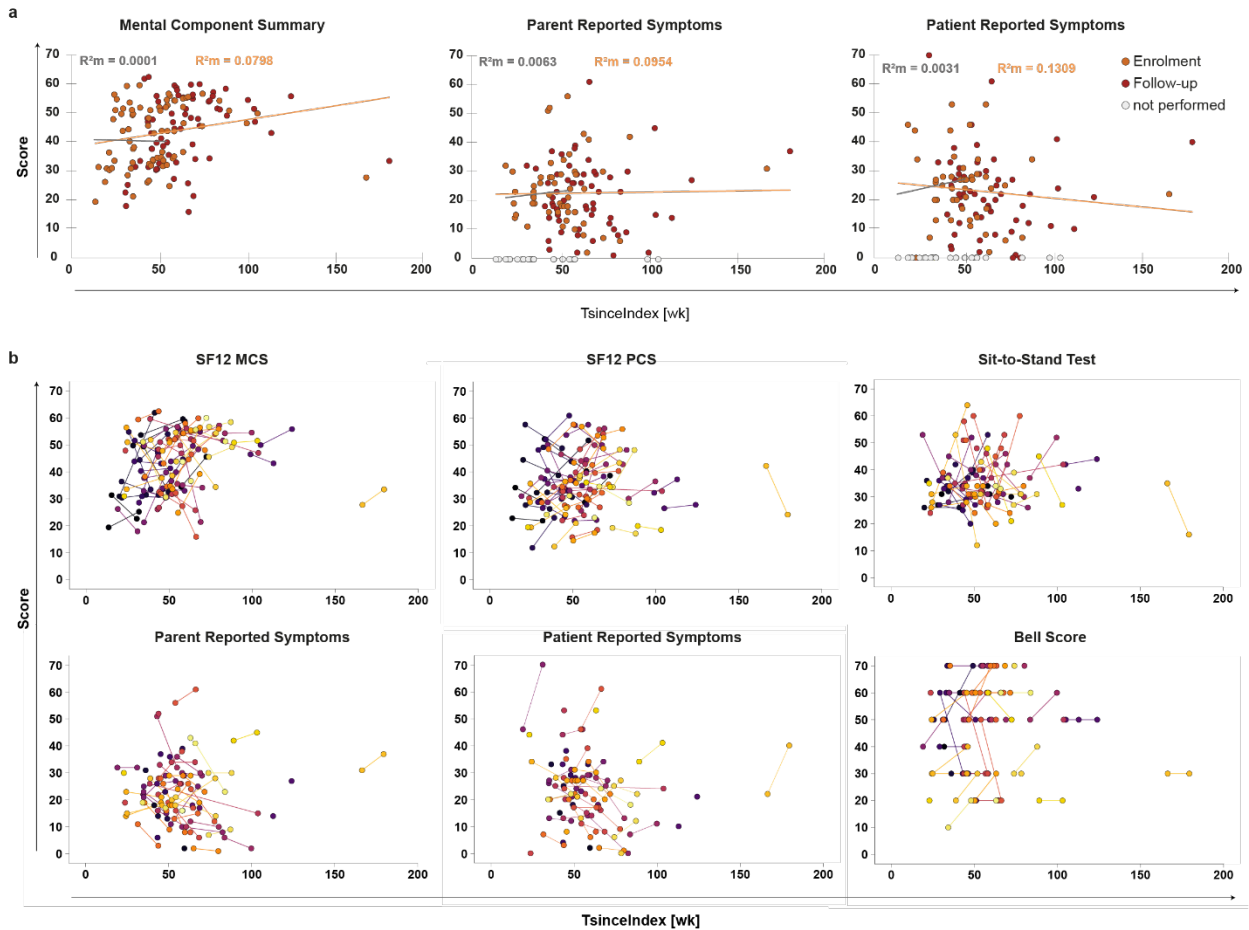


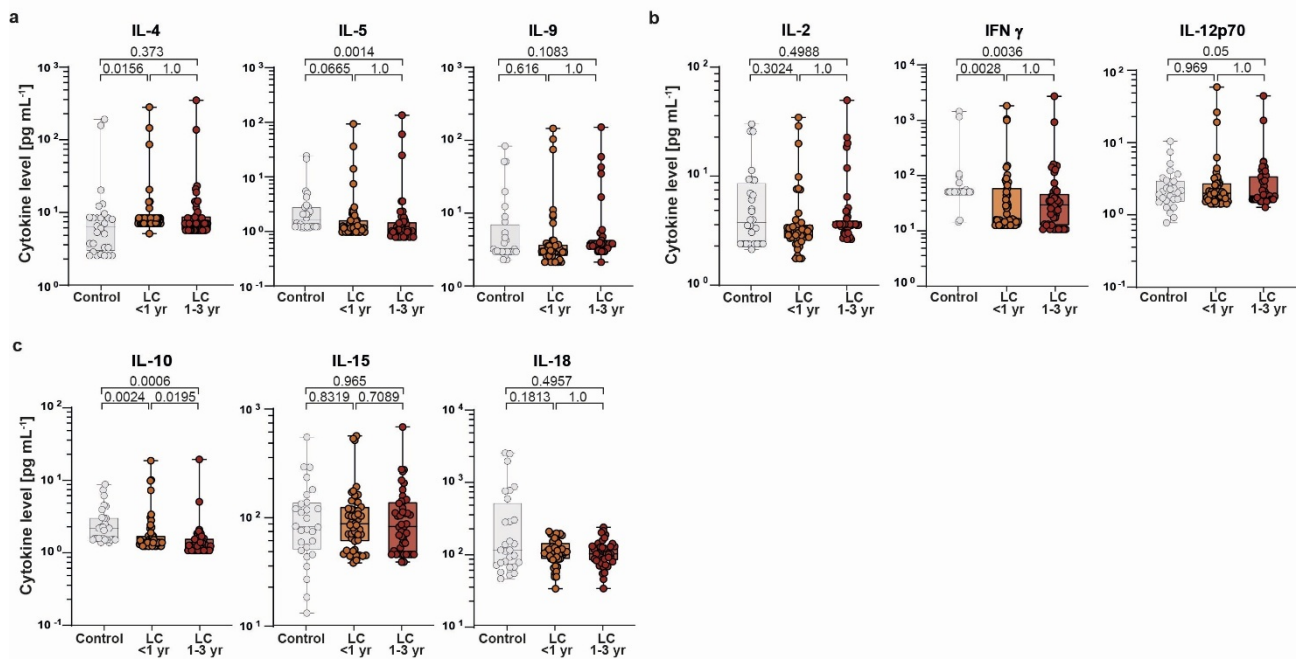
1 Immune-metabolic trajectories delineate subgroups in paediatric long COVID

2 Vilser et al. and Brunner-Weinzierl

3 Supplementary Figures and Tables



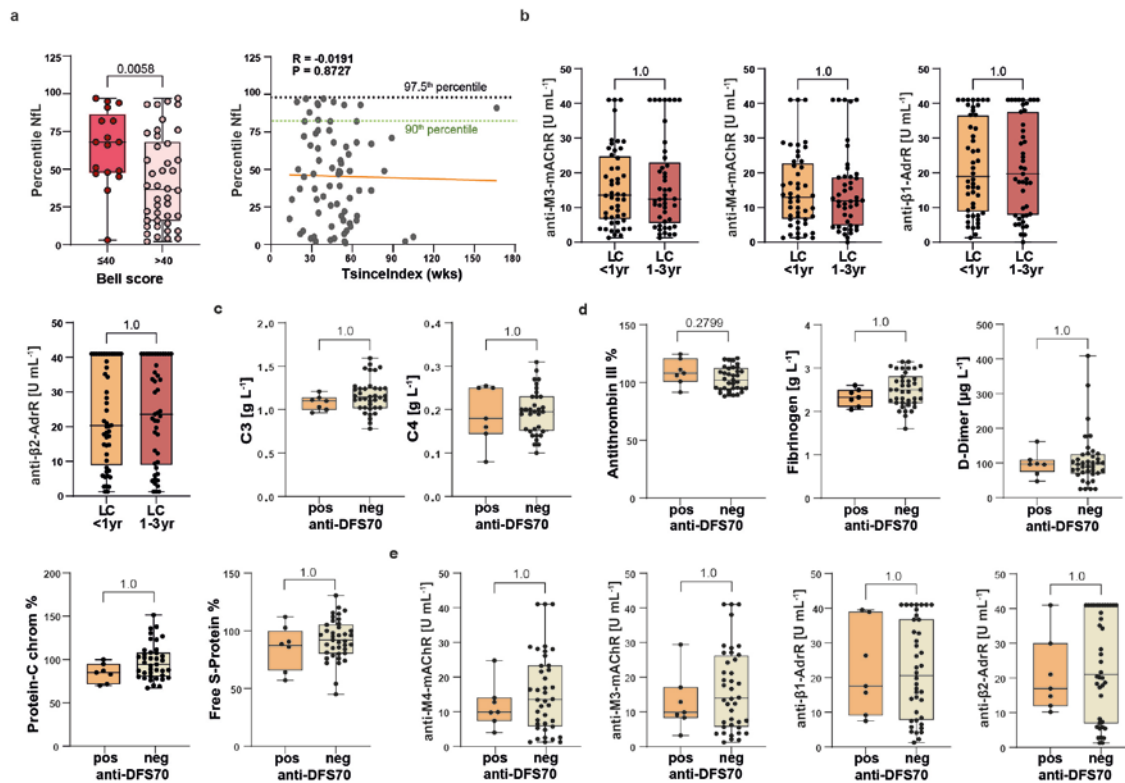
4  
5 **Supplementary Fig. 1 |** Related to Fig. 1e. a, Additional LC-related scores versus TsinceIndex are  
6 shown for Mental Component Summary (n = 143 observations), parent-reported symptoms (n = 112  
7 observations), and patient-reported symptoms (n = 104 observations). Associations were assessed  
8 using the same two-sided linear mixed-effects models (LMMs) as in Fig. 1e, with participant ID  
9 included as a random intercept. Numbers indicate marginal  $R^2$  ( $R^2_m$ ) values for two time intervals:  
10 black numbers denote the first year post-SARS-CoV-2 infection, and red values denote the entire  
11 observational period. Each dot represents one assessment at one visit; most participants contributed  
12 data from two visits (see Supplementary Table 1b). Black and red lines are shown for visual guidance  
13 only and represent descriptive regression lines for the respective intervals. b, Selected symptom  
14 scores are plotted against TsinceIndex, with lines connecting repeated measurements from the  
15 same participant across visits. Shown are Mental Component Summary (SF-12 MCS; n = 143  
16 observations), Physical Component Summary (SF-12 PCS; n = 143 observations), Sit-to-Stand test  
17 (n = 120 observations), parent-reported symptoms (n = 112 observations), patient-reported  
18 symptoms (n = 104 observations), and Bell score (n = 121 observations). Each dot represents one  
19 assessment at one visit.



