants had control siblings. We did not have information on other potentially important variables, for example, on participants' mental health status (e.g. sadness or anxiousness[39]) or on social support[40], which could have provided useful information in the conditional inference tree analysis. There were also not many fullterm born children with chronic health conditions in the FLiP sample, which would have allowed us to further explore the associations between very preterm birth, chronic health conditions and HRQOL. Like other studies of very preterm born children, our sample may have had selection bias[5,7]. Although this research took place during the COVID-19 pandemic which may have affected HRQOL of the children, but if so, this was likely true for all included groups. Nevertheless, we cannot exclude that premature born children were especially shielded, which would compromise HRQOL even more. Yet, this was not the case and HRQOL was similar in normal school children and previously premature children.

It is a gift of medicine that children born <32 weeks gestation generally have a HRQOL comparable to fullterm born children[6]. Nevertheless, as observed in this large cohort of very preterm born children, there are children that clearly show compromised HRQOL. Low HRQOL was not restricted to those born prior to 28 weeks of gestational age or less than 1000g birthweight, as seen in our stratified analyses. While an association between HRQOL and older age or chronic health conditions may often be expected and considered plausible, the association with respiratory symptoms observed in our analysis may be neglected and often not addressed[41].

A better understanding of the complex picture of pulmonary disease following prematurity throughout life and interventions to treat respiratory symptoms, such as medical treatment or those targeting aerobic exercise and physical activity, may be leveraged to improve HRQOL as very preterm born children and adolescents grow.

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Ethical approval The FLiP study was approved by the Ethics Committee of the Canton of Zurich, Switzerland (2020–02396). Filling out the online survey was considered as providing consent. The Ciao Corona study was approved by the Ethics Committee of the Canton of Zurich, Switzerland (2020-01336). All participants provided written informed consent before being enrolled in the study.

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Figures and Tables

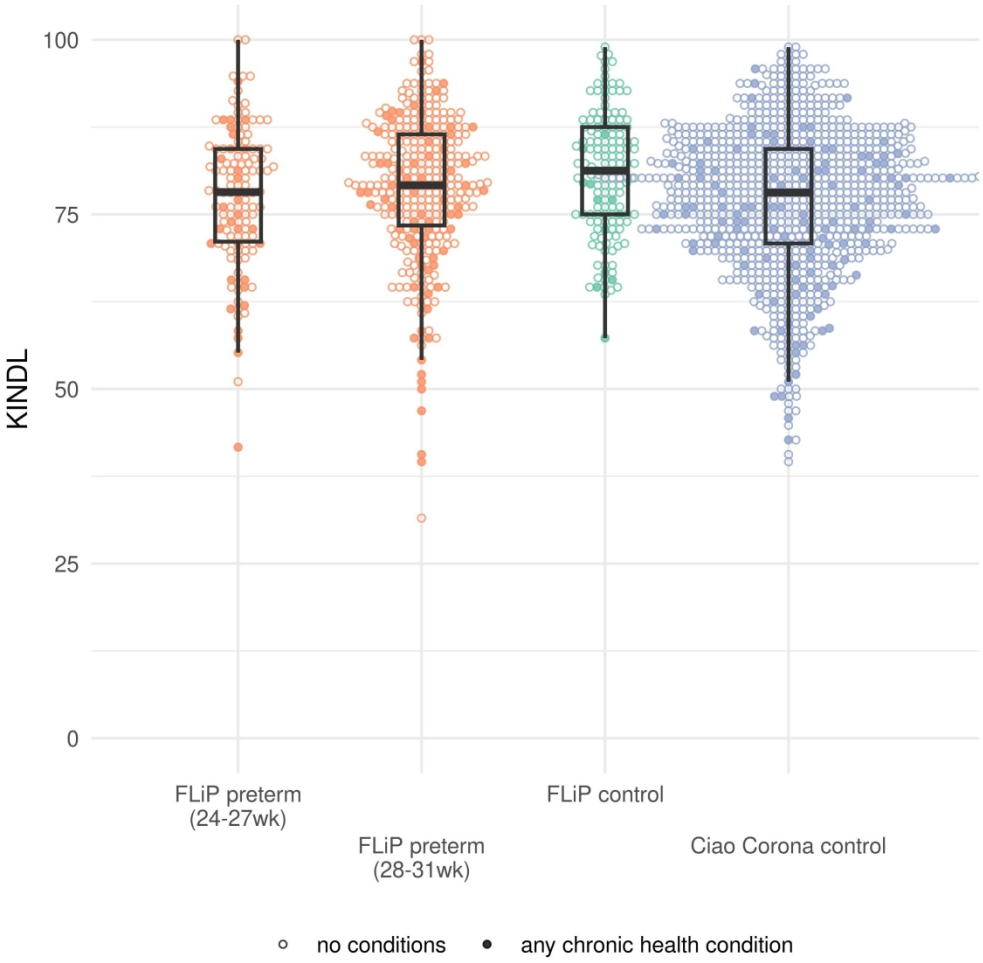
Table 1: Key characteristics of FLiP very preterm born children and adolescents, their control siblings, and age, sex and nationality matched control participants from Ciao Corona. BPD indicates bronchopulmonary dysplasia. Chronic health conditions included asthma, cystic fibrosis, congenital heart defects, heart disease, celiac, diabetes, inflammatory bowel disease, high blood pressure, attention deficit hyperactivity disorder, epilepsy, joint disorders, depression/anxiety, and cerebral palsy. Socio-economic status is measured on the basis of parents' education from 2 (both parents having university education) to 12 (both parents less than compulsory education) points, though the categories differed somewhat in FLiP and Ciao Corona. As physical activity was assessed using different questions in Ciao Corona than in FLiP that were not comparable, we did not include physical activity in Ciao Corona here.

Characteristic	**FLiP preterm** N = 442	**FLiP control** N = 145	**Ciao Corona control** N = 882
age (years)	10 (5 - 16)	9 (5 - 19)	10 (6 - 16)
sex (male)	236 (53%)	84 (59%)	472 (54%)
gestational age (weeks)			
24-27 wks	130 (29%)		
28-31 wks	312 (71%)		
birthweight			
<1000g	158 (36%)		
1000+g	284 (64%)		
multiple gestation	140 (32%)		
socio-economic status	5 [3, 6]	5 [3, 6]	4 [3, 5]
non-Swiss nationality	66 (15%)	20 (14%)	121 (14%)
moderate to severe BPD	55 (12%)		
coughing / wheezing restrict daily activities	13 (2.9%)	1 (0.7%)	
any chronic health condition	104 (24%)	12 (8.3%)	122 (14%)
chronic non-respiratory conditions	67 (15%)	11 (7.6%)	96 (11%)
chronic respiratory conditions	24 (5.4%)	3 (2.1%)	34 (3.9%)
cerebral palsy	33 (7.5%)	1 (0.7%)	0 (0%)
physical activity (hours per day)	0.71 [0.50, 1.00]	0.71 [0.57, 1.14]	

Figure 1: KINDL total score, for very preterm born children (FLiP preterm, stratified by gestational age 24-27 weeks or 28-31 weeks) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control). Solid circles indicate participants without chronic health

conditions, while empty diamonds indicate those with any chronic health condition, respiratory or non-respiratory.

Figure 2: Classification tree for KINDL total score in very preterm born children, based on a range of possible correlates (see Table S7). Identified correlates are chronic non-respiratory conditions, age group (5-9 vs 10+), and whether respiratory symptoms negatively affect daily life. For each identified subgroup, mean ± standard deviation for KINDL total score is given, along with the number of participants.



KINDL total score, for very preterm born children (FLiP preterm, stratified by gestational age 24-27 weeks or 28-31 weeks) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control). Solid circles indicate participants without chronic health conditions, while empty diamonds indicate those with any chronic health condition, respiratory or non-respiratory.

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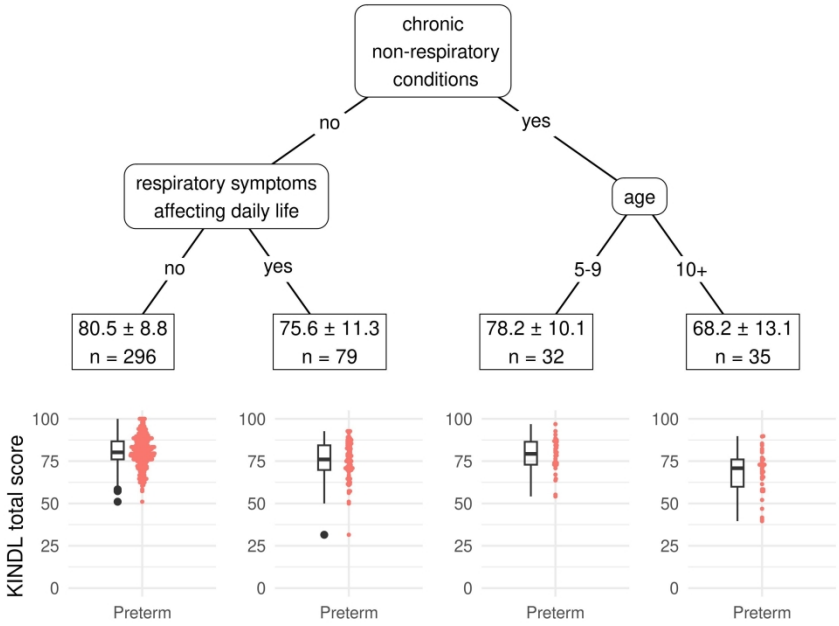

Classification tree for KINDL total score in very preterm born children, based on a range of possible correlates (see Table S7). Identified correlates are chronic non-respiratory conditions, age group (5-9 vs 10+), and whether respiratory symptoms negatively affect daily life. For each identified subgroup, mean ± standard deviation for KINDL total score is given, along with the number of participants.

203x152mm (450 x 450 DPI)

Health-related quality of life in children and adolescents born very preterm and its correlates - supplementary material

Sarah R Haile, Gabriela P Peralta, Mark Adams, Ajay N Bharadwaj, Dirk Bassler, Alexander Moeller, Giancarlo Natalucci, Thomas Radtke, Susi Kriemler

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Supplementary Methods

The KINDL score

The KINDL-R score (hereafter, KINDL) is a validated instrument for measuring health-related quality of life} [1], with scores ranging from 0 (worst) to 100 (best). In FLiP, we used slightly adapted versions of the parent (proxy) versions for 4-6 year olds and for 7-17 year old children and adolescents (https://www.kindl.org/contacts/english/). In Ciao Corona, we used the parent (proxy) version, for 7-17 year old children and adolescents. All questions as asked are listed in Table S1. The KINDL contains 24 items, 4 in each of 6 subscales: physical well-being, emotional well-being, self-esteem, family, social contacts / friends, and school. To compute the KINDL score, certain items are first recoded. A subscale can be analysed as long as no more than 30% of its items are missing. Mean value replacement is used to deal with missing item scores. The 6 subscales are then added and rescaled to 0-100 to form the KINDL total score. Sample code is available at https://www.kindl.org/english/analysis/. Text in English for each of the items is provided below, but FLiP and Ciao Corona used German versions of the questionnaires.