21

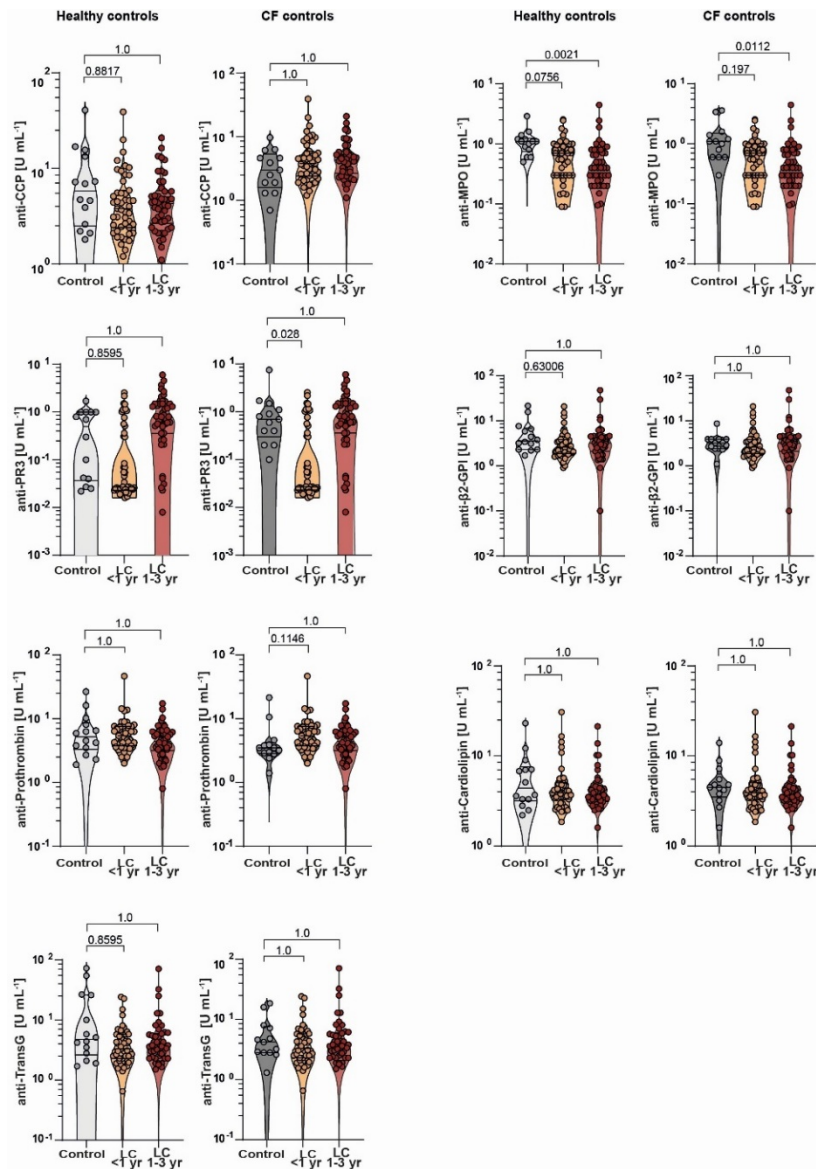
22 **Supplementary Fig. 2 | Systemic cytokines not significantly elevated in paediatric LC.** a-c,  
 23 Cytokine concentrations in controls (n = 27) and paediatric LC stratified by TsincelIndex; repeated  
 24 measurements were averaged within participant and TsincelIndex, yielding one value per participant  
 25 per window (< 1 yr, n = 47; 1–3 yr, n = 45). Overall group differences were assessed using two-sided  
 26 Kruskal–Wallis tests followed by unadjusted Dunn’s post hoc pairwise comparisons versus controls.  
 27 P values from Dunn’s post hoc tests were adjusted using the Holm–Bonferroni method. Within-LC  
 28 comparisons across TsincelIndex windows were assessed using two-sided linear mixed-effects  
 29 models (LMMs), with TsincelIndex as a fixed effect and participant ID as a random intercept (see  
 30 Supplementary Table 2.4). Cytokines shown here did not differ significantly from controls and did  
 31 not increase significantly between LC < 1 yr and LC 1–3 yr. Box plots show the median (centre line)  
 32 and interquartile range (box, 25th–75th percentiles); whiskers indicate the minimum and maximum  
 33 values. Exact P values, as well as Holm–Bonferroni-adjusted P values, are reported in  
 34 Supplementary Table 2.3.