Table S1: KINDL questions as used in the FLiP and Ciao Corona studies. Item are noted with an asterisk (*) if the wording has been adapted for FLiP.

item	FLiP (age 3 - 6 years)	FLiP (age 7 – 17 years)	Ciao Corona
1. Physical Well-being			
	During the past week...	During the past week...	During the past week...
1	... my child felt ill.	... my child felt ill.	... my child felt ill.
2	... my child had a headache or tummyache.	... my child had a headache or tummyache.	... my child had a headache or tummyache.
3	... my child my child was tired and worn-out.	... my child my child was tired and worn-out.	... my child my child was tired and worn-out.
4	... my child felt strong and full of energy.	... my child felt strong and full of energy.	... my child felt strong and full of energy.
2. Emotional Well-being			
	During the past week...	During the past week...	During the past week...
1	... my child had fun and laughed a lot	... my child had fun and laughed a lot	... my child had fun and laughed a lot
2	... my child didn't feel much like doing anything	... my child didn't feel much like doing anything	... my child didn't feel much like doing anything
3	... my child felt alone	... my child felt alone	... my child felt alone
4	... my child felt alone	... my child felt alone	... my child felt alone
3. Self-esteem			
	During the past week...	During the past week...	During the past week...
1	... my child was proud of him-/herself	... my child was proud of him-/herself	... my child was proud of him-/herself
2	... my child felt on top of the world	... my child felt on top of the world	... my child felt on top of the world
3	... my child felt pleased with him-/herself	... my child felt pleased with him-/herself	... my child felt pleased with him-/herself
4	... my child had lots of good ideas	... my child had lots of good ideas	... my child had lots of good ideas
4. Family			
	During the past week...	During the past week...	During the past week...
1	... my child got on well with us as parents	... my child got on well with us as parents	... my child got on well with us as parents
2	... my child felt fine at home	... my child felt fine at home	... my child felt fine at home
3	... we quarrelled at home	... we quarrelled at home	... we quarrelled at home
4	... my child felt that I was bossing him/her around	... my child felt that I was bossing him/her around	... my child felt that I was bossing him/her around
5. Social Contacts			

Table S1: KINDL questions as used in the FLiP and Ciao Corona studies. Item are noted with an asterisk (*) if the wording has been adapted for FLiP. *(continued)*

item	FLiP (age 3 - 6 years)	FLiP (age 7 – 17 years)	Ciao Corona
	During the past week. . .	During the past week. . .	During the past week. . .
1*	... my child played or did things together with friends	... my child played or did things together with friends	... my child did things together with friends
2	... my child was liked by other kids	... my child was liked by other kids	... my child was liked by other kids
3	... my child got along well with his/ her friends	... my child got along well with his/ her friends	... my child got along well with his/ her friends
4	... my child felt different from other children	... my child felt different from other children	... my child felt different from other children
6. School			
	During the past week. . .	During the past week. . .	During the last week in which my child was at school . . .
1*	... my child coped well with the assignments set in nursery school/ kindergarten	... my child easily coped with schoolwork	... my child easily coped with schoolwork
2*	... my child enjoyed the nursery school/ kindergarten	... my child enjoyed the school lessons	... my child enjoyed the school lessons
3*	... my child looked forward to nursery school/kindergarten	... my child worried about his/her future	... my child worried about his/her future
4*	... my child made lots of mistakes when doing minor assignments or homework	... my child was afraid of bad marks or grades	... my child was afraid of bad marks or grades

Chronic health conditions listed on the surveys

- **FLiP**: asthma, cystic fibrosis, congenital heart defects, heart disease, celiac / gluten allergy , lactose intolerance, allergies (other than hay fever), diabetes mellitus, chronic inflammation of the bowel (ulcerative colitis or Crohn's disease), high blood pressure (hypertension), attention deficit disorder (ADHD, ADD), epilepsy, joint disease (e.g. arthritis), depression/anxiety disorder, other [comment field], cerebral palsy [with severity]
- **Ciao Corona**: asthma, hay fever, celiac, lactose intolerance, allergies (other than hay fever), neurodermatitis / excema, Diabetes Mellitus, chronic inflammation of the bowel (ulcerative colitis or Crohn's disease), high blood pressure (hypertension), attention deficit disorder (ADHD, ADD), epilepsy, joint disease (e.g. arthritis), depression/anxiety disorder, other [comment field]

The following conditions were not counted as chronic health conditions for the purposes of this analysis: hay fever, celiac, gluten allergy, lactose intolerance, allergies (other than hay fever). The Ciao Corona study did not ask specifically about cerebral palsy, but it was also not reported under "other".

Selected Questions from FLiP

- **Respiratory symptoms affecting daily life**: Yes to any of the following questions:
    a) *In the last 12 months, has your child ever had whistling or wheezing breathing during or after physical exertion?*
    b) *Have any of the following situations triggered a cough in your child in the last 12 months? Physical exertion (running, sports)*
    c) *Have any of the following situations triggered whistling or wheezing in your child in the last 12 months? Physical exertion (running, sports)*
    d) *Does your child sometimes have difficulty breathing during physical exertion?*
    e) *In the last 12 months, how much was your child's daily activities (or play behaviour) restricted by the cough?*
    f) *In the last 12 months, how much was your child restricted in his/her daily activities (or play behaviour) because of whistling or wheezing breathing or shortness of breath?*
- **Physical Activity**: *On average, how many hours per week does your child spend in physical activity that causes at least some sweating or heavy breathing? (School sport INCLUDED)* This value was converted to hours per day.
- **Screen Time**: These values were converted to average hours per day.
    a) *How many hours per day does your child CURRENTLY spend using electronic devices on a typical weekday? NOT counting school lessons and schoolwork. For example: Mobile phone, tablet, Playstation, Xbox, Nintendo, computer, TV*
    b) *How many hours per day does your child CURRENTLY spend using electronic devices on a typical weekend day? NOT counting school lessons and schoolwork. For example: Mobile phone, tablet, Playstation, Xbox, Nintendo, computer, TV*
- **Sports**: *Does your child participate regularly (at least once every 2 weeks) in the following activities? Yes, sport activities such as gymnastics club, ballet, dance, tennis, basketball, football club etc.*
- **Music**: *Does your child participate regularly (at least once every 2 weeks) in the following activities? Yes, music lessons, musical activities, theatre, circus, etc.*
- **Scouts**: *Does your child participate regularly (at least once every 2 weeks) in the following activities? Yes, other activities such as Scouts, Cevi [YMCA / YWCA], Blauring / Jungwacht [similar Catholic organization], etc.*
- **SES**: Sum of *What is the highest educational qualification of the mother?* and *What is the highest educational qualification of the father?* as defined by SwissNeoNet https://app.swissneonet.ch/data/live/structure/38/show
    1. University
    2. University of applied science, technical college, higher level job training, college of education, university entrance qualification (Matura or Berufsmatura)
    3. Apprenticeship or secondary school diploma
    4. Job requiring minimal training
    5. Regular school without job training
    6. No education, or unfinished regular school

Detailed Statistical Methods: Conditional Inference Trees

We used conditional inference trees [2, 3] estimated by binary recursive partitioning to identify possible determinants of health-related quality of life (HRQOL) in very preterm born children and adolescents. These models seek to make homogeneous subgroups, i.e. clusters, of the sample with respect to the outcome of interest. Generally, the algorithm 1) searches for the variable with the strongest association to the outcome, and then 2) splits the values of that variable into two groups, and repeats this process until some stopping criteria (in this analysis, p-value < 0.05 or sample size < 25) are reached. While all types of variables can be selected in step 1 of this algorithm, categorical and continuous variables have more flexibility in terms of selected thresholds in step 2 than binary variables do. Conditional inference trees select variables in an unbiased manner, without being affected by overfitting [2]. Such models identify subgroups defined by combinations of covariates, without needing to *a priori* specify interaction terms or consider multicollinearity [4], and thresholds do not need to be prespecified. Standard regression models, even when combined with model selection, do not identify homogenous subgroups. Due the presence of missing observations in some of the variables, we employed so-called surrogate splits to account for this missingness without excluding subjects [2].

The conditional inference trees were fit using `ctree` from the R package `partykit` [2, 5]. Missing covariate information was handled by `ctree` directly. All analysis was performed in R (R version 4.4.1 (2024-06-14)).

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Supplementary Results

Analysis Population

Flowchart

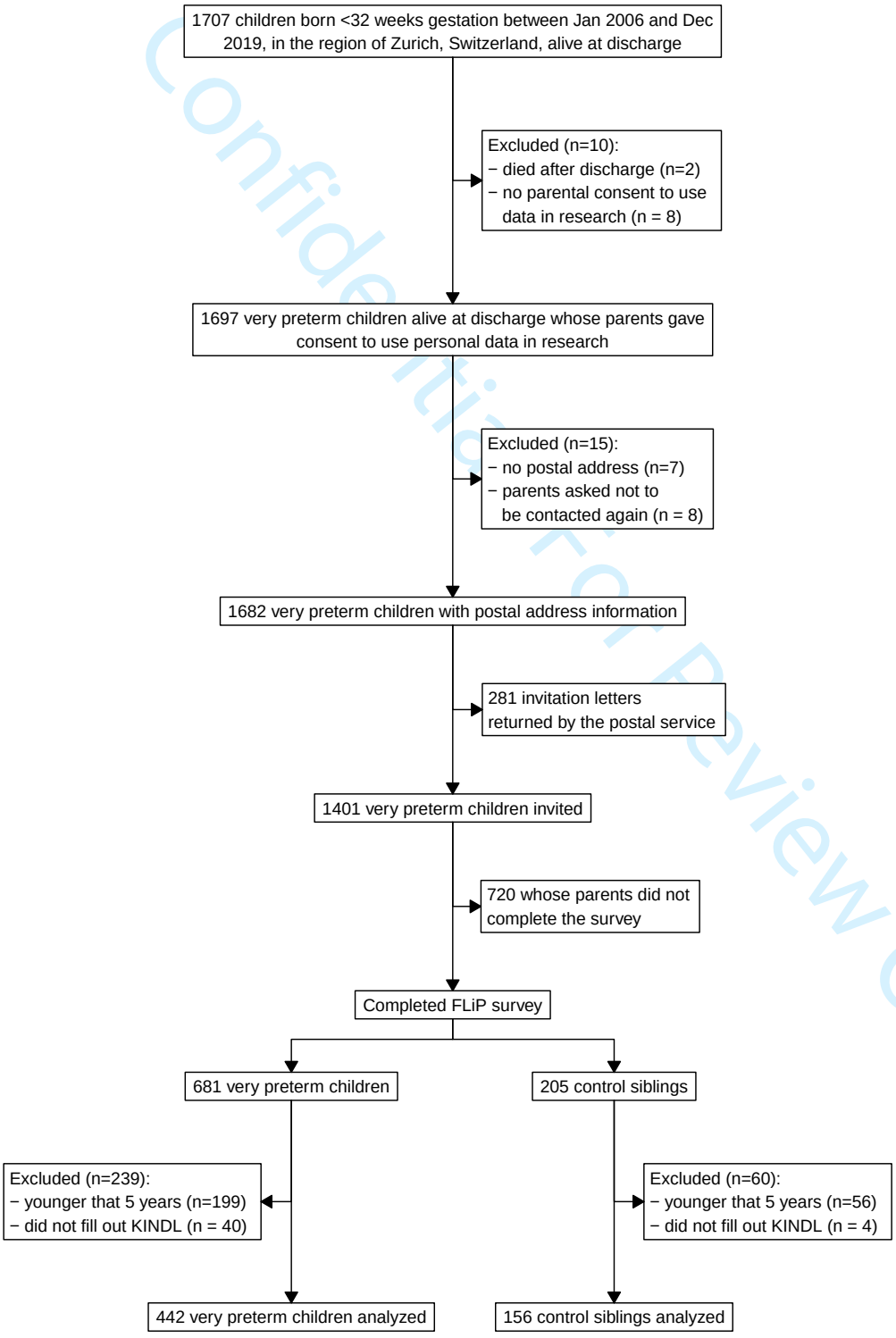

Figure S1: Flowchart of children and adolescents included in the FLiP cohort study.

Analyzed vs not analyzed very preterm born children

Very preterm born children included in our analysis were generally comparable to those not included, though with slightly lower gestational age and birthweight, and more likely to have had supplemental oxygen at 36 weeks, as moderate to severe BPD is often defined. Notably, none of the other morbidities typical for very preterm children are different between participants and non-participants (**Supplementary Table S2**).