35

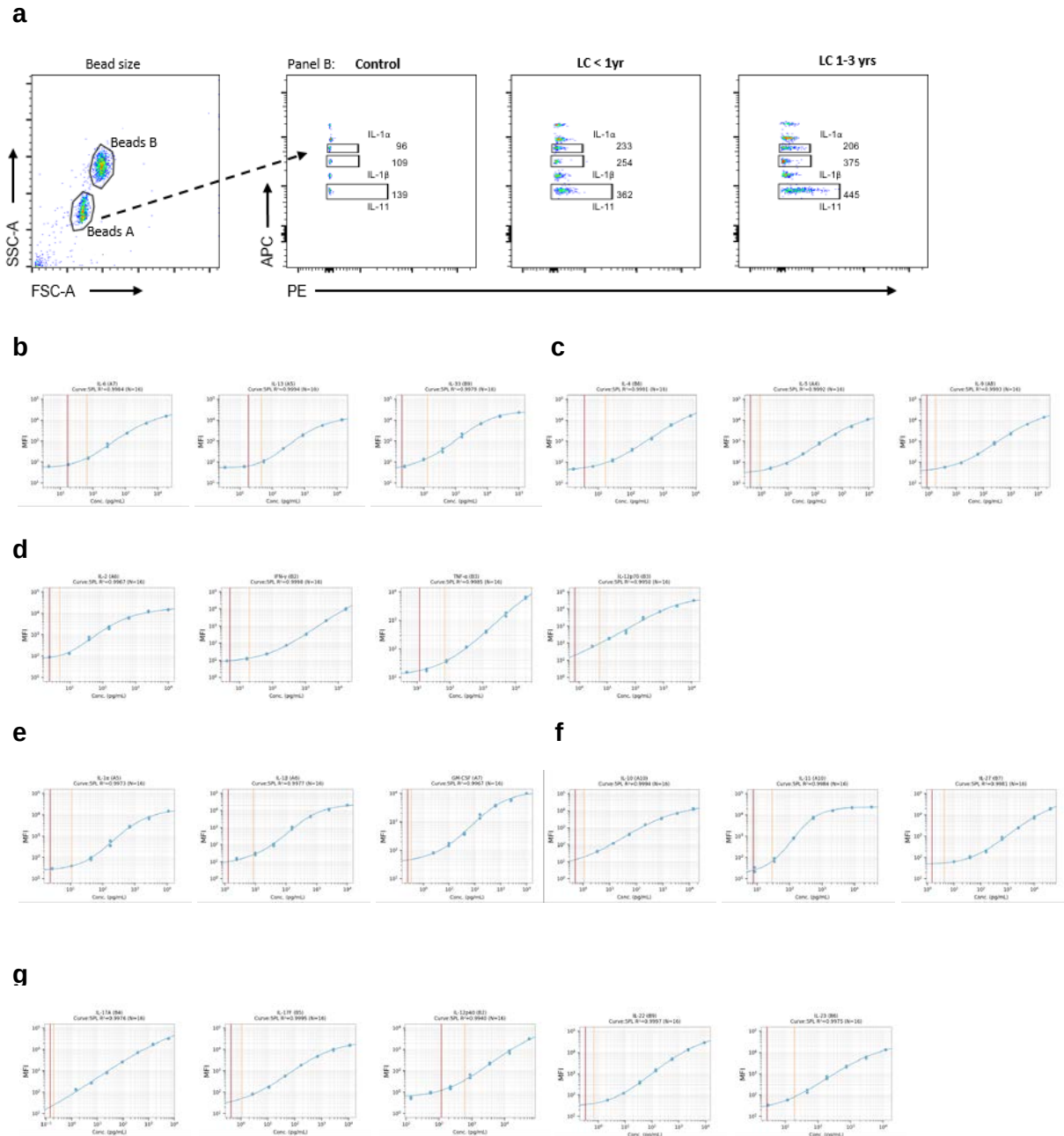


### Supplementary Fig. 3 | NfL, autoantibodies, complement, coagulation and anti-DFS70.

**a** Serum NfL percentile levels in LC patients at enrolment. **Left**, NfL percentiles stratified by Bell score ( $\leq 40$ ,  $n = 17$ ; red);  $> 40$ ,  $n = 42$ ; pink). Statistical analysis was performed using a two-sided Welch's t-test (mean difference =  $-22.60$ , 95% CI =  $-38.22$  to  $-6.99$ ,  $P = 0.0058$ , effect size =  $0.1969$ ). **Right**, NfL percentiles ( $n = 73$ ) were plotted against TsincIndex (wk); Pearson's correlation coefficient  $r$ , two-sided  $P$  value and the fitted regression line (brown) are shown. The 97.5th and 90th percentiles are indicated as dotted reference lines. **b**, AAb readouts against muscarinic acetylcholine receptors (anti-M-mAChR) and  $\beta$ -adrenergic receptors (anti- $\beta$ -AdrR) in paediatric LC stratified by TsincIndex. For visualisation, LC patients were grouped in TsincIndex windows and repeated measurements were averaged within each participant and TsincIndex window to one value per individual ( $< 1$  yr,  $n = 48$ ; light orange; 1–3 yr,  $n = 45$ ; dark orange). Within-LC comparisons over the complete time course were assessed using a two-sided LMM ( $n = 139$  observations), with TsincIndex as a fixed effect and participant ID as a random intercept;  $P$  values were adjusted for multiple comparisons using Holm–Bonferroni. **c**, Concentrations of complement factors C3 and C4 in anti-DFS70-positive patients (orange) versus anti-DFS70-negative patients (beige).  $P$  values were adjusted using the Holm–Bonferroni method. **d**, Box plots showing coagulation factors in anti-DFS70-positive ( $n = 7$ ; orange) and anti-DFS70-negative patients ( $n = 39$ ; beige), as indicated. **e**, AAb readouts against muscarinic acetylcholine receptors (anti-M-mAChR) and  $\beta$ -adrenergic receptors (anti- $\beta$ -AdrR) in anti-DFS70-positive (orange) versus anti-DFS70-negative (beige) paediatric LC participants, as indicated. For **c–e**, associations were assessed using a two-sided LMM; participant ID included as a random intercept;  $P$  values were adjusted using the Holm–Bonferroni method. **a–e**, Each dot represents an individual participant; box plots show the median (centre line) and interquartile range (box, 25th–75th percentiles); whiskers indicate the minimum and maximum values. Exact  $P$  values are reported for **b** in Supplementary Table 3.2, for **c–e** in Supplementary Table 3.4.



**Supplementary Fig. 4 | Sensitivity analysis of pooled controls (Fig. 3): autoantibodies using stratified control subgroups.** AAb titres (anti-CCP, anti-MPO, anti-PR3, anti-β2-glycoprotein I (anti-β2GPI), anti-Cardiolipin and anti-Prothrombin; U mL<sup>-1</sup>; log<sub>10</sub> scale) are shown. Overall group differences were assessed using a two-sided Kruskal–Wallis test, followed by adjusted Dunn’s post hoc pairwise comparisons versus controls. Left panels: healthy controls (light grey) versus LC subgroups (LC < 1 yr light orange; 1–3 yr dark orange). Right panels: clinically stable cystic fibrosis (CF) controls (dark grey) versus LC subgroups (LC < 1 yr light orange; 1–3 yr dark orange). Violin plots show distributions with individual data points overlaid; centre line indicates the median and boxes the IQR; whiskers indicate the minimum and maximum values. P values are reported in Supplementary Table 3.3b, c in addition to adjusted P values using the Holm–Bonferroni method across all autoantibodies (n = 6). This figure serves as a sensitivity analysis for the pooled-control comparisons reported in Fig. 3. Exact P values are reported in Supplementary Table 3.3. The direction of effects was similar for both control subgroups and the pooled-control analysis shown in Figs. 2 and 3.



**Supplementary Fig. 5 | Standard settings for cytokine quantification.** (a) Representative dot plots of multiplex bead-based assay serum analysis from control group, LC patients within the first year and later years of disease. Analysis is shown for the Human Cytokine Panel 2 cytokines IL-1 $\alpha$ , IL-1 $\beta$ , and IL-11 among others. Each population represents the acquisition of a specific cytokine, the numbers represent the mean fluorescence intensity (MFI). (b-g) Standard curve concentration range measured for cytokines in the LEGENDplex Human Th Cytokine Panel or LEGENDplex Human Cytokine Panel 2 for (b) SARS-CoV-2 related cytokines, (c) Th2/9 related cytokines, (d) Th1 related cytokines, (e) innate like cytokines, (f) regulatory cytokines and (g) Th17/22 related cytokines. The blue line represents the measured standard curve (mean fluorescence intensity), which was fitted using a five-parameter logistic (5PL) model with the LEGENDplex™ Data Analysis Software. The red vertical line indicates the calculated limit of detection (LOD) and the orange line indicates the limit of quantification (LOQ). These limits are derived from the fitted curve in the software and represent the theoretical concentrations at which the assay can detect and quantify the analyte, respectively.

**Supplementary Table 1a | Demographic and clinical characteristics of participants.** Values are shown as mean/SD or n (%), unless otherwise indicated. Group comparisons were performed using two-sided Pearson's  $\chi^2$  tests for categorical variables, and  $\chi^2$  statistics with corresponding P values are reported in the table unless otherwise indicated. Although age is displayed as a continuous variable (mean/SD), the reported group comparison for age is based on the prespecified age category of 0–14 years versus >14 years, as shown in Fig. 1b. Holm–Bonferroni-adjusted P values were applied only to the prespecified comparisons of age category and sex; all remaining P values are unadjusted. Atopy was defined based on parent-reported physician-diagnosed atopy, excluding drug allergies, and was analysed only among participants with known atopy status. VOC denotes variant of concern. In cases in which two SARS-CoV-2 variants qualified as variants of concern (VOCs), the later-emerging variant was assigned because of its higher transmissibility (Robert-Koch Institute (2025), Berlin, Germany. [www.rki.de](http://www.rki.de) (Accessed: 11\_03\_2025)). For participants with multiple infections,  $t_0$  was defined as the infection after which LC symptoms first appeared, typically the most recent infection preceding LC onset.

|                                                 | LC patients | Control participants | LC to Control $\chi^2$ (P) |
|-------------------------------------------------|-------------|----------------------|----------------------------|
| <b>General</b>                                  |             |                      |                            |
| N                                               | 74          | 27                   |                            |
| Age (mean/SD)                                   | 14.1/2.5    | 10.9/5.15            | 0.0589 (0.5800)            |
| Sex female                                      | 43 (58 %)   | 15 (56 %)            | 1.1300 (0.6341)            |
| Percentile BMI (mean/SD)                        | 48.5/31.7   |                      |                            |
| Enrollment (TsinceIndex) (wk) (mean/SD)         | 47.5/23.2   |                      |                            |
| Follow-up (TsinceIndex) (wk) (mean/SD)          | 64.2/24.0   |                      |                            |
| Pre-born (< 37 GA) yes/no/not reported          | 7/66/1      | 0/0/27               |                            |
| <b>SARS-CoV-2-related</b>                       |             |                      |                            |
| Tested for COVID-19                             |             |                      |                            |
| Anti-Nucleocapsid ab                            | 72/74       |                      |                            |
| Anti-Spike ab                                   | 71/74       |                      |                            |
| Parents reported yes/no/not reported            | 74/0/0      | 10/10/7              |                            |
| SARS-CoV-2 infections prior LC, N° 1/2/3        | 45/28/1     |                      |                            |
| SARS-CoV-2 vaccinations prior LC, N° 0/1/2/3/4  | 37/9/21/6/1 |                      |                            |
| <b>Chronic disease prior LC</b>                 |             |                      |                            |
| Attention Deficit Hyperactivity Disorder (ADHD) | 4 (5.4 %)   |                      |                            |
| Lactose or Fructose Malabsorption               | 7 (9.5 %)   |                      |                            |
| Obesity                                         | 2 (2.7 %)   |                      |                            |
| Dyslexia                                        | 2 (2.7 %)   |                      |                            |
| Migraine (including chronic headaches)          | 4 (5.4 %)   |                      |                            |
| Gilbert-Meulengracht-Syndrome                   | 1 (1.4 %)   |                      |                            |
| Fetal Alcohol Spectrum Disorder                 | 1 (1.4 %)   |                      |                            |
| Loeys-Dietz Syndrome                            | 1 (1.4 %)   |                      |                            |
| Non-Alcoholic Fatty Liver Disease               | 1 (1.4%)    |                      |                            |
| Scoliosis                                       | 1 (1.4%)    |                      |                            |

|                                                                                                 | LC patients | Control participants | LC to Control $\chi^2$ (P) |
|-------------------------------------------------------------------------------------------------|-------------|----------------------|----------------------------|
| Acne                                                                                            | 1 (1.4 %)   |                      |                            |
| Visual Disturbances                                                                             | 1 (1.4 %)   |                      |                            |
| Sensory Processing Disorder                                                                     | 1 (1.4 %)   |                      |                            |
| Bronchial Asthma                                                                                | 3 (4.1 %)   |                      |                            |
| Coronary Fistula,<br>Tricuspid Functionally Bicuspid Aortic Valve,<br>Mild Mitral Regurgitation | 1 (1.4%)    |                      |                            |
| Divergent Strabismus                                                                            | 1 (1.4 %)   |                      |                            |
| Myofascial Pain Syndrome (Thoracolumbar)                                                        | 1 (1.4 %)   |                      |                            |
| Psychogenic Gait Disorder, Suspected Arterial Hypertension                                      | 1 (1.4 %)   |                      |                            |
| Hashimoto's Thyroiditis                                                                         | 1 (1.4 %)   |                      |                            |
| Chromosome 13 Anomaly                                                                           | 1 (1.4 %)   |                      |                            |
| Cystic Fibrosis                                                                                 | 0 (0 %)     | 13 (48 %)            | 40.8800 (< 0.0001)         |
| Atopy (excluding drug allergies) yes/no/unknown                                                 | 26/48/0     | 3/16/8               | 1.6070 (0.2049)            |
| No Prior Illness                                                                                | 37 (50.0 %) | 14 (52 %)            | 0.0274 (0.8685)            |
| <b>Dominant VOC in Germany during SARS-CoV-2 infection, N° (%)</b>                              |             |                      |                            |
| Ancestral and Alpha                                                                             | 6 (8.1 %)   |                      |                            |
| Delta                                                                                           | 18 (24.3 %) |                      |                            |
| Omicron                                                                                         | 50 (67.6 %) |                      |                            |

\* Group comparison for age is based on the prespecified age category of 0–14 years versus >14 years. Holm–Bonferroni-adjusted P values were applied to age category and sex (see Fig. 1b).