Table S2: Comparisons of very preterm born children included in this analysis ('analyzed') vs not included in this analysis. IVH indicates intraventricular hemorrhage, PVL periventricular leukomalacia, NEC necrotizing enterocolitis, ROP retinopathy of prematurity, and NDI neurodevelopmental impairment.

variable	not analyzed	analyzed	p-value	Total
N	1031 (70%)	442 (30%)		1473
Gestational age (IQR)	30.6 (28.6 to 31.7)	29.4 (27.4 to 30.7)	<0.0001	30.1 (28.1 to 31.4)
Birth weight z-score (Voigt 2006) (IQR)	-0.2 (-1.2 to 0.4)	0 (-0.6 to 0.4)	<0.0001	-0.1 (-1 to 0.4)
Sex male N (%)	563 (54.6 %)	236 (53.4 %)	0.710	799 (54.2 %)
Outborn N (%)	29 (2.8 %)	9 (2 %)	0.495	38 (2.6 %)
Multiple births N (%)	376 (36.5 %)	140 (31.7 %)	0.088	516 (35 %)
Any antenatal steroids N (%)	910 (91.6 %)	397 (92.5 %)	0.642	1307 (91.9 %)
Caesarean section N (%)	889 (86.2 %)	382 (86.4 %)	0.985	1271 (86.3 %)
Congenital malformation (validated) N (%)	20 (1.9 %)	7 (1.6 %)	0.799	27 (1.8 %)
Severe IVH N (%)	35 (3.4 %)	18 (4.1 %)	0.625	53 (3.6 %)
Cystic PVL N (%)	9 (0.9 %)	4 (0.9 %)	1.000	13 (0.9 %)
Supplemental oxygen at 36 weeks GA* N (%)	72 (7 %)	55 (12.4 %)	0.001	127 (8.6 %)
NEC stage >=2 N (%)	16 (1.6 %)	7 (1.6 %)	1.000	23 (1.6 %)
Severe ROP* N (%)	21 (2.8 %)	12 (3 %)	0.977	33 (2.9 %)
Moderate to severe NDI at 2 years corr. N (%)	147 (24.4 %)	85 (22.1 %)	0.450	232 (23.5 %)
Cerebral palsy at 2 years corr. N (%)	36 (6.3 %)	18 (4.8 %)	0.394	54 (5.7 %)

Main Analyses

Stratified by Gestational Age

Table S3: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP or participants from Ciao Corona, stratified by gestational age (24-27 weeks vs 28-31 weeks). Mean differences denote either differences in health-related quality of life between FLIP very preterm born siblings and their control siblings, or between FLIP very preterm born siblings and controls from Ciao Corona. Negative mean differences indicate that very preterm born children had lower HRQOL than controls. Mean differences and 95% confidence intervals account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

Gestational Age	cohort	Preterm	Control	difference	confidence interval
Total					
24 - 27 weeks	FLiP	77.6 (10.0)	80.8 (8.7)	-2.27	(-4.36 to -0.17)
	Ciao Corona		77.2 (10.2)	0.45	(-1.42 to 2.32)
28 - 31 weeks	FLiP	78.9 (10.5)	80.8 (8.7)	-2.29	(-3.86 to -0.73)
	Ciao Corona		77.2 (10.2)	1.72	(0.40 to 3.04)
Physical					
24 - 27 weeks	FLiP	77.4 (17.7)	82.9 (14.7)	-5.17	(-9.02 to -1.31)
	Ciao Corona		77.6 (14.9)	-0.19	(-3.02 to 2.63)
28 - 31 weeks	FLiP	82.3 (15.0)	82.9 (14.7)	-0.44	(-3.08 to 2.20)
	Ciao Corona		77.6 (14.9)	4.74	(2.81 to 6.67)
Emotional					
24 - 27 weeks	FLiP	79.5 (13.0)	83.6 (11.6)	-3.35	(-6.10 to -0.61)
	Ciao Corona		80.5 (14.1)	-0.99	(-3.55 to 1.56)
28 - 31 weeks	FLiP	80.8 (14.0)	83.6 (11.6)	-3.12	(-5.49 to -0.75)
	Ciao Corona		80.5 (14.1)	0.32	(-1.50 to 2.14)
Self-esteem					
24 - 27 weeks	FLiP	73.9 (13.3)	76.8 (12.9)	-2.25	(-5.25 to 0.75)
	Ciao Corona		72.3 (13.5)	1.64	(-0.83 to 4.11)
28 - 31 weeks	FLiP	73.2 (13.8)	76.8 (12.9)	-3.68	(-5.98 to -1.37)
	Ciao Corona		72.3 (13.5)	0.87	(-0.87 to 2.60)
Family					
24 - 27 weeks	FLiP	80.5 (12.6)	80.3 (12.8)	1.18	(-1.60 to 3.96)
	Ciao Corona		79.1 (12.8)	1.44	(-0.91 to 3.79)
28 - 31 weeks	FLiP	80.2 (13.3)	80.3 (12.8)	-0.84	(-2.83 to 1.15)
	Ciao Corona		79.1 (12.8)	1.25	(-0.41 to 2.92)
Friends					
24 - 27 weeks	FLiP	75.5 (14.2)	78.4 (13.1)	-2.20	(-5.34 to 0.95)
	Ciao Corona		77.8 (13.5)	-2.22	(-4.73 to 0.29)
28 - 31 weeks	FLiP	76.7 (15.4)	78.4 (13.1)	-2.07	(-4.76 to 0.61)
	Ciao Corona		77.8 (13.5)	-1.06	(-2.88 to 0.75)
School					
24 - 27 weeks	FLiP	77.5 (16.5)	82.5 (13.6)	-4.02	(-7.63 to -0.41)
	Ciao Corona		75.6 (15.9)	1.58	(-1.44 to 4.60)
28 - 31 weeks	FLiP	80.5 (14.8)	82.5 (13.6)	-2.11	(-4.59 to 0.36)
	Ciao Corona		75.6 (15.9)	4.81	(2.83 to 6.80)

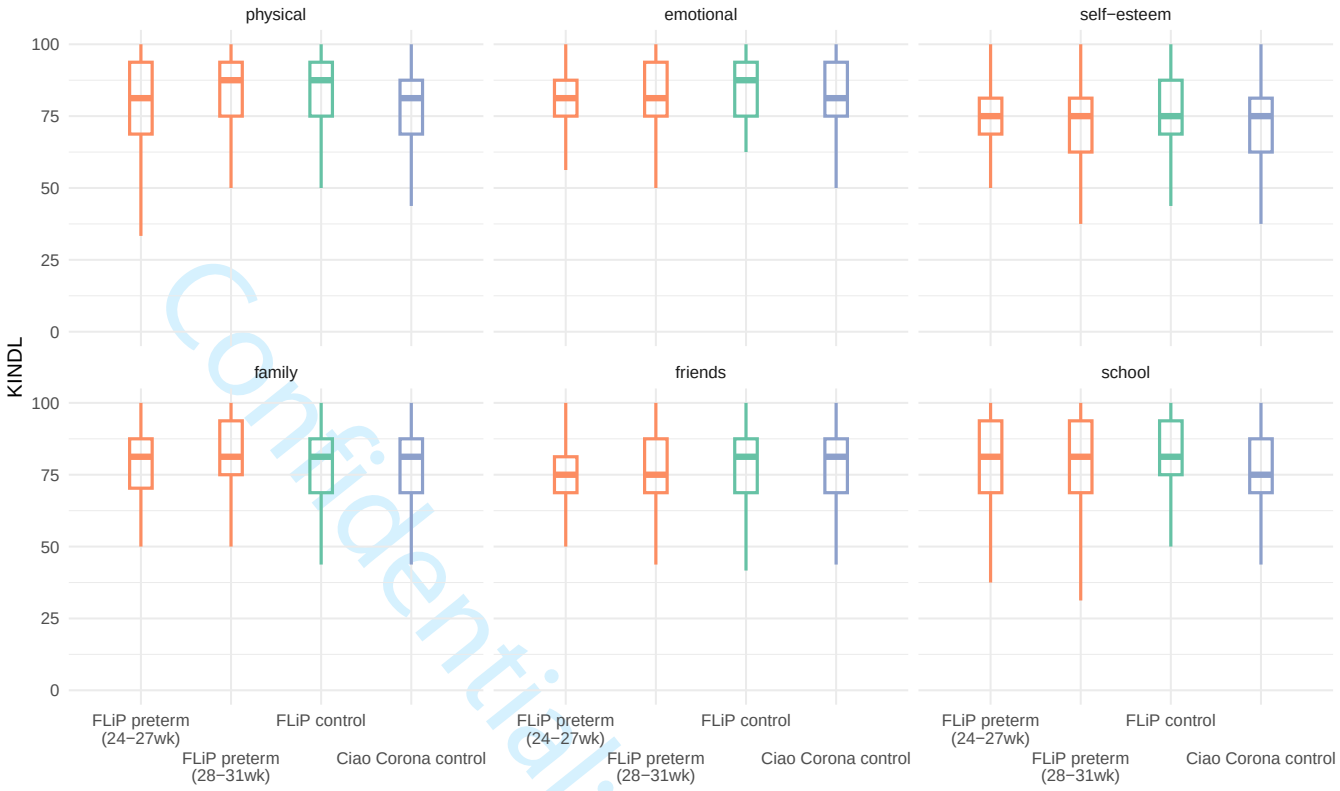

Figure S2: KINDL subscales, for very preterm born children (FLiP preterm, stratified by gestational age 24-27 weeks vs 28-31 weeks) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control).

Stratified by Birthweight

Table S4: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP and participants from Ciao Corona, stratified by birthweight ($<$ 1000g vs $\geq$ 1000g). Mean differences denote either differences in health-related quality of life between FLIP very preterm born siblings and their control siblings, or between FLIP very preterm born siblings and controls from Ciao Corona. Mean differences and 95% confidence intervals account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

Birthweight	cohort	Preterm	Control	difference	confidence interval
Total					
< 1000g	FLiP	76.6 (10.4)	80.8 (8.7)	-3.44	(-5.48 to -1.41)
	Ciao Corona		77.2 (10.2)	-0.54	(-2.27 to 1.19)
1000g +	FLiP	79.5 (10.1)	80.8 (8.7)	-1.46	(-3.05 to 0.12)
	Ciao Corona		77.2 (10.2)	2.40	(1.04 to 3.76)
Physical					
< 1000g	FLiP	77.0 (16.9)	82.9 (14.7)	-5.33	(-8.84 to -1.83)
	Ciao Corona		77.6 (14.9)	-0.58	(-3.17 to 2.01)
1000g +	FLiP	83.0 (15.1)	82.9 (14.7)	0.43	(-2.35 to 3.21)
	Ciao Corona		77.6 (14.9)	5.43	(3.43 to 7.43)
Emotional					
< 1000g	FLiP	79.8 (13.8)	83.6 (11.6)	-2.99	(-5.72 to -0.27)
	Ciao Corona		80.5 (14.1)	-0.72	(-3.10 to 1.65)
1000g +	FLiP	80.8 (13.6)	83.6 (11.6)	-3.10	(-5.46 to -0.74)
	Ciao Corona		80.5 (14.1)	0.30	(-1.58 to 2.17)
Self-esteem					
< 1000g	FLiP	72.3 (13.4)	76.8 (12.9)	-3.90	(-6.73 to -1.06)
	Ciao Corona		72.3 (13.5)	-0.01	(-2.278 to 2.25)
1000g +	FLiP	74.0 (13.8)	76.8 (12.9)	-2.71	(-5.08 to -0.33)
	Ciao Corona		72.3 (13.5)	1.72	(-0.076 to 3.52)
Family					
< 1000g	FLiP	80.0 (12.6)	80.3 (12.8)	-0.01	(-2.65 to 2.63)
	Ciao Corona		79.1 (12.8)	0.94	(-1.21 to 3.09)
1000g +	FLiP	80.5 (13.3)	80.3 (12.8)	-0.19	(-2.20 to 1.82)
	Ciao Corona		79.1 (12.8)	1.52	(-0.22 to 3.25)
Friends					
< 1000g	FLiP	73.6 (16.0)	78.4 (13.1)	-4.51	(-7.79 to -1.22)
	Ciao Corona		77.8 (13.5)	-4.17	(-6.53 to -1.82)
1000g +	FLiP	77.9 (14.2)	78.4 (13.1)	-0.93	(-3.46 to 1.60)
	Ciao Corona		77.8 (13.5)	0.15	(-1.68 to 1.98)
School					
< 1000g	FLiP	76.4 (16.8)	82.5 (13.6)	-5.20	(-8.73 to -1.67)
	Ciao Corona		75.6 (15.9)	0.67	(-2.08 to 3.41)
1000g +	FLiP	81.3 (14.3)	82.5 (13.6)	-1.61	(-4.02 to 0.81)
	Ciao Corona		75.6 (15.9)	5.63	(3.58 to 7.68)

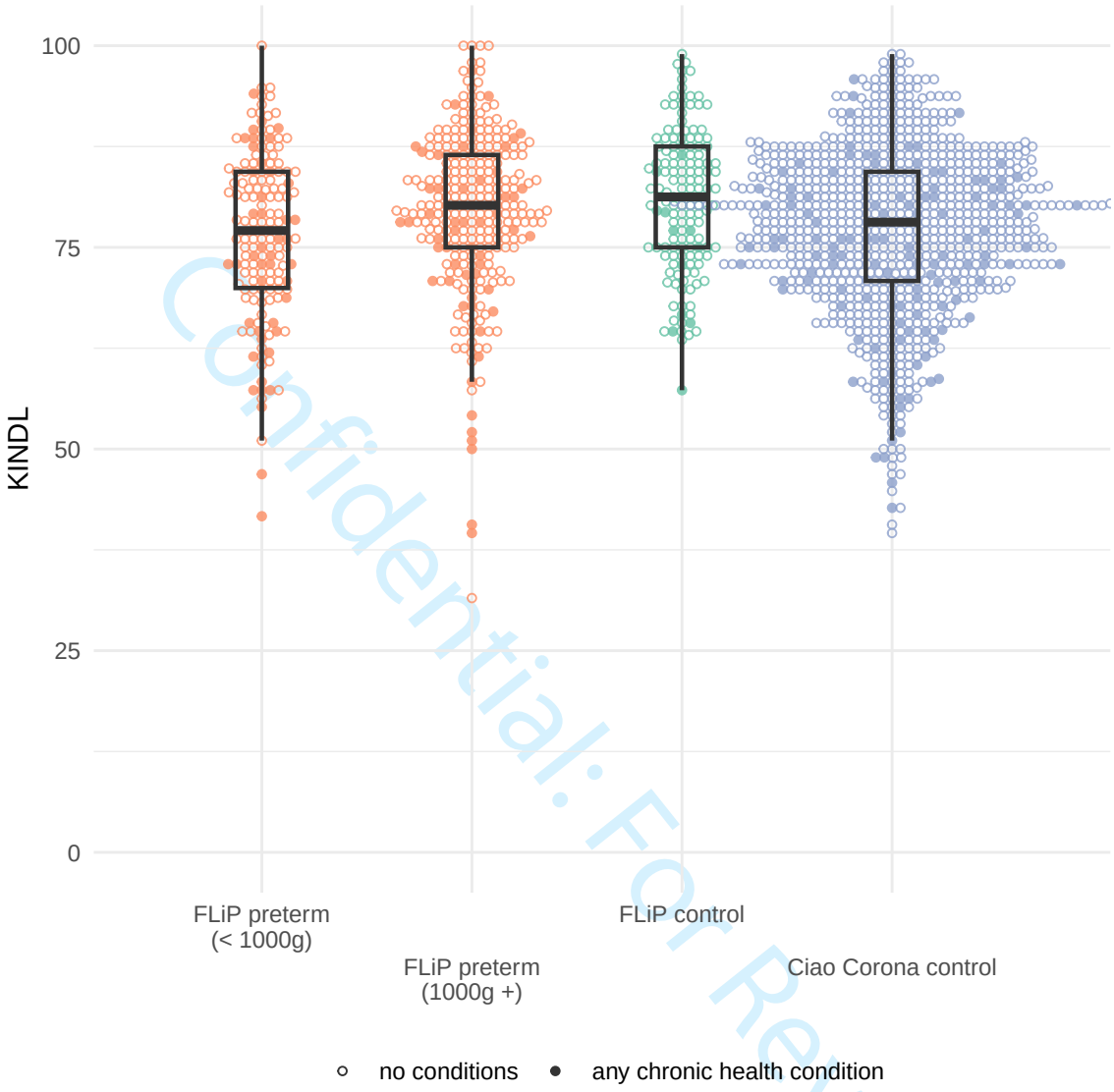

Figure S3: KINDL total score, for very preterm born children (FLiP preterm, stratified by birthweight $<$ 1000g vs $\geq$ 1000g) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control). Solid circles indicate participants without chronic health conditions, while empty diamonds indicate those with any chronic health condition.

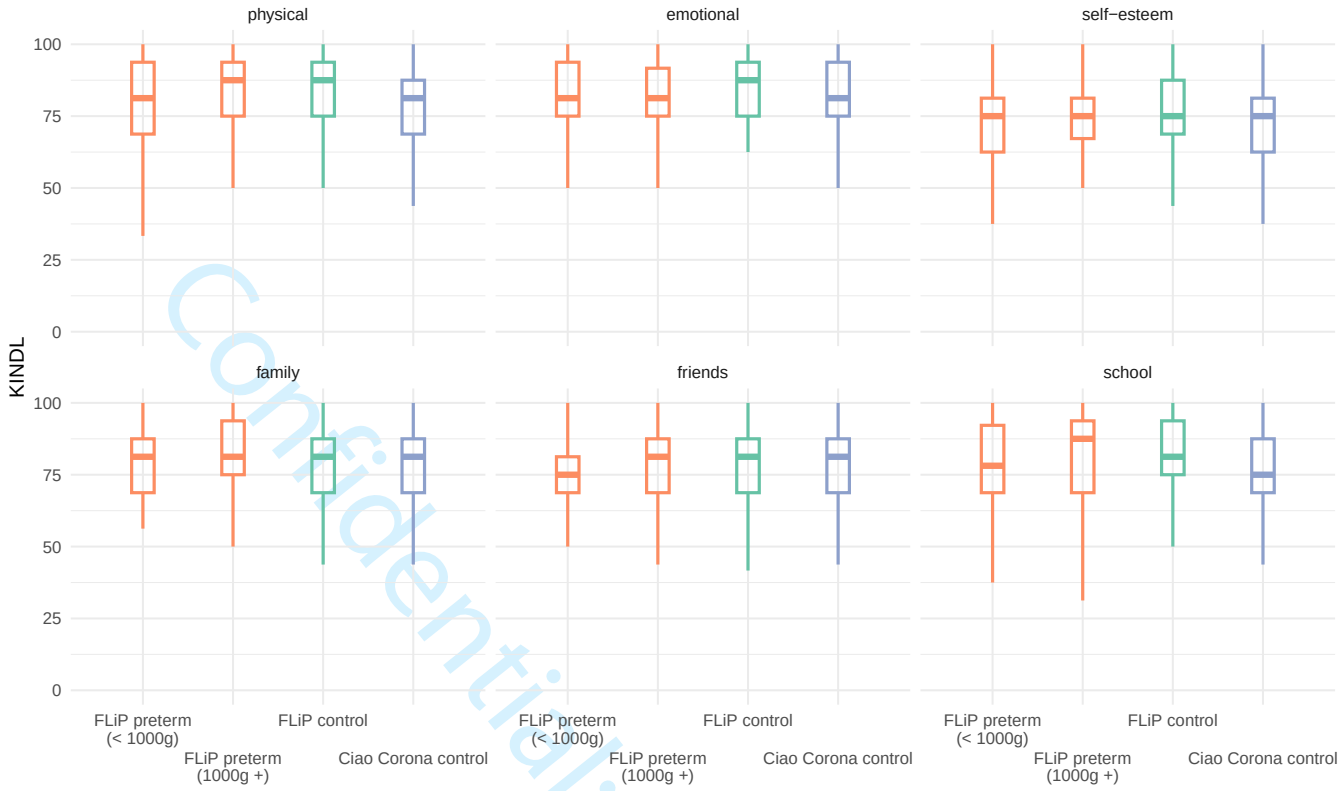

Figure S4: KINDL subscales, for very preterm born children (FLiP preterm, stratified by birthweight: <1000g vs >1000g) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control).

All very preterm born children, regardless of gestational age or birthweight

Table S5: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP and participants from Ciao Corona. Mean differences denote either differences in health-related quality of life between FLIP very preterm born siblings and their control siblings, or between FLIP very preterm born siblings and controls from Ciao Corona. Mean differences and 95% confidence intervals account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

cohort	Preterm	Control	difference	confidence interval
Total				
FLiP	78.5 (10.3)	80.8 (8.7)	-2.09	(-3.56 to -0.62)
Ciao Corona		77.2 (10.2)	1.35	(0.19 to 2.51)
Physical				
FLiP	80.9 (16.0)	82.9 (14.7)	-1.34	(-4.02 to 1.34)
Ciao Corona		77.6 (14.9)	3.28	(1.53 to 5.03)
Emotional				
FLiP	80.4 (13.7)	83.6 (11.6)	-3.16	(-5.31 to -1.00)
Ciao Corona		80.5 (14.1)	-0.08	(-1.67 to 1.52)
Self-esteem				
FLiP	73.4 (13.6)	76.8 (12.9)	-3.22	(-5.39 to -1.06)
Ciao Corona		72.3 (13.5)	1.10	(-0.42 to 2.61)
Family				
FLiP	80.3 (13.1)	80.3 (12.8)	-0.20	(-2.04 to 1.64)
Ciao Corona		79.1 (12.8)	1.31	(-0.16 to 2.77)
Friends				
FLiP	76.4 (15.0)	78.4 (13.1)	-2.21	(-4.68 to 0.26)
Ciao Corona		77.8 (13.5)	-1.40	(-3.01 to 0.20)
School				
FLiP	79.7 (15.3)	82.5 (13.6)	-2.49	(-4.87 to -0.11)
Ciao Corona		75.6 (15.9)	3.94	(2.19 to 5.69)

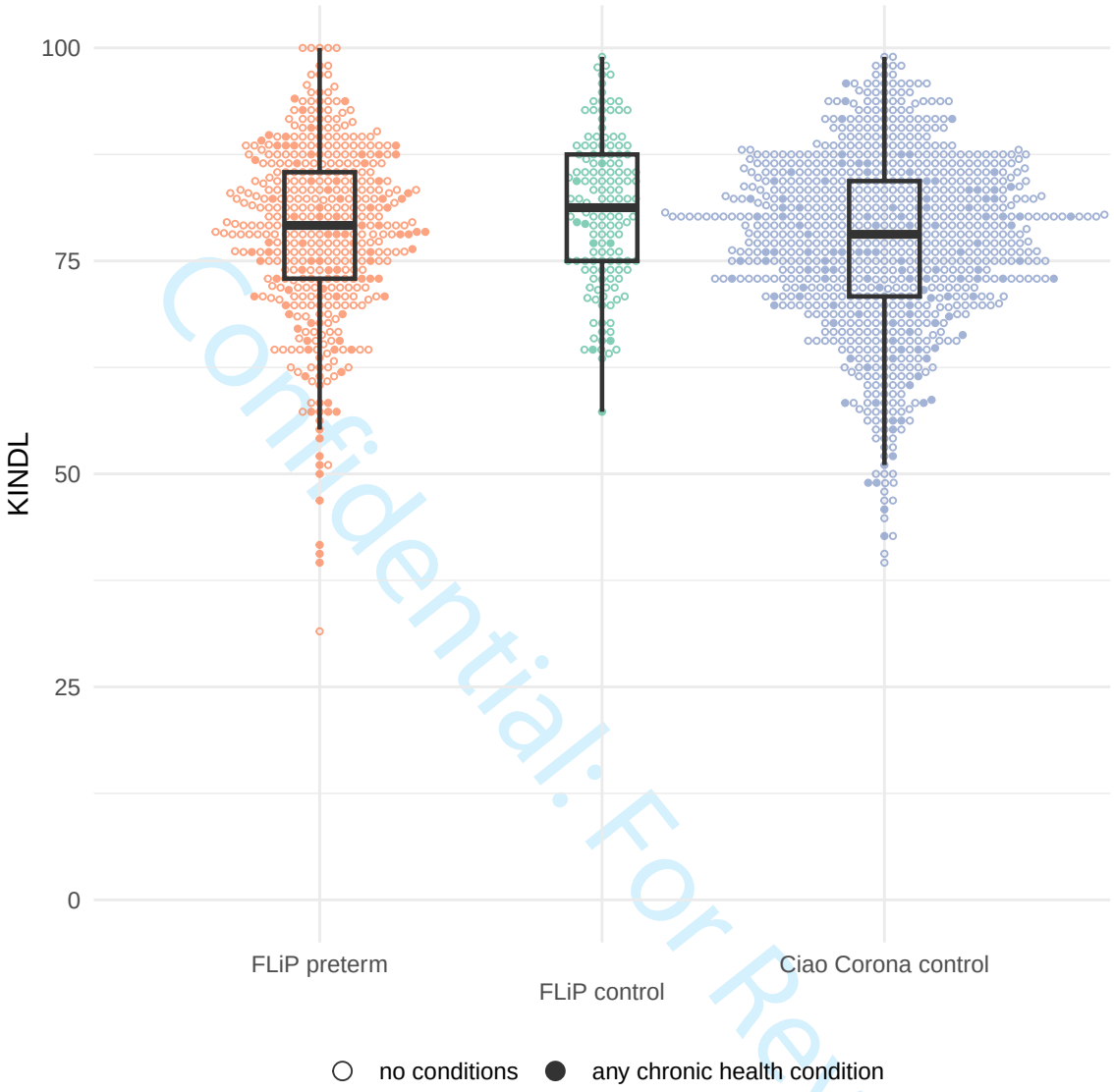

Figure S5: KINDL total score, for very preterm born children (FLiP preterm) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control). Solid circles indicate participants without chronic health conditions, while empty diamonds indicate those with any chronic health condition.