**Supplementary Table 1b | Upper part:** Lack of physical and mental health recovery in paediatric LC patients over time. **Lower part:** Summary details of two-sided LMMs for predisposing factors of paediatric LC and their association with disease severity within the first year after LC onset and across the whole disease course. Related to Fig. 1e. Dependent variables are listed in the leftmost column. In the upper part, two-sided LMMs included TsinceIndex as the only fixed effect and participant ID as a random intercept. In the lower part, extended two-sided LMMs included TsinceIndex, comorbidity, number of vaccinations, sex, and age as fixed effects, with participant ID included as a random intercept to account for repeated measurements. Marginal  $R^2$  ( $R^2_m$ ), reflecting the variance explained by the fixed effects, and corresponding raw P values are shown for models within the first year after LC onset and across the whole disease course; Holm–Bonferroni-adjusted P values are additionally reported for the extended models. In whole-disease-course models, TsinceIndex was modelled as a continuous covariate. Additional lower panels summarize the corresponding model outputs for each outcome, reporting marginal  $R^2$ , F statistics with numerator and residual degrees of freedom, parameter estimates, 95% confidence intervals, and raw P values. Multiple-testing correction was performed using the Holm–Bonferroni method. Abbreviations: CSHQ, Children's Sleep Habits Questionnaire; FSS, Fatigue Severity Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; KIDSCREEN, KIDSCREEN Questionnaire; PHQ-9, Patient Health Questionnaire 9-item; SF-12 MCS, Short Form-12 Mental Component Summary; SF-12 PCS, Short Form-12 Physical Component Summary; STS, Sit-to-Stand Test.

| Outcome                            | LC < 1 yr        |        | LC whole disease course |        | Adj. P | LC whole disease course<br>Extended for potential confounders |        |        |
|------------------------------------|------------------|--------|-------------------------|--------|--------|---------------------------------------------------------------|--------|--------|
|                                    | R <sup>2</sup> m | P      | R <sup>2</sup> m        | P      |        | R <sup>2</sup> m                                              | P      | Adj. P |
| SF-12 PCS                          | 0.0077           | 0.4360 | 0.0387                  | 0.0308 | 0.2980 | 0.1194                                                        | 0.0936 | 0.8424 |
| Bell score                         | 0.0215           | 0.1498 | 0.0059                  | 0.4176 | 1.0000 | 0.0969                                                        | 0.3534 | 1.0000 |
| SF-12 MCS                          | 0.0001           | 0.9085 | 0.0150                  | 0.1582 | 0.7910 | 0.0798                                                        | 0.4276 | 1.0000 |
| PHQ-9                              | 0.0003           | 0.8574 | 0.0715                  | 0.0017 | 0.0187 | 0.1046                                                        | 0.0661 | 0.6610 |
| GAD-7                              | 0.0033           | 0.5359 | 0.0346                  | 0.0298 | 0.2980 | 0.0595                                                        | 0.5244 | 1.0000 |
| FSS                                | 0.0001           | 0.9154 | 0.0147                  | 0.1703 | 0.7910 | 0.0445                                                        | 0.7531 | 1.0000 |
| Sit-to-Stand                       | 0.0095           | 0.4619 | 0.0004                  | 0.8365 | 1.0000 | 0.0350                                                        | 0.8796 | 1.0000 |
| KIDSCREEN-10                       | 0.0007           | 0.7870 | 0.0332                  | 0.0429 | 0.3430 | 0.0992                                                        | 0.1904 | 1.0000 |
| Parents-reported symptoms (acute)  | 0.0063           | 0.3962 | 0.0177                  | 0.1312 | 0.7872 | 0.0954                                                        | 0.3468 | 1.0000 |
| Patients-reported symptoms (acute) | 0.0031           | 0.6277 | 0.0070                  | 0.3759 | 1.0000 | 0.1309                                                        | 0.1976 | 1.0000 |
| CSHQ Post                          | 0.0163           | 0.1403 | 0.0306                  | 0.0492 | 0.3432 | 0.1754                                                        | 0.0086 | 0.0946 |

129

| Outcome                            | obs (n) | R <sup>2</sup> m | F (df1, df2)        | Estimate | 95% CI            |
|------------------------------------|---------|------------------|---------------------|----------|-------------------|
| SF-12 PCS                          | 71      | 0.0077           | 0.6152 (1, 57.9754) | 0.9617   | -1.6327 to 3.2216 |
| Bell score                         | 57      | 0.0215           | 2.2046 (1, 25.6833) | 3.3658   | -1.1809 to 7.9126 |
| SF-12 MCS                          | 71      | 0.0001           | 0.0134 (1, 36.9996) | 0.1116   | -1.8133 to 2.0365 |
| PHQ-9                              | 71      | 0.0003           | 0.0327 (1, 39.9166) | -0.0085  | -0.1020 to 0.0838 |
| GAD-7                              | 71      | 0.0033           | 0.3900 (1, 39.9347) | -0.2625  | -1.0393 to 0.5526 |
| FSS                                | 71      | 0.0001           | 0.0114 (1, 40.9838) | 0.0144   | -0.2324 to 0.2901 |
| Sit-to-Stand                       | 58      | 0.0095           | 0.5487 (1, 56.0000) | 1.0707   | -1.6073 to 3.6838 |
| KIDSCREEN-10                       | 71      | 0.0007           | 0.0739 (1, 44.2334) | -0.1983  | -1.6648 to 1.2983 |
| Parents-reported symptoms (acute)  | 49      | 0.0063           | 0.7625 (1, 15.0926) | -0.9424  | -2.9751 to 1.2933 |
| Patients-reported symptoms (acute) | 46      | 0.0031           | 0.2427 (1, 19.8793) | -0.8713  | -4.3426 to 2.7957 |
| CSHQ Post                          | 66      | 0.0163           | 2.2844 (1, 32.4731) | -0.9825  | -2.3042 to 0.2920 |

130

| Outcome                            | obs (n) | R <sup>2</sup> m | F (df1, df2)          | Estimate | 95% CI             |
|------------------------------------|---------|------------------|-----------------------|----------|--------------------|
| SF-12 PCS                          | 141     | 0.0387           | 4.7776 (1, 121.3861)  | 2.2258   | 0.2304 to 4.2190   |
| Bell score                         | 121     | 0.0059           | 0.6616 (1, 118.0879)  | 1.6777   | -2.4072 to 5.7626  |
| SF-12 MCS                          | 141     | 0.015            | 2.0126 (1, 138.2573)  | 1.3858   | -0.5458 to 3.3174  |
| PHQ-9                              | 141     | 0.0715           | 10.2400 (1, 138.4613) | -0.0588  | -0.0934 to -0.0216 |
| GAD-7                              | 141     | 0.0346           | 4.8220 (1, 138.7378)  | -0.8741  | -1.6058 to -0.1301 |
| FSS                                | 139     | 0.0147           | 1.9005 (1, 135.7324)  | -0.1892  | -0.4487 to 0.0688  |
| Sit-to-Stand                       | 115     | 0.0004           | 0.0428 (1, 113.0000)  | -0.1806  | -1.8232 to 1.5667  |
| KIDSCREEN-10                       | 141     | 0.0332           | 4.1804 (1, 130.3642)  | 1.633    | 0.0178 to 3.0429   |
| Parents-reported symptoms (acute)  | 112     | 0.0177           | 2.3145 (1, 103.0605)  | -1.6274  | -3.6211 to 0.5942  |
| Patients-reported symptoms (acute) | 104     | 0.007            | 0.7913 (1, 98.9570)   | -1.1288  | -3.4045 to 1.4820  |
| CSHQ Post                          | 134     | 0.0306           | 3.9399 (1, 131.4937)  | -1.2849  | -2.4790 to -0.0358 |

131

## Lower part | Predisposing factors for paediatric LC do not associate with disease severity.

Two-sided LMMs across the whole LC disease course were fitted with disease severity outcomes, including Bell score, questionnaire-based measures, and sit-to-stand performance. Fixed effects included comorbidity (yes vs no), sex (male = 1, female = 0), SARS-CoV-2 variant of concern (VOC) wave, number of infections prior to LC onset, number of vaccinations, TsincIndex (wk), and age (yr); participant ID was modelled as a random intercept. Degrees of freedom were approximated using Satterthwaite's method, and 95% confidence intervals were obtained from 1,000 bootstrap samples. Shown are marginal  $R^2$  values ( $R^2_m$ ), F statistics with numerator and residual degrees of freedom, fixed-effect estimates, 95% confidence intervals (CI), and raw P values; Holm–Bonferroni-adjusted P values are additionally reported for the extended models in Supplementary Table 1b, upper part. Positive estimates indicate higher outcome values relative to the reference category or per unit increase in the predictor. Continuous predictors were standardized. VOC wave was tested as a global omnibus factor; only omnibus F statistics are shown in this summary table. Individual category contrasts of each VOC wave are not displayed.