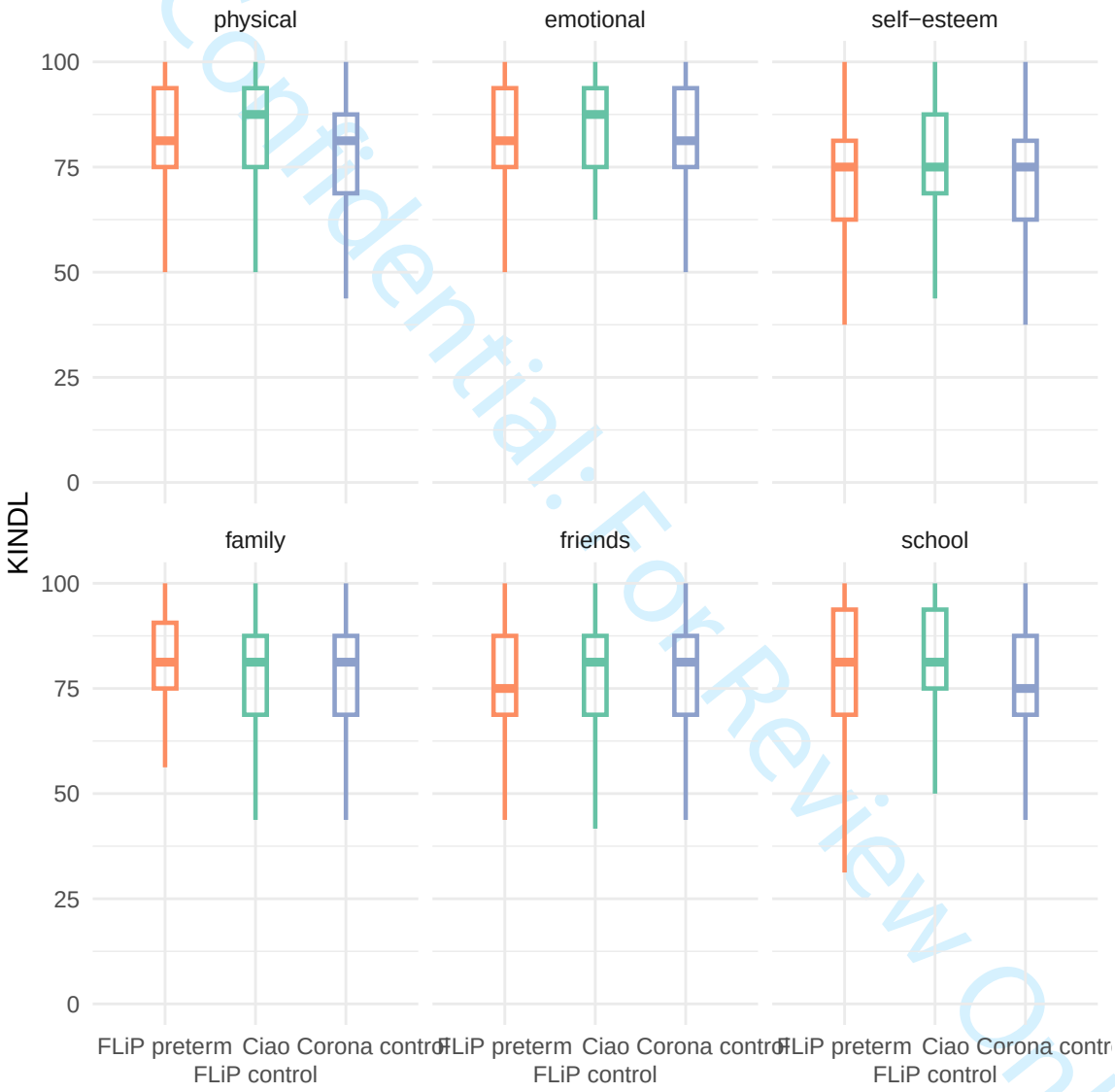

Figure S6: KINDL subscales, for very preterm born children (FLiP preterm) and their fullterm born siblings (FLiP control), as well as age, sex and nationality-matched participants from Ciao Corona (Ciao Corona control).

Table of potential determinants

Table S6: Table of potential determinants of health-related quality of life in FLiP among very preterm born children and adolescents, by age group.

Characteristic	**Overall**, N = 442	**5-9**, N = 227	**10+**, N = 215	**p-value**
KINDL total score	79 (73, 85)	80 (74, 85)	79 (72, 86)	0.11
sex (male)	236 (53%)	116 (51%)	120 (56%)	0.3
overweight	56 (13%)	26 (12%)	30 (15%)	0.5
Unknown	27	17	10	
non-Swiss nationality	66 (15%)	39 (17%)	27 (13%)	0.2
Unknown	1	1	0	
socio-economic status	5 (3, 6)	5 (3, 6)	5 (3, 6)	0.14
Unknown	12	1	11	
unemployed	103 (24%)	50 (22%)	53 (25%)	0.4
Unknown	6	1	5	
siblings				0.6
0	91 (21%)	49 (22%)	42 (20%)	
1	229 (53%)	120 (54%)	109 (52%)	
2+	114 (26%)	54 (24%)	60 (28%)	
Unknown	8	4	4	
smoking				0.007
no	349 (79%)	174 (77%)	175 (81%)	
outside	84 (19%)	52 (23%)	32 (15%)	
in the house	9 (2.0%)	1 (0.4%)	8 (3.7%)	
pets	169 (38%)	59 (26%)	110 (51%)	<0.001
physical activity (hrs / day)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	0.4
Unknown	5	2	3	
screen time (hrs / day)	1.1 (0.6, 2.0)	0.8 (0.5, 1.1)	1.9 (1.0, 2.6)	<0.001
Unknown	11	6	5	
Participation in sports outside of school	319 (73%)	167 (74%)	152 (72%)	0.7
Unknown	3	0	3	
Participation in music lessons or activities	128 (29%)	58 (26%)	70 (33%)	0.085
Unknown	3	0	3	
Participation in scouts or similar	48 (11%)	20 (8.8%)	28 (13%)	0.14
Unknown	3	0	3	
Gestational age				0.006
24-27 wks	130 (29%)	80 (35%)	50 (23%)	
28-31 wks	312 (71%)	147 (65%)	165 (77%)	
birthweight				0.2
<1000g	158 (36%)	87 (38%)	71 (33%)	
1000+g	284 (64%)	140 (62%)	144 (67%)	
BPD	55 (12%)	29 (13%)	26 (12%)	0.8
chronic non-respiratory conditions	67 (15%)	32 (14%)	35 (16%)	0.5
chronic respiratory conditions	24 (5.4%)	9 (4.0%)	15 (7.0%)	0.2
cerebral palsy	33 (7.5%)	12 (5.3%)	21 (9.8%)	0.073
therapy				0.032
no therapy	307 (69%)	145 (64%)	162 (75%)	
1-2	116 (26%)	70 (31%)	46 (21%)	
3+	19 (4.3%)	12 (5.3%)	7 (3.3%)	
assistive devices	15 (3.4%)	7 (3.1%)	8 (3.7%)	0.7
respiratory symptoms affecting daily life	99 (22%)	54 (24%)	45 (21%)	0.5

[1] Median (IQR); n (%)

Sensitivity Analyses

Sensitivity analyses included

a) excluding participants with chronic health conditions;

- Because very preterm born children were much more likely to report chronic non-respiratory conditions, respiratory conditions or cerebral palsy than fullterm children (24% vs 8% in our sample), we also examined a subset of FLiP participants that did not report any chronic health condition. In this subset, preterm children had on average a 1.3 point lower total KINDL score that their fullterm siblings (95% CI -2.8 to 0.2) and 2.0 points higher KINDL total score (0.7 to 3.2) than controls in Ciao Corona (**Table S7, Figures S7 and S8**).

b) restricting to preterm born children with control siblings;

- To ensure comparable groups with respect to family characteristics, including socioeconomic status and general level of physical activity, we restricted to those families with both preterm and fullterm siblings as a sensitivity analysis, leaving 119 preterm children and 119 controls (**Table S8**). Among those families, very preterm born children had on average 2.0 points lower KINDL total score than their fullterm born siblings (95% CI -3.7 to -0.3, **Table S9, Figure S9**).

c) stratification by age; and

- We noted similar patterns in both younger and older children (**Figures S10 and S11, Table S10**). The mean difference in KINDL total score between preterm and controls was -2.1 (95% CI -4.0 to -0.1) among children 5-9 years of age, and -1.7 (-4.2 to 0.7) among those 10 and older.

d) adjusting for SES.

- SES was directly influenced by family unit, and likely contributes to HRQOL. We therefore considered models with and without SES. The two models showed similar fit (BIC 4194 vs 4201), and the estimates were of very similar magnitude (-2.1 [-3.6 to -0.6] in both cases).

e) accounting for family unit using fixed rather than random effects.

- The random effects and fixed effects models gave very similar results, both for all participants in FLiP (**Figure S12 and Table S11**) and for subgroups stratified by gestational age (**Figure S13 and Table S12**).

None of the sensitivity analyses led to a different conclusion regarding HRQOL in very preterm born children compared to their peers.

a) excluding participants with chronic health conditions

Table S7: Differences in KINDL total score between very preterm born children, their fullterm born siblings, and Ciao Corona participants (stratified by presence of any chronic health conditions). In FLiP, 104 of very preterm born children had chronic health conditions (24%), while n = 12 of their control siblings did (8%). Among controls from Ciao Corona, 122 (14%) reported chronic health conditions. Mean differences denote either differences in health-related quality of life between FLIP very preterm born siblings and their control siblings, or between FLIP very preterm born siblings and controls from Ciao Corona. Mean differences and 95% confidence intervals account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

chronic health conditions	cohort	Preterm	Control	difference	confidence interval
Total					
any chronic health condition	FLiP	74.5 (12.2)	73.8 (8.7)	-4.50	(-10.39 to 1.39)
	Ciao Corona		73.8 (10.3)	0.69	(-2.26 to 3.65)
no chronic health conditions	FLiP	79.7 (9.4)	81.4 (8.5)	-1.30	(-2.82 to 0.21)
	Ciao Corona		77.7 (10.1)	1.99	(0.74 to 3.23)
Physical					
any chronic health condition	FLiP	77.0 (17.2)	75.5 (10.8)	0.58	(-9.44 to 10.60)
	Ciao Corona		74.0 (14.3)	3.17	(-0.96 to 7.30)
no chronic health conditions	FLiP	82.1 (15.4)	83.5 (14.9)	-0.75	(-3.59 to 2.09)
	Ciao Corona		78.2 (15.0)	3.87	(1.93 to 5.81)
Emotional					
any chronic health condition	FLiP	78.4 (15.2)	77.6 (17.2)	-2.36	(-10.72 to 5.99)
	Ciao Corona		77.3 (14.7)	1.31	(-2.63 to 5.24)
no chronic health conditions	FLiP	81.0 (13.1)	84.1 (10.9)	-3.14	(-5.38 to -0.89)
	Ciao Corona		81.1 (13.9)	-0.09	(-1.81 to 1.64)
Self-esteem					
any chronic health condition	FLiP	68.1 (16.7)	70.3 (10.0)	-5.38	(-14.27 to 3.52)
	Ciao Corona		68.7 (13.3)	-0.52	(-4.48 to 3.43)
no chronic health conditions	FLiP	75.0 (12.2)	77.3 (13.0)	-1.93	(-4.03 to 0.16)
	Ciao Corona		72.9 (13.5)	2.03	(0.38 to 3.67)
Family					
any chronic health condition	FLiP	78.9 (14.1)	76.0 (12.5)	-1.92	(-9.49 to 5.66)
	Ciao Corona		75.9 (13.8)	3.25	(-0.43 to 6.93)
no chronic health conditions	FLiP	80.7 (12.7)	80.6 (12.8)	0.37	(-1.50 to 2.24)
	Ciao Corona		79.6 (12.5)	1.15	(-0.44 to 2.75)
Friends					
any chronic health condition	FLiP	71.4 (15.6)	69.6 (14.9)	1.05	(-8.22 to 10.33)
	Ciao Corona		73.2 (15.7)	-1.80	(-5.85 to 2.24)
no chronic health conditions	FLiP	77.9 (14.5)	79.2 (12.7)	-1.28	(-3.84 to 1.28)
	Ciao Corona		78.5 (13.0)	-0.57	(-2.30 to 1.16)
School					
any chronic health condition	FLiP	72.6 (18.0)	72.2 (19.2)	-3.29	(-12.48 to 5.89)
	Ciao Corona		73.8 (16.8)	-1.44	(-6.08 to 3.20)
no chronic health conditions	FLiP	81.9 (13.7)	83.5 (12.7)	-1.52	(-4.05 to 1.00)
	Ciao Corona		75.9 (15.8)	5.77	(3.89 to 7.66)