| SF12 PCS                       |                      |          |                    |        |
|--------------------------------|----------------------|----------|--------------------|--------|
| Predictor                      | F (df1, df2)         | Estimate | 95% CI             | P      |
| Comorbidity                    | 0.5600 (1, 65.3422)  | -3.0869  | -11.2485 to 5.0747 | 0.4570 |
| Time since last infection (wk) | 4.5990 (1, 130.9852) | 2.9366   | 0.2273 to 5.6459   | 0.0338 |
| Number of vaccinations         | 0.3351 (1, 67.4851)  | 0.7201   | -1.7410 to 3.1812  | 0.5646 |
| Age                            | 2.1222 (1, 70.9744)  | -1.7549  | -4.1384 to 0.6285  | 0.1496 |
| Sex (M=1, F=0)                 | 1.9002 (1, 68.4230)  | 3.3895   | -1.4754 to 8.2545  | 0.1725 |
| Infections since LC onset      | 0.4874 (1, 66.4257)  | 0.8654   | -1.5871 to 3.3179  | 0.4875 |
| VOC wave                       | 1.1936 (3, 69.8388)  |          |                    | 0.3186 |

| Bell score                     |                     |          |                    |        |
|--------------------------------|---------------------|----------|--------------------|--------|
| Predictor                      | F (df1, df2)        | Estimate | 95% CI             | P      |
| Comorbidity                    | 1.2924 (1, 60.1293) | -10.1347 | -27.8038 to 7.5343 | 0.2601 |
| Time since last infection (wk) | 0.9240 (1, 95.4803) | 2.6750   | -2.8403 to 8.1903  | 0.3388 |
| Number of vaccinations         | 1.4056 (1, 67.9018) | -3.2270  | -8.6217 to 2.1677  | 0.2399 |
| Age                            | 2.9240 (1, 73.6458) | 4.4614   | -0.7096 to 9.6324  | 0.0915 |
| Sex (M=1, F=0)                 | 1.8030 (1, 70.3705) | 7.1735   | -3.4149 to 17.7620 | 0.1837 |
| Infections since LC onset      | 0.1607 (1, 66.6720) | -1.0839  | -6.4430 to 4.2752  | 0.6898 |
| VOC wave                       | 0.7066 (3, 73.3764) |          |                    | 0.5511 |

| SF12 MCS                       |                      |          |                   |        |
|--------------------------------|----------------------|----------|-------------------|--------|
| Predictor                      | F (df1, df2)         | Estimate | 95% CI            | P      |
| Comorbidity                    | 0.0005 (1, 63.9367)  | -0.0999  | -9.2065 to 9.0068 | 0.9828 |
| Time since last infection (wk) | 2.5236 (1, 116.1654) | 1.9484   | -0.4783 to 4.3751 | 0.1149 |
| Number of vaccinations         | 0.4374 (1, 69.7870)  | -0.9082  | -3.6252 to 1.8088 | 0.5106 |
| Age                            | 2.7907 (1, 76.4903)  | 2.1925   | -0.4042 to 4.7892 | 0.0989 |
| Sex (M=1, F=0)                 | 0.1985 (1, 70.4260)  | 1.2064   | -4.1511 to 6.5638 | 0.6573 |
| Infections since LC onset      | 0.0655 (1, 67.3989)  | 0.3518   | -2.3676 to 3.0712 | 0.7988 |
| VOC wave                       | 1.0488 (3, 70.1080)  |          |                   | 0.3765 |

| PHQ-9       |                     |          |                   |        |
|-------------|---------------------|----------|-------------------|--------|
| Predictor   | F (df1, df2)        | Estimate | 95% CI            | P      |
| Comorbidity | 0.2679 (1, 65.2099) | 1.1118   | -3.2105 to 5.1007 | 0.6065 |

|                                |                       |         |                    |        |
|--------------------------------|-----------------------|---------|--------------------|--------|
| Time since last infection (wk) | 10.9641 (1, 117.8810) | -1.9200 | -3.0522 to -0.8317 | 0.0012 |
| Number of vaccinations         | 0.1949 (1, 70.8146)   | -0.2831 | -1.5601 to 0.9624  | 0.6602 |
| Age                            | 2.4997 (1, 77.3251)   | 0.9699  | -0.1664 to 2.2829  | 0.1180 |
| Sex (M=1, F=0)                 | 0.0460 (1, 71.5129)   | -0.2712 | -2.7087 to 2.2526  | 0.8308 |
| Infections since LC onset      | 0.4677 (1, 68.5373)   | -0.4389 | -1.7189 to 0.7897  | 0.4963 |
| VOC wave                       | 0.7534 (3, 71.3377)   |         |                    | 0.5240 |

| GAD-7                          |                      |          |                    |        |
|--------------------------------|----------------------|----------|--------------------|--------|
| Predictor                      | F (df1, df2)         | Estimate | 95% CI             | P      |
| Comorbidity                    | 0.1469 (1, 64.0794)  | 0.7399   | -2.8061 to 4.6602  | 0.7028 |
| Time since last infection (wk) | 3.9282 (1, 114.0392) | -0.9965  | -2.0017 to -0.0747 | 0.0499 |
| Number of vaccinations         | 1.3680 (1, 70.3584)  | -0.6727  | -1.8649 to 0.5133  | 0.2461 |
| Age                            | 1.2044 (1, 77.3295)  | 0.6023   | -0.4794 to 1.7046  | 0.2759 |
| Sex (M=1, F=0)                 | 0.0050 (1, 70.8732)  | -0.0799  | -2.3701 to 2.1551  | 0.9440 |
| Infections since LC onset      | 0.0909 (1, 67.7733)  | -0.1737  | -1.2652 to 0.9806  | 0.7639 |
| VOC wave                       | 0.3045 (3, 70.3033)  |          |                    | 0.8221 |

| FSS                            |                      |          |                   |        |
|--------------------------------|----------------------|----------|-------------------|--------|
| Predictor                      | F (df1, df2)         | Estimate | 95% CI            | P      |
| Comorbidity                    | 0.1847 (1, 65.4013)  | 0.2794   | -1.0527 to 1.5825 | 0.6688 |
| Time since last infection (wk) | 4.1631 (1, 114.9780) | -0.3574  | -0.6951 to 0.0015 | 0.0436 |
| Number of vaccinations         | 0.4699 (1, 71.7878)  | 0.1334   | -0.2302 to 0.4988 | 0.4952 |
| Age                            | 0.0493 (1, 77.7964)  | 0.0412   | -0.3073 to 0.4123 | 0.8249 |
| Sex (M=1, F=0)                 | 0.0703 (1, 72.1810)  | 0.1016   | -0.6163 to 0.8438 | 0.7916 |
| Infections since LC onset      | 0.0230 (1, 69.2800)  | -0.0295  | -0.4037 to 0.3755 | 0.8798 |
| VOC wave                       | 1.0019 (3, 71.8813)  |          |                   | 0.3971 |

| Sit-to-Stand                   |                      |          |                   |        |
|--------------------------------|----------------------|----------|-------------------|--------|
| Predictor                      | F (df1, df2)         | Estimate | 95% CI            | P      |
| Comorbidity                    | 0.1948 (1, 105.0000) | 1.4477   | -4.8471 to 7.9192 | 0.6598 |
| Time since last infection (wk) | 0.1598 (1, 105.0000) | -0.5703  | -3.3318 to 2.2614 | 0.6902 |
| Number of vaccinations         | 0.0165 (1, 105.0000) | 0.1325   | -1.7183 to 2.0435 | 0.8980 |
| Age                            | 0.0300 (1, 105.0000) | -0.1791  | -2.2784 to 1.7360 | 0.8628 |
| Sex (M=1, F=0)                 | 0.0030 (1, 105.0000) | -0.1127  | -4.0655 to 3.8068 | 0.9564 |
| Infections since LC onset      | 2.3320 (1, 105.0000) | -1.5764  | -3.5202 to 0.4445 | 0.1297 |
| VOC wave                       | 0.1913 (3, 105.0000) |          |                   | 0.9021 |

| KIDSCREEN-10                   |                      |          |                   |        |
|--------------------------------|----------------------|----------|-------------------|--------|
| Predictor                      | F (df1, df2)         | Estimate | 95% CI            | P      |
| Comorbidity                    | 0.7976 (1, 66.6497)  | -3.0969  | -9.9059 to 3.3736 | 0.3750 |
| Time since last infection (wk) | 5.6512 (1, 127.5320) | 2.4870   | 0.4585 to 4.7356  | 0.0189 |
| Number of vaccinations         | 0.3752 (1, 70.3257)  | -0.6381  | -2.6421 to 1.2969 | 0.5421 |
| Age                            | 0.1711 (1, 75.2767)  | -0.4150  | -2.3034 to 1.5889 | 0.6803 |
| Sex (M=1, F=0)                 | 0.0547 (1, 71.3058)  | -0.4812  | -4.5413 to 3.5913 | 0.8157 |
| Infections since LC onset      | 2.2721 (1, 68.7965)  | 1.5673   | -0.3321 to 3.4805 | 0.1363 |

|          |                     |  |  |        |
|----------|---------------------|--|--|--------|
| VOC wave | 1.3854 (3, 72.1633) |  |  | 0.2541 |
|----------|---------------------|--|--|--------|