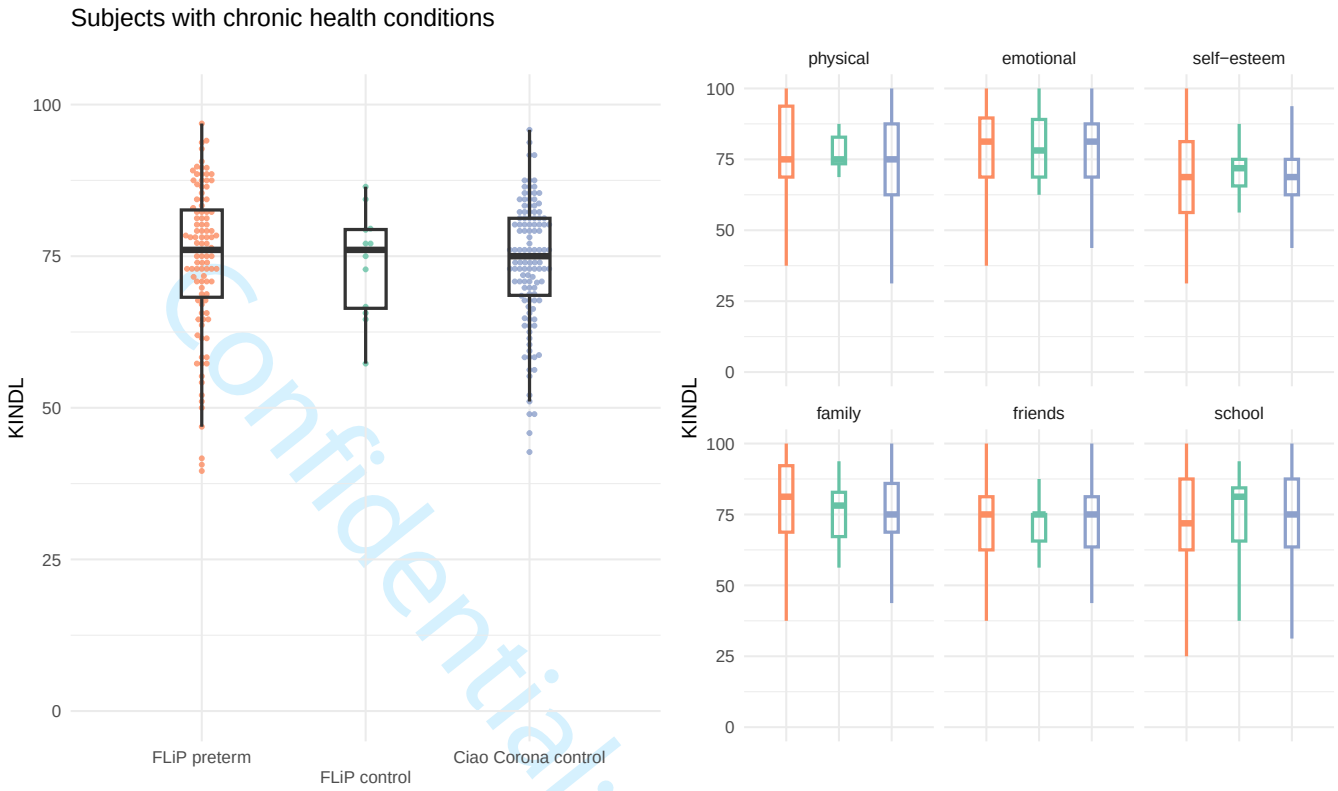

Figure S7: KINDL total score and its subscales, for preterm children and their fullterm siblings (with any chronic health condition)

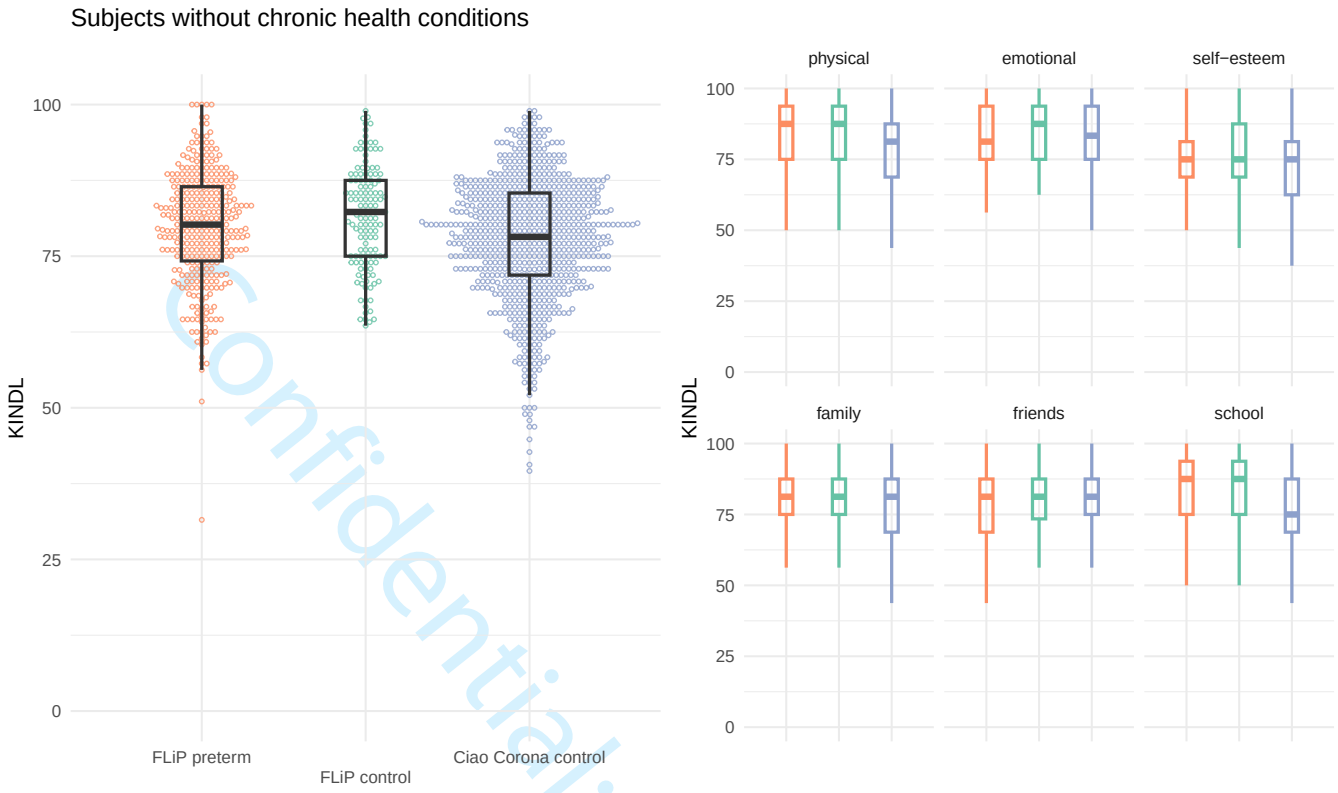

Figure S8: KINDL total score and its subscales, for preterm children and their fullterm siblings (with no chronic health conditions)

b) restricting to preterm born children with control siblings

Table S8: Differences in KINDL total score between preterm children and their fullterm siblings (only matched siblings).

KINDL	Preterm	Control	difference	confidence interval
total	78.5 (10.5)	80.6 (8.9)	-1.99	(-3.66 to -0.32)
physical	82.1 (15.0)	81.9 (15.6)	0.19	(-3.08 to 3.45)
emotional	80.5 (13.7)	83.6 (11.5)	-3.02	(-5.66 to -0.38)
self-esteem	72.6 (14.0)	76.3 (13.1)	-3.26	(-5.79 to -0.74)
family	80.1 (12.8)	80.9 (12.5)	-0.52	(-2.52 to 1.48)
friends	75.8 (15.3)	78.2 (13.2)	-2.46	(-5.36 to 0.45)
school	79.4 (14.7)	82.5 (13.7)	-2.67	(-5.58 to 0.23)

Table S9: Key characteristics of preterm and control participants in full data (preterm children with included control siblings)

Characteristic	**FLiP preterm**, N = 119	**FLiP control**, N = 119
age (years)	11 (5 - 16)	10 (5 - 19)
sex (male)	62 (52%)	71 (61%)
gestational age (weeks)		
24-27 wks	25 (21%)	
28-31 wks	94 (79%)	
birthweight		
<1000g	28 (24%)	
1000+g	91 (76%)	
multiple gestation	28 (24%)	
socio-economic status	5 [3, 6]	5 [3, 6]
non-Swiss nationality	15 (13%)	12 (10%)
moderate to severe BPD	15 (13%)	
coughing / wheezing restrict daily activities	4 (3.4%)	1 (0.8%)
any chronic health condition	31 (26%)	10 (8.4%)
chronic non-respiratory conditions	21 (18%)	9 (7.6%)
chronic respiratory conditions	9 (7.6%)	2 (1.7%)
cerebral palsy	8 (6.7%)	1 (0.8%)
physical activity (hours per week)	0.71 [0.57, 1.00]	0.75 [0.57, 1.14]

[1] Median (Range); n (%); Median [IQR]

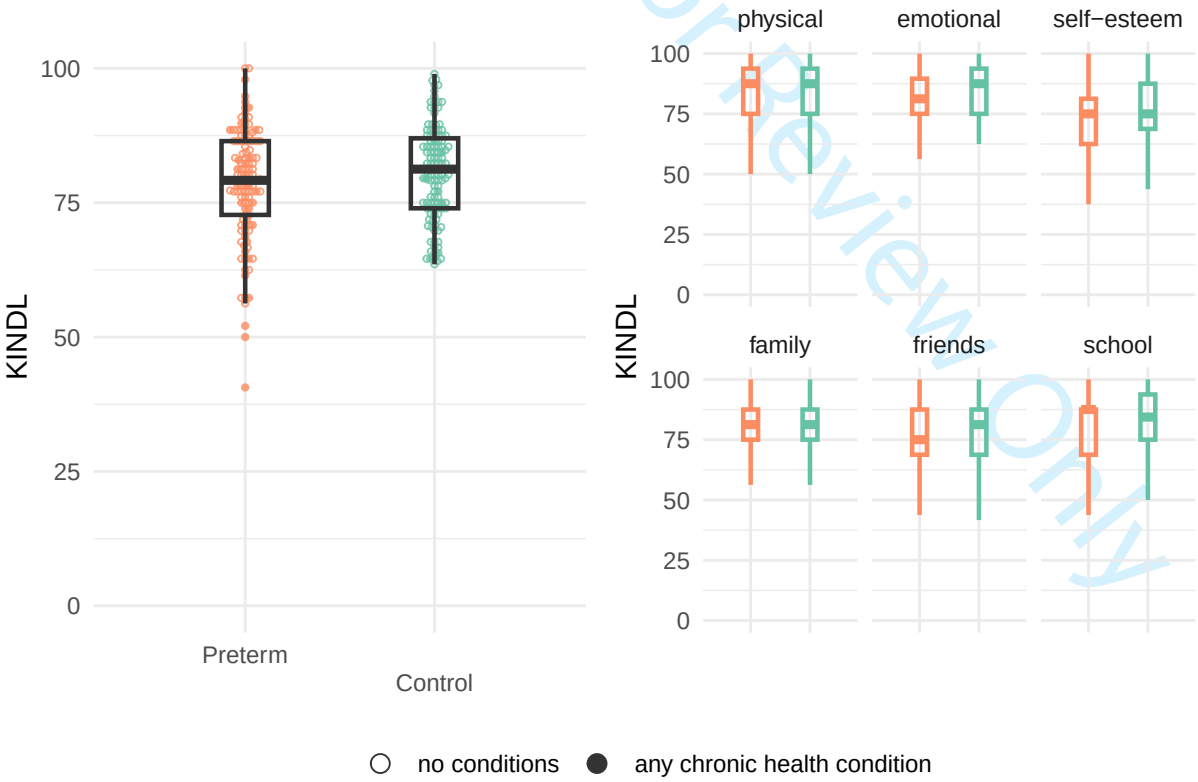

Figure S9: KINDL total score and its subscales, for preterm children and their fullterm siblings (matched siblings only)

c) stratification by age

Table S10: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP and participants from Ciao Corona, by age group (5-9, 10+). Mean differences, 95% confidence intervals and p-values account for either family unit or matching and therefore may not strictly correspond to the means for each group given in the first and second columns.

age	cohort	Preterm	Control	difference	confidence interval
Total					
5-9	FLiP	79.6 (8.7)	82.1 (8.0)	-2.06	(-3.97 to -0.14)
	Ciao Corona		79.8 (9.0)	-0.07	(-1.49 to 1.35)
10+	FLiP	77.3 (11.7)	78.8 (9.5)	-1.73	(-4.18 to 0.73)
	Ciao Corona		75.3 (10.7)	2.00	(0.24 to 3.75)
Physical					
5-9	FLiP	81.2 (16.1)	85.5 (13.1)	-4.14	(-7.74 to -0.54)
	Ciao Corona		80.9 (13.6)	0.37	(-2.05 to 2.79)
10+	FLiP	80.5 (16.0)	79.1 (16.1)	2.09	(-2.01 to 6.20)
	Ciao Corona		75.2 (15.4)	5.29	(2.83 to 7.76)
Emotional					
5-9	FLiP	81.0 (12.6)	84.3 (11.0)	-3.31	(-6.14 to -0.49)
	Ciao Corona		82.3 (13.0)	-1.19	(-3.29 to 0.92)
10+	FLiP	79.8 (14.8)	82.6 (12.5)	-3.23	(-6.65 to 0.19)
	Ciao Corona		79.3 (14.7)	0.52	(-1.83 to 2.87)
Self-esteem					
5-9	FLiP	74.9 (12.1)	78.8 (11.4)	-3.51	(-6.35 to -0.68)
	Ciao Corona		74.4 (13.0)	0.51	(-1.48 to 2.51)
10+	FLiP	71.8 (15.0)	73.8 (14.4)	-2.76	(-6.45 to 0.94)
	Ciao Corona		70.8 (13.7)	1.05	(-1.17 to 3.27)
Family					
5-9	FLiP	79.0 (12.2)	79.7 (12.8)	-0.43	(-3.13 to 2.27)
	Ciao Corona		79.0 (12.2)	0.08	(-1.91 to 2.07)
10+	FLiP	81.7 (13.8)	81.1 (12.7)	-0.22	(-2.97 to 2.54)
	Ciao Corona		79.1 (13.2)	2.59	(0.48 to 4.71)
Friends					
5-9	FLiP	77.9 (12.5)	79.3 (12.0)	-1.28	(-4.22 to 1.66)
	Ciao Corona		79.4 (12.5)	-1.60	(-3.67 to 0.47)
10+	FLiP	74.8 (17.1)	77.0 (14.5)	-2.29	(-6.43 to 1.84)
	Ciao Corona		76.6 (14.1)	-1.74	(-4.15 to 0.66)
School					
5-9	FLiP	84.4 (12.4)	85.2 (11.9)	0.03	(-2.93 to 2.99)
	Ciao Corona		82.5 (13.1)	1.85	(-0.30 to 4.00)
10+	FLiP	74.5 (16.5)	78.7 (14.9)	-3.50	(-7.29 to 0.29)
	Ciao Corona		70.7 (16.0)	3.85	(1.20 to 6.50)

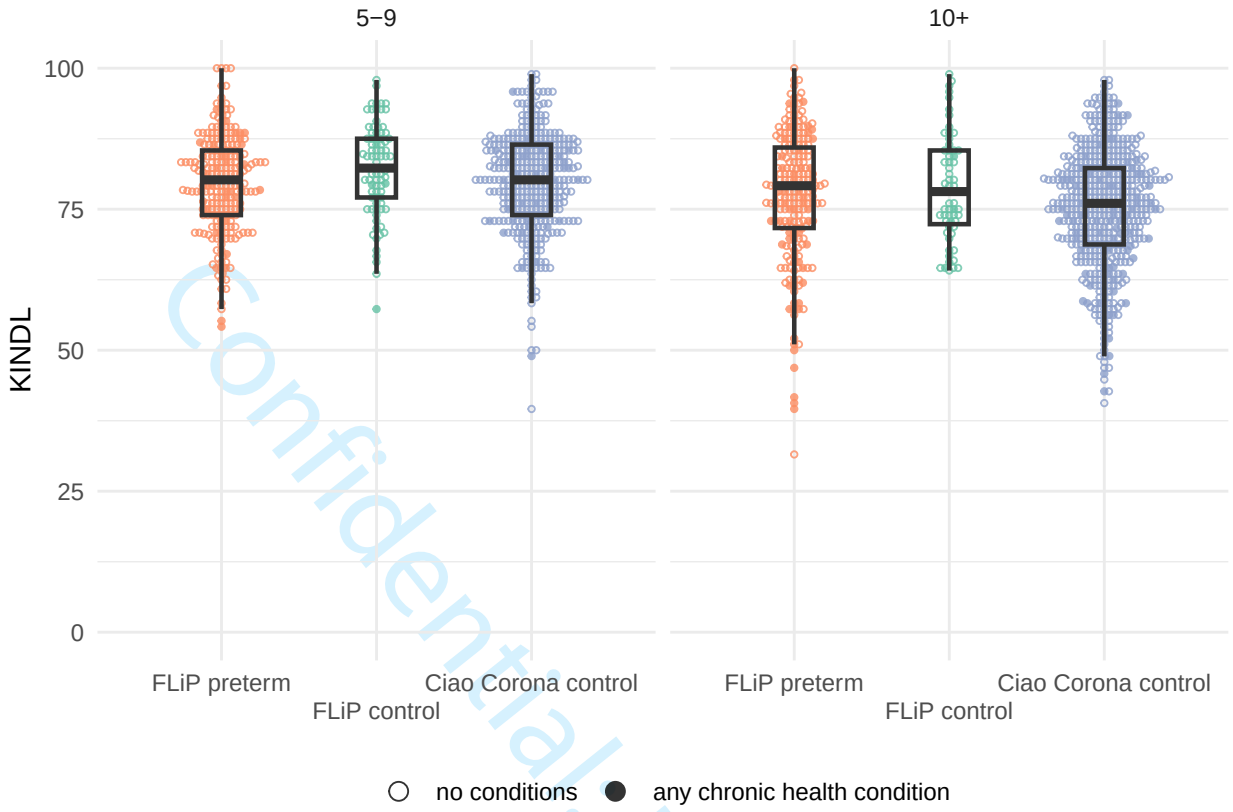

Figure S10: KINDL total score in very preterm born children and fullterm born controls from FLiP, as well as controls from Ciao Corona, by age group. Solid circles indicate participants without chronic health conditions, while empty circles indicate those with any chronic health condition.

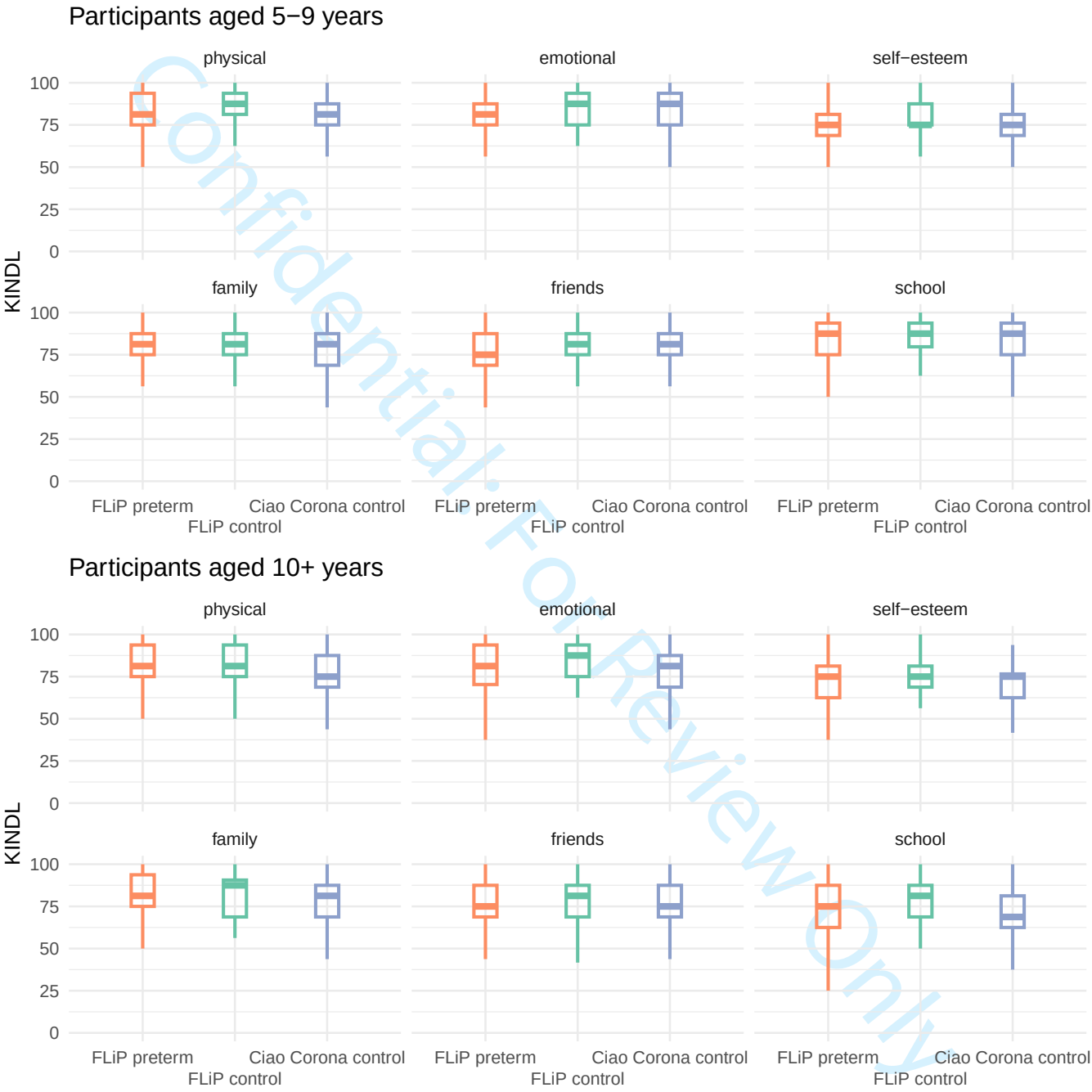

Figure S11: KINDL subscales in very preterm born children and fullterm born controls from FLiP, as well as controls from Ciao Corona, by age group.

d) adjusting for SES

SES was directly influenced by family unit, and likely contributes to HRQOL. We therefore considered models with and without SES. The two models showed similar fit (BIC 4194 vs 4201), and the estimates were of very similar magnitude (-2.1 [-3.6 to -0.6] in both cases).

```
sm2 <- sm %>%
  ungroup() %>%
  select(kindl_total, group, family_id, SES_Score_total) %>%
  filter(complete.cases(.))
mod_noSES <- lmer(kindl_total ~ group + (1 | family_id), data = sm2)
tidy(mod_noSES, conf.int = TRUE) %>%
  filter(term == "groupPreterm") %>%
  select(term, estimate, conf.low, conf.high, p.value) %>%
  mutate(BIC = BIC(mod_noSES),
         AIC = AIC(mod_noSES))
```

```
## # A tibble: 1 x 7
##   term         estimate conf.low conf.high p.value   BIC   AIC
##   <chr>           <dbl>    <dbl>     <dbl>   <dbl> <dbl> <dbl>
## 1 groupPreterm    -2.10    -3.59    -0.613 0.00581 4194. 4176.
```

```
mod_SES <- lmer(kindl_total ~ group + SES_Score_total + (1 | family_id), data = sm2)
tidy(mod_SES, conf.int = TRUE) %>%
  filter(term == "groupPreterm") %>%
  select(term, estimate, conf.low, conf.high, p.value) %>%
  mutate(BIC = BIC(mod_SES),
         AIC = AIC(mod_SES))
```

```
## # A tibble: 1 x 7
##   term         estimate conf.low conf.high p.value   BIC   AIC
##   <chr>           <dbl>    <dbl>     <dbl>   <dbl> <dbl> <dbl>
## 1 groupPreterm    -2.09    -3.58    -0.605 0.00600 4201. 4179.
```

e) accounting for family unit using fixed rather than random effects

The random effects and fixed effects models gave very similar results, both for all participants in FLiP (**Figure S12 and Table S11**) and for subgroups stratified by gestational age (**Figure S13 and Table S12**).