| Parent-reported symptoms       |                     |          |                    |        |
|--------------------------------|---------------------|----------|--------------------|--------|
| Predictor                      | F (df1, df2)        | Estimate | 95% CI             | P      |
| Comorbidity                    | 0.3839 (1, 61.7676) | 3.1457   | -6.8637 to 13.3701 | 0.5378 |
| Time since last infection (wk) | 3.2688 (1, 65.0432) | -2.4876  | -5.3153 to 0.2793  | 0.0752 |
| Number of vaccinations         | 0.0733 (1, 63.5671) | -0.4193  | -3.3004 to 2.7563  | 0.7875 |
| Age                            | 0.7672 (1, 74.0777) | 1.2872   | -1.5525 to 4.1955  | 0.3839 |
| Sex (M=1, F=0)                 | 2.2378 (1, 66.4193) | -4.4794  | -9.9808 to 1.0259  | 0.1394 |
| Infections since LC onset      | 0.7852 (1, 63.8024) | -1.3765  | -4.4935 to 1.4554  | 0.3789 |
| VOC wave                       | 1.1118 (3, 68.3231) |          |                    | 0.3504 |

| Patient-reported symptoms      |                     |          |                    |        |
|--------------------------------|---------------------|----------|--------------------|--------|
| Predictor                      | F (df1, df2)        | Estimate | 95% CI             | P      |
| Comorbidity                    | 0.9669 (1, 59.1974) | 5.4884   | -6.1590 to 16.4502 | 0.3295 |
| Time since last infection (wk) | 0.6565 (1, 65.5877) | -1.3456  | -4.5342 to 1.9493  | 0.4207 |
| Number of vaccinations         | 0.1125 (1, 59.7655) | -0.5829  | -4.0278 to 2.9011  | 0.7385 |
| Age                            | 6.4961 (1, 73.2604) | 4.7332   | 0.8450 to 8.2929   | 0.0129 |
| Sex (M=1, F=0)                 | 1.7257 (1, 61.6299) | -4.4647  | -11.2433 to 2.3144 | 0.1938 |
| Infections since LC onset      | 0.0624 (1, 62.4659) | -0.4405  | -3.8429 to 2.8847  | 0.8036 |
| VOC wave                       | 0.1761 (3, 64.4650) |          |                    | 0.9122 |

| CSHQ                           |                      |          |                    |        |
|--------------------------------|----------------------|----------|--------------------|--------|
| Predictor                      | F (df1, df2)         | Estimate | 95% CI             | P      |
| Comorbidity                    | 0.1534 (1, 67.0516)  | 1.0812   | -4.0973 to 6.5358  | 0.6965 |
| Time since last infection (wk) | 2.3962 (1, 113.9604) | -1.2340  | -2.8364 to 0.3266  | 0.1244 |
| Number of vaccinations         | 0.4726 (1, 68.6310)  | -0.5639  | -2.2104 to 1.0328  | 0.4941 |
| Age                            | 9.6150 (1, 74.7450)  | -2.4777  | -3.9515 to -0.9407 | 0.0027 |
| Sex (M=1, F=0)                 | 0.0233 (1, 70.6122)  | -0.2473  | -3.2816 to 2.8808  | 0.8792 |
| Infections since LC onset      | 0.3570 (1, 67.3047)  | 0.4887   | -1.1410 to 2.0781  | 0.5522 |
| VOC wave                       | 1.4520 (3, 69.9846)  |          |                    | 0.2351 |

**Supplementary Table 1c | No differences in systemic cytokine concentrations between control subgroups.** Controls with CF (n = 14) were compared with controls without CF (n = 13). Two-sided Mann–Whitney U test P values (P), U statistics (U), rank-biserial correlations (r<sub>rb</sub>), and Holm–Bonferroni-adjusted P values are given for all cytokines included in this comparison. The significance concentration was set at  $\alpha = 0.05$ . Adjusted P values (Adj. P) were capped at 1.0.

| Cytokine     | U statistics | P      | r <sub>rb</sub> | Adj. P |
|--------------|--------------|--------|-----------------|--------|
| IL-1 $\beta$ | 85.0         | 0.7882 | -0.0659         | 1.0000 |
| GM-CSF       | 90.0         | 0.9797 | -0.0110         | 1.0000 |
| IL-11        | 80.0         | 0.6030 | -0.1209         | 1.0000 |
| IL-12p40     | 81.0         | 0.6445 | -0.1099         | 1.0000 |
| IL-12p70     | 83.0         | 0.7158 | 0.0879          | 1.0000 |
| IL-15        | 75.5         | 0.4666 | -0.1703         | 1.0000 |

| Cytokine      | U statistics | P      | r <sub>rb</sub> | Adj. P |
|---------------|--------------|--------|-----------------|--------|
| IL-18         | 75.0         | 0.4583 | 0.1758          | 1.0000 |
| IL-23         | 70.0         | 0.3195 | 0.2308          | 1.0000 |
| IL-27         | 51.0         | 0.0543 | -0.4396         | 1.0000 |
| IL-5          | 77.5         | 0.5218 | 0.1484          | 1.0000 |
| IL-13         | 76.5         | 0.478  | -0.1593         | 1.0000 |
| IL-6          | 82.0         | 0.6618 | 0.0989          | 1.0000 |
| IL-10         | 66.0         | 0.2293 | 0.2747          | 1.0000 |
| IFN $\gamma$  | 88.5         | 0.3400 | -0.1868         | 1.0000 |
| TNF $\alpha$  | 71.0         | 0.9226 | 0.0275          | 1.0000 |
| IL-22         | 62.0         | 0.3438 | 0.2198          | 1.0000 |
| IFN $\alpha$  | 62.0         | 0.1665 | -0.3187         | 1.0000 |
| IL-1 $\alpha$ | 78.0         | 0.5252 | 0.1429          | 1.0000 |

**Supplementary Table 1d | Full analysis and sensitivity analysis of lead cytokines using stratified control subgroups.** Related to Table 2 of the main text. Predefined lead cytokines, one representing each functional cytokine family, are shown for pairwise comparisons between paediatric LC subgroups stratified by time since index infection and different control subgroups. LC subgroups were defined as LC < 1 year and LC 1–3 yr. The top panels show comparisons of all controls combined (healthy + CF) versus LC subgroups and healthy controls versus LC subgroups, whereas the lower panel shows comparisons of clinically stable cystic fibrosis (CF) controls versus LC subgroups. Arrows indicate the direction of change relative to the respective control subgroup ( $\uparrow$  higher in LC,  $\downarrow$  lower in LC,  $\leftrightarrow$  no difference). These analyses were performed to assess the robustness of the pooled-control comparisons reported in Table 2. Overall group differences were assessed using two-sided Kruskal–Wallis tests, followed by unadjusted Dunn’s post hoc pairwise comparisons, where applicable, versus the respective control subgroup. P values are reported for each comparison. Holm–Bonferroni adjustment for multiple testing was applied across all five lead cytokines within each pairwise comparison set, and adjusted P values are shown. H statistics, 95% confidence intervals for each subgroup, Dunn’s Z values, and effect sizes (E) are reported.

#### All controls (healthy + CF) versus LC subgroups.

| Functional families  | Lead cytokines          | H statistic | 95% CI control | 95% CI LC < 1 yr | 95% CI LC 1–3 yr |
|----------------------|-------------------------|-------------|----------------|------------------|------------------|
| SARS-CoV-2-related   | IL-13                   | 18.33       | 14.88 to 32.27 | 17.96 to 47.90   | 11.95 to 30.08   |
| Th2/Th1-like balance | IL-4/IFN $\gamma$ ratio | 28.28       | 0.095 to 0.201 | 0.318 to 0.448   | 0.271 to 0.372   |
| Innate-related       | IL-1 $\beta$            | 23.62       | 2.334 to 13.08 | 4.965 to 14.13   | 6.190 to 16.41   |
| Regulatory-related   | IL-11                   | 12.32       | 7.102 to 12.27 | 13.42 to 26.46   | 11.22 to 23.83   |
| Th17/22-related      | IL-12p40                | 23.60       | 372.9 to 1039  | 668.8 to 1552    | 971.4 to 1770    |

| Functional families         | Lead cytokines          | P, direction<br>LC < 1 yr | Dunn's Z<br>LC < 1 yr | E<br>LC < 1 yr | Adj. P<br>LC < 1 yr | P, direction<br>LC 1–3 yr | Dunn's Z<br>LC 1–3 yr | E,<br>LC 1–3 yr | Adj. P<br>LC 1–3 yr |
|-----------------------------|-------------------------|---------------------------|-----------------------|----------------|---------------------|---------------------------|-----------------------|-----------------|---------------------|
| <b>SARS-CoV-2-related</b>   | IL-13                   | 0.0242 ↑                  | 2.508                 | 0.2894         | <b>0.048</b>        | 0.2466 ↔                  | 1.159                 | 0.4926          | 0.2466              |
| <b>Th2/Th1-like balance</b> | IL-4/IFN $\gamma$ ratio | <0.0001 ↑                 | 5.222                 | 0.6070         | <b>0.0005</b>       | <0.0001 ↑                 | 4.070                 | 0.4796          | <b>0.0005</b>       |
| <b>Innate-related</b>       | IL-1 $\beta$            | 0.0294 ↑                  | 2.178                 | 0.2515         | <b>0.0294</b>       | 0.002 ↑                   | 4.757                 | 0.5570          | <b>0.034</b>        |
| <b>Regulatory-related</b>   | IL-11                   | 0.001 ↑                   | 3.500                 | 0.4041         | <b>0.004</b>        | 0.017 ↑                   | 2.386                 | 0.2793          | <b>0.034</b>        |
| <b>Th17/22-related</b>      | IL-12p40                | 0.0102 ↑                  | 2.570                 | 0.2969         | <b>0.0306</b>       | 0.0002 ↑                  | 4.827                 | 0.5650          | <b>0.0008</b>       |