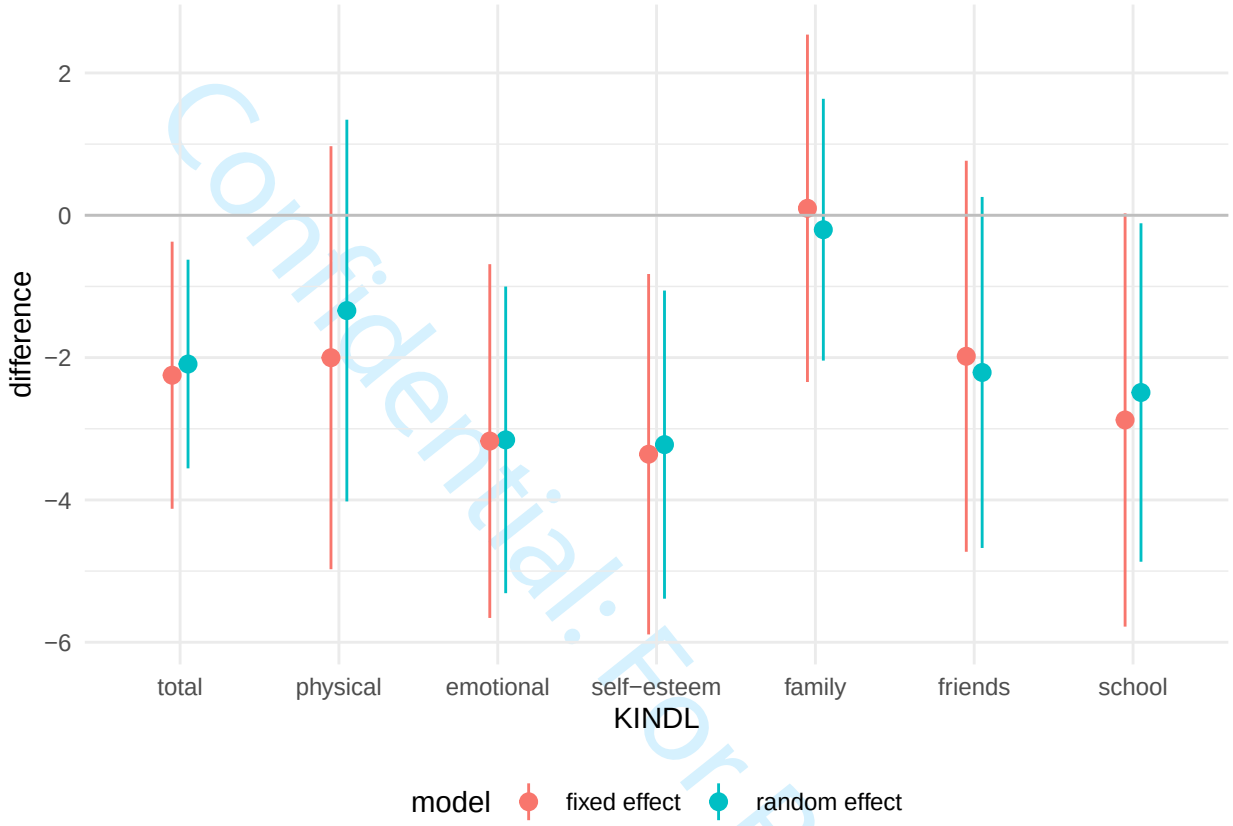

Figure S12: Results from models comparing FLiP participants, accounting for family unit using fixed effects.

Table S11: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP. Results from models accounting for family unit as 1) random effect, or 2) fixed effect are shown. Mean differences and 95% confidence intervals are shown.

KINDL	random effect	fixed effect
total	-2.09 (-3.56 to -0.62)	-2.25 (-4.12 to -0.37)
physical	-1.34 (-4.02 to 1.34)	-2.00 (-4.97 to 0.97)
emotional	-3.16 (-5.31 to -1.00)	-3.17 (-5.66 to -0.69)
self-esteem	-3.22 (-5.39 to -1.06)	-3.36 (-5.89 to -0.82)
family	-0.203 (-2.04 to 1.64)	0.098 (-2.34 to 2.54)
friends	-2.21 (-4.68 to 0.26)	-1.98 (-4.73 to 0.77)
school	-2.49 (-4.87 to -0.11)	-2.88 (-5.78 to 0.027)

Table S12: Differences in KINDL total score between very preterm born children and their fullterm siblings from FLiP, by gestational age. Results from models accounting for family unit as 1) random effect, or 2) fixed effect are shown. Mean differences and 95% confidence intervals are shown.

KINDL	Gestational Age	random effect	fixed effect
total	24 - 27 weeks	-2.27 (-4.36 to -0.17)	0.94 (-2.99 to 4.88)
total	28 - 31 weeks	-2.29 (-3.86 to -0.73)	-2.65 (-4.48 to -0.82)
physical	24 - 27 weeks	-5.169 (-9.02 to -1.31)	1.119 (-6.99 to 9.23)
physical	28 - 31 weeks	-0.441 (-3.08 to 2.20)	-0.046 (-3.35 to 3.26)
emotional	24 - 27 weeks	-3.35 (-6.10 to -0.61)	-0.79 (-5.84 to 4.26)
emotional	28 - 31 weeks	-3.12 (-5.49 to -0.75)	-3.42 (-6.40 to -0.43)
self-esteem	24 - 27 weeks	-2.25 (-5.25 to 0.75)	-0.18 (-6.07 to 5.72)
self-esteem	28 - 31 weeks	-3.68 (-5.98 to -1.37)	-3.89 (-6.74 to -1.03)
family	24 - 27 weeks	1.18 (-1.60 to 3.96)	3.79 (-0.96 to 8.53)
family	28 - 31 weeks	-0.84 (-2.83 to 1.15)	-1.57 (-3.84 to 0.71)
friends	24 - 27 weeks	-2.20 (-5.34 to 0.95)	0.56 (-5.53 to 6.65)
friends	28 - 31 weeks	-2.07 (-4.76 to 0.61)	-3.24 (-6.69 to 0.20)
school	24 - 27 weeks	-4.02 (-7.63 to -0.41)	-2.08 (-9.44 to 5.27)
school	28 - 31 weeks	-2.11 (-4.59 to 0.36)	-2.18 (-5.21 to 0.85)

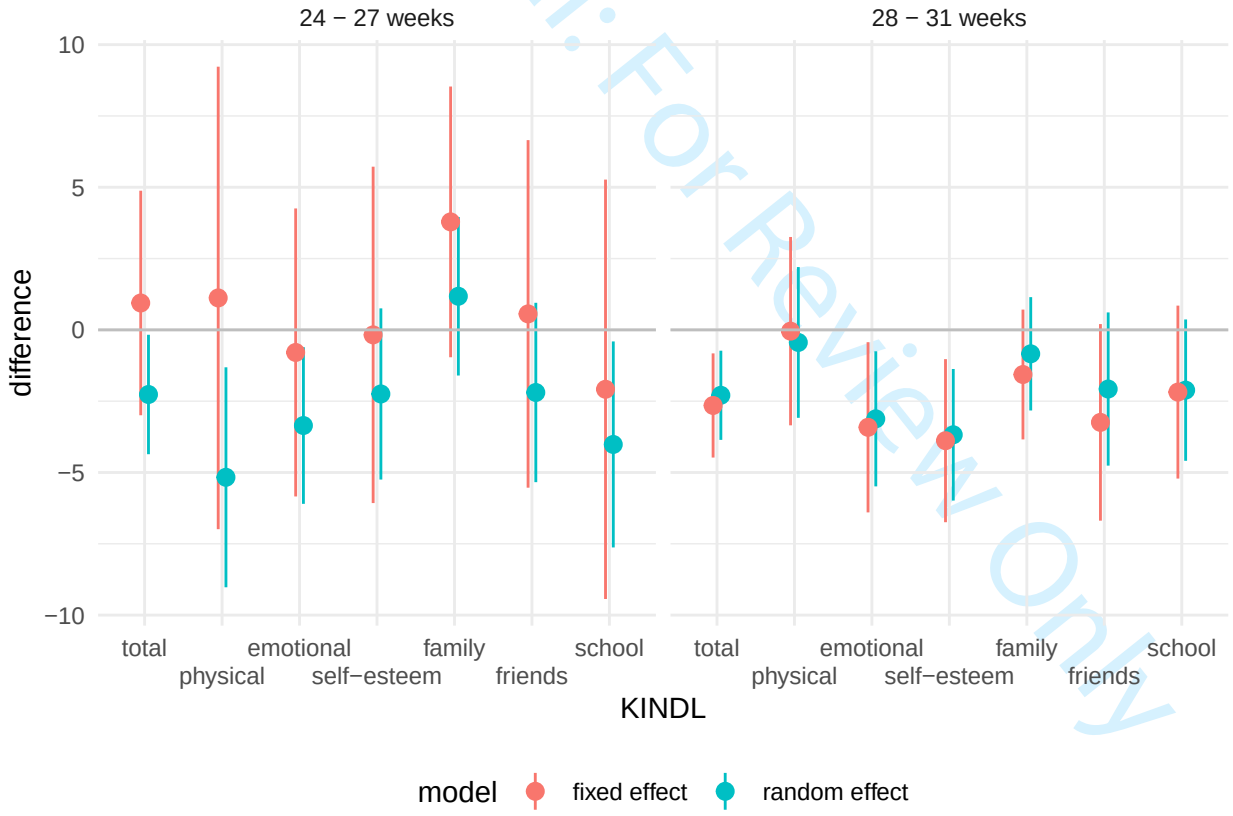

Figure S13: Results from models comparing FLiP participants, by age group, accounting for family unit using fixed effects.

Computational Details

- R version: R version 4.4.1 (2024-06-14)
- Base packages: grid, stats, graphics, grDevices, utils, datasets, methods, base
- Other packages: consort 1.2.1, kableExtra 1.4.0, ggparty 1.0.0, partykit 1.2.20, mvtnorm 1.2.4, libcoin 1.0.10, patchwork 1.2.0, ggdag 0.2.12, gtsummary 1.7.2, lmerTest 3.1.3, lme4 1.1.35.5, Matrix 1.7.0, broom.mixed 0.2.9.5, broom 1.0.5, ggbeeswarm 0.7.2, lubridate 1.9.3, forcats 1.0.0, stringr 1.5.1, dplyr 1.1.4, purrr 1.0.2, readr 2.1.5, tidyr 1.3.1, tibble 3.2.1, ggplot2 3.5.1, tidyverse 2.0.0

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