174

## 175 Healthy controls versus LC subgroups

| Functional families         | Lead cytokines    | H statistic | 95% CI<br>Healthy controls | 95% CI<br>LC < 1 yr | 95% CI<br>LC 1–3 yr |
|-----------------------------|-------------------|-------------|----------------------------|---------------------|---------------------|
| <b>SARS-CoV-2-related</b>   | IL-13             | 17.22       | 14.03 to 34.06             | 17.96 to 47.90      | 11.95 to 30.08      |
| <b>Th2/Th1-like balance</b> | IL-4/IFN $\gamma$ | 13.65       | 0.075 to 0.275             | 0.318 to 0.448      | 0.271 to 0.372      |
| <b>Innate-related</b>       | IL-1 $\beta$      | 15.40       | 0.537 to 21.17             | 4.965 to 14.13      | 6.190 to 16.41      |
| <b>Regulatory-related</b>   | IL-11             | 2.986       | 7.360 to 15.96             | 13.42 to 26.46      | 11.22 to 23.83      |
| <b>Th17/22-related</b>      | IL-12p40          | 10.92       | 323.1 to 1593              | 668.8 to 1552       | 971.4 to 1770       |

| Functional families         | Lead cytokines    | P & direction<br>LC <1 yr | Dunn's Z<br>LC < 1 yr | E<br>LC < 1 yr | Adj. P<br>LC <1 yr | P & direction<br>LC 1–3 yr | Dunn's Z<br>LC 1–3 yr | E<br>LC 1–3 yr | Adj. P<br>LC 1–3 yr |
|-----------------------------|-------------------|---------------------------|-----------------------|----------------|--------------------|----------------------------|-----------------------|----------------|---------------------|
| <b>SARS-CoV-2-related</b>   | IL-13             | 0.2143 ↑                  | 1.242                 | 0.1590         | 0.5826             | 0.1047 ↓                   | 1.623                 | 0.2113         | 0.2094              |
| <b>Th2/Th1-like balance</b> | IL-4/IFN $\gamma$ | 0.00021 ↑                 | 3.690                 | 0.4725         | <b>0.0011</b>      | 0.0053 ↑                   | 2.788                 | 0.3629         | <b>0.0196</b>       |
| <b>Innate-related</b>       | IL-1 $\beta$      | 0.1942 ↑                  | 1.298                 | 0.1662         | 0.5826             | 0.0008 ↑                   | 3.351                 | 0.4362         | <b>0.0040</b>       |
| <b>Regulatory-related</b>   | IL-11             | 0.0694 ↑                  | 1.816                 | 0.2325         | 0.2776             | 0.3356 ↑                   | 0.9629                | 0.1254         | 0.3356              |
| <b>Th17/22-related</b>      | IL-12p40          | 0.3118 ↑                  | 1.011                 | 0.1295         | 0.5826             | 0.0049 ↑                   | 2.813                 | 0.3662         | <b>0.0196</b>       |

## 182 CF controls versus LC subgroups.

| Functional families         | Lead cytokines    | H statistic | 95% CI<br>CF controls | 95% CI<br>LC < 1 yr | 95% CI<br>LC 1–3 yr |
|-----------------------------|-------------------|-------------|-----------------------|---------------------|---------------------|
| <b>SARS-CoV-2-related</b>   | IL-13             | 19.33       | 6.805 to 40.47        | 17.96 to 47.90      | 11.95 to 30.08      |
| <b>Th2/Th1-like balance</b> | IL-4/IFN $\gamma$ | 21.43       | 0.081 to 0.156        | 0.318 to 0.448      | 0.271 to 0.372      |
| <b>Innate-related</b>       | IL-1 $\beta$      | 19.50       | 1.887 to 8.787        | 4.965 to 14.13      | 6.190 to 16.41      |
| <b>Regulatory-related</b>   | IL-11             | 12.90       | 4.620 to 11.26        | 13.42 to 26.46      | 11.22 to 23.83      |
| <b>Th17/22-related</b>      | IL-12p40          | 24.55       | 216.6 to 745.0        | 668.8 to 1552       | 971.4 to 1770       |

183

| Functional families         | Lead cytokines    | P & direction LC <1 yr | Dunn's Z LC < 1 yr | E LC < 1 yr | Adj. P LC < 1 yr | P & direction LC 1–3 yr | Dunn's Z LC 1–3 yr | E LC 1–3 yr | Adj. P LC 1–3 yr |
|-----------------------------|-------------------|------------------------|--------------------|-------------|------------------|-------------------------|--------------------|-------------|------------------|
| <b>SARS-CoV-2-related</b>   | IL-13             | 0.0154 ↑               | 2.424              | 0.3129      | <b>0.0308</b>    | 0.7146 ↔                | 0.3657             | 0.0480      | 0.7146           |
| <b>Th2/Th1-like balance</b> | IL-4/IFN $\gamma$ | <0.0001 ↑              | 4.496              | 0.5805      | <b>0.0005</b>    | 0.0003 ↑                | 3.617              | 0.4750      | <b>0.0009</b>    |
| <b>Innate-related</b>       | IL-1 $\beta$      | 0.0644 ↑               | 1.850              | 0.2388      | 0.0644           | 0.0001 ↑                | 3.843              | 0.5047      | <b>0.0005</b>    |
| <b>Regulatory-related</b>   | IL-11             | 0.0006 ↑               | 3.451              | 0.4456      | <b>0.0024</b>    | 0.0089 ↑                | 2.615              | 0.3434      | <b>0.0178</b>    |
| <b>Th17/22-related</b>      | IL-12p40          | 0.0053 ↑               | 2.789              | 0.3597      | <b>0.0159</b>    | <0.0001 ↑               | 4.529              | 0.5945      | <b>0.0005</b>    |

**Supplementary Table 2.1 | LMM analysis of FEV1 z-scores. Related to Fig. 2d.**

**Predisposing factors for paediatric LC do not associate with lung function, as determined by FEV1 z-score, over the disease course.** Two-sided linear mixed-effects model (LMM) was fitted with FEV1 z-score as the outcome. Fixed effects included comorbidity, number of vaccinations prior to LC onset, age, sex, SARS-CoV-2 variant-of-concern (VOC) wave, TsinceIndex (cut-off 52 weeks), and number of infections since LC onset; participant ID was modelled as a random intercept. Degrees of freedom were approximated using Satterthwaite's method, and 95% confidence intervals were estimated using the Wald method. Continuous covariates were standardized; categorical predictors were modelled as factors. Model fit statistics (n = 131 observations) are: conditional R<sup>2</sup> = 0.7318 and marginal R<sup>2</sup> = 0.0757.

| Predictors                           | F (df1, df2)         | Estimate     | 95% CI              | raw P  |
|--------------------------------------|----------------------|--------------|---------------------|--------|
| Comorbidity                          | 0.6858 (1, 65.4774)  | -0.3103      | -1.0521 to 0.4315   | 0.4106 |
| Vaccination number prior to LC onset | 0.0137 (1, 69.7572)  | -0.0131      | -0.2339 to 0.2077   | 0.9071 |
| Age                                  | 0.0401 (1, 62.8733)  | 0.0222       | -0.1972 to 0.2416   | 0.8420 |
| Sex (M=1, F=0)                       | 0.5985 (1, 63.9730)  | 0.1721       | -0.2683 to 0.6126   | 0.4420 |
| VOC wave                             | 1.0831 (3, 62.2966)  | omnibus test | see contrasts below | 0.3629 |
| TsinceIndex                          | 1.5049 (1, 100.9152) | -0.1777      | -0.4646 to 0.1091   | 0.2228 |
| Infections since LC onset            | 3.0659 (1, 64.4461)  | 0.1995       | -0.0261 to 0.4251   | 0.0847 |

| VOC wave contrast | Estimate | 95% CI            | raw P  |
|-------------------|----------|-------------------|--------|
| 2 vs 3            | 0.0799   | -0.4061 to 0.5660 | 0.7458 |
| 1 vs 3            | 0.8880   | -0.1643 to 1.9404 | 0.0998 |
| 0 vs 3            | -0.2387  | -1.2853 to 0.8079 | 0.6531 |

**Supplementary Table 2.2 | a Base linear mixed-effects model for FEV1 (force expiratory volume in 1 sec) z-score. Related to Fig. 2d.** A two-sided linear mixed-effects model (LMM) was used to assess associations of IL-6 and IL-13 with FEV1 z-score in paediatric LC, with participant ID included as a random intercept to account for repeated measurements. Model fit (n = 131 observations) showed marginal and conditional R<sup>2</sup> values of 0.1622 and 0.7210, respectively, and was significant by likelihood-ratio testing (P < 0.0001). Degrees of freedom were approximated using Satterthwaite's method, and 95% confidence intervals were obtained by percentile bootstrap (1,000 resamples). No multiple-comparison adjustment was applied.

| Predictor | F (df1, df2)          | Estimate | 95% CI             | raw P   |
|-----------|-----------------------|----------|--------------------|---------|
| IL-6      | 9.0981 (1, 125.1064)  | -0.4432  | -0.7339 to -0.1524 | 0.0031  |
| IL-13     | 19.2841 (1, 126.6395) | 0.6806   | 0.3739 to 0.9873   | <0.0001 |

**b Confounder-adjusted LMM for FEV1 z-score.** Related to Fig. 2d. A two-sided linear mixed-effects model (LMM) was used to assess associations of IL-6 and IL-13 with FEV1 z-score in paediatric LC after adjustment for comorbidity, SARS-CoV-2 VOC wave, number of infections prior to LC onset, number of vaccinations, TsincelIndex, sex and age, with participant ID included as a random intercept. Model fit (n = 131 observations) showed marginal and conditional R<sup>2</sup> values of 0.1974 and 0.7426, respectively, and was significant by likelihood-ratio testing (P = 0.0128). Degrees of freedom were approximated using Satterthwaite's method, and 95% confidence intervals were obtained by percentile bootstrap (1,000 resamples). No multiple-comparison adjustment was applied.

| Predictor                            | F (df1, df2)          | Estimate     | 95% CI              | raw P  |
|--------------------------------------|-----------------------|--------------|---------------------|--------|
| Comorbidity                          | 0.0915 (1, 65.2597)   | -0.1065      | -0.8299 to 0.5732   | 0.7632 |
| Vaccination number prior to LC onset | 0.1274 (1, 68.5419)   | 0.0380       | -0.1635 to 0.2419   | 0.7223 |
| Age                                  | 0.0098 (1, 60.7239)   | -0.0103      | -0.2090 to 0.2058   | 0.9216 |
| Sex (M=1, F=0)                       | 0.0582 (1, 61.7337)   | 0.0514       | -0.3695 to 0.4371   | 0.8102 |
| VOC wave                             | 1.1576 (3, 60.1613)   | omnibus test | see contrasts below | 0.3334 |
| TsincelIndex                         | 0.0135 (1, 105.3448)  | -0.0170      | -0.3009 to 0.2741   | 0.9078 |
| Infections since LC onset            | 1.8162 (1, 62.3162)   | 0.1448       | -0.0730 to 0.3462   | 0.1826 |
| IL-6                                 | 7.4258 (1, 113.9670)  | -0.4209      | -0.7345 to -0.1299  | 0.0074 |
| IL-13                                | 15.2538 (1, 117.4568) | 0.6598       | 0.3431 to 0.9912    | 0.0002 |

| VOC wave contrast | Estimate | 95% CI            | raw P  |
|-------------------|----------|-------------------|--------|
| 2 vs 3            | -0.0833  | -0.5454 to 0.3677 | 0.7248 |
| 1 vs 3            | 0.7972   | -0.1055 to 1.7461 | 0.1109 |
| 0 vs 3            | -0.2944  | -1.2174 to 0.6858 | 0.5506 |

**Supplementary Table 2.3: Systemic cytokines are increased within predefined functional cytokine families in paediatric LC. Control vs. LC (< 1 yr) and control vs LC (1–3 yr).** Additional information for Fig. 2c, e–h of the main text. Cytokines were grouped into predefined functional cytokine families and compared across three cohorts: healthy controls, paediatric LC within the first year after TsincelIndex (LC < 1 yr), and paediatric LC 1–3 yr after the initial infection. For each cytokine, overall group differences were assessed using the two-sided Kruskal–Wallis test, followed by Dunn's post-hoc tests for pairwise comparisons between controls and LC < 1 yr, and between controls and LC 1–3 yr. In addition to between-family testing using lead cytokines (Table 1), within-family multiplicity was controlled using the Holm–Bonferroni method, yielding adjusted P values for each contrast (adj. P (C vs LC < 1 yr) and adj. P (C vs LC 1–3 yr)). Lead cytokines used to probe predefined biological subgroups are listed first within each functional cytokine family. Exception: Th1/Th2 ratio as IL-4/IFN $\gamma$  was used as lead in B) that was significantly increased at both TsincelIndex windows compared to Control. Significant entries (adjusted P < 0.05) are shown in **bold**; \* indicates increases relative to controls. Adjusted P values > 1.0000 were truncated to 1.0; E, effect size.

| Cytokine                               | P<br>(C vs. LC < 1 yr) | P<br>(C vs. LC 1–3 yr) | Adj. P<br>(C vs. LC < 1yr) | Adj. P<br>(C vs. LC 1–3 yr) |
|----------------------------------------|------------------------|------------------------|----------------------------|-----------------------------|
| <b>A) SARS-CoV-2-related cytokines</b> |                        |                        |                            |                             |
| IL-13                                  | 0.0242                 | 0.2466                 | <b>0.0484*</b>             | 0.4932                      |
| IL-6                                   | 0.7979                 | 0.3828                 | 0.7979                     | 0.3828                      |
| IL-33                                  | 0.0032                 | 0.185                  | <b>0.0096*</b>             | 0.5500                      |
| <b>B) Th2/Th1-related balance</b>      |                        |                        |                            |                             |
| IL-4                                   | 0.0026                 | 0.1865                 | <b>0.0156*</b>             | 0.3730                      |
| IL-5                                   | 0.0133                 | 0.0002                 | 0.0665                     | <b>0.0014</b>               |

| Cytokine                            | P<br>(C vs. LC < 1 yr) | P<br>(C vs. LC 1–3 yr) | Adj. P<br>(C vs. LC < 1yr) | Adj. P<br>(C vs. LC 1–3 yr) |
|-------------------------------------|------------------------|------------------------|----------------------------|-----------------------------|
| IL-9                                | 0.2581                 | 0.0361                 | 0.616                      | 0.1083                      |
| IL-2                                | 0.0756                 | 0.4988                 | 0.3024                     | 0.4988                      |
| IFN $\gamma$                        | 0.0004                 | 0.0006                 | <b>0.0028</b>              | <b>0.0036</b>               |
| TNF $\alpha$                        | 0.308                  | 0.0152                 | 0.616                      | 0.0608                      |
| IL-12p70                            | 0.969                  | 0.01                   | 0.969                      | 0.0500                      |
| IL-15                               | 0.8877                 | 0.965                  | 0.8319                     | 0.9650                      |
| IL-18                               | 0.4721                 | 0.8654                 | 0.1813                     | 0.4957                      |
| <b>C) Innate-like cytokines</b>     |                        |                        |                            |                             |
| IL-1 $\beta$                        | 0.0294                 | 0.002                  | 0.0588                     | <b>0.0040*</b>              |
| IL-1 $\alpha$                       | 0.0061                 | <b>0.001</b>           | <b>0.0183*</b>             | <b>0.0030*</b>              |
| GM-CSF                              | 0.5663                 | 0.4488                 | 0.5663                     | 0.4488                      |
| <b>D) Regulatory cytokines</b>      |                        |                        |                            |                             |
| IL-11                               | 0.001                  | 0.017                  | <b>0.003*</b>              | <b>0.0340*</b>              |
| IL-10                               | 0.0008                 | 0.0002                 | <b>0.0024</b>              | <b>0.0006</b>               |
| IL-27                               | 0.4262                 | 0.6388                 | 0.4262                     | 0.6388                      |
| <b>E) Th17-associated cytokines</b> |                        |                        |                            |                             |
| IL-12p40                            | 0.0102                 | <b>0.0002</b>          | <b>0.041</b>               | <b>0.0010*</b>              |
| IL-22                               | 0.0396                 | 0.002                  | 0.1092                     | <b>0.0060</b>               |
| IL-23                               | 0.1244                 | 0.0002                 | 0.2488                     | <b>0.0010*</b>              |
| IL-17A                              | 0.3408                 | 0.2976                 | 0.3408                     | 0.5952                      |
| IL-17F                              | 0.01                   | 0.8823                 | 0.05                       | 0.8823                      |

| Cytokine                               | H statistic | 95% CI<br>control | 95% CI<br>LC < 1 yr | 95% CI<br>LC 1–3 yr | Dunn's Z<br>C vs.<br>LC < 1yr | E<br>C vs.<br>LC < 1yr | Dunn's Z<br>C vs. LC<br>1–3 yr | E<br>C vs. LC<br>1–3 yr |
|----------------------------------------|-------------|-------------------|---------------------|---------------------|-------------------------------|------------------------|--------------------------------|-------------------------|
| <b>A) SARS-CoV-2-related cytokines</b> |             |                   |                     |                     |                               |                        |                                |                         |
| IL-13                                  | 18.33       | 14.88 to 32.27    | 17.96 to 47.90      | 11.95 to 30.08      | 2.508                         | 0.2894                 | 1.159                          | 0.4926                  |
| IL-6                                   | 3.566       | 10.73 to 22.32    | 11.67 to 33.31      | 6.652 to 28.19      | 0.256                         | 0.0296                 | 1.307                          | 0.1529                  |
| IL-33                                  | 10.68       | 14.31 to 96.09    | 34.28 to 106.6      | 22.79 to 100.7      | 3.164                         | 0.3653                 | 1.325                          | 0.1551                  |
| <b>B) Th2/Th1-related balance</b>      |             |                   |                     |                     |                               |                        |                                |                         |
| IL-4                                   | 11.08       | 1.200 to 35.77    | 5.380 to 32.11      | 2.541 to 35.10      | 3.214                         | 0.3710                 | 1.321                          | 0.1546                  |
| IL-5                                   | 16.72       | 1.349 to 5.717    | 0.259 to 8.653      | 0.480 to 12.63      | 2.476                         | 0.2859                 | 4.088                          | 0.4785                  |
| IL-9                                   | 14.04       | 3.375 to 18.19    | 2.300 to 18.09      | 2.830 to 17.41      | 1.131                         | 0.1306                 | 2.096                          | 0.2453                  |
| IL-2                                   | 10.62       | 4.063 to 9.965    | 3.084 to 6.854      | 3.530 to 8.341      | 2.077                         | 0.2398                 | 0.676                          | 0.0791                  |
| IFN $\gamma$                           | 15.53       | 14.12 to 269.6    | 19.12 to 210.6      | 7.773 to 243.1      | 3.519                         | 0.4063                 | 3.578                          | 0.4187                  |
| TNF $\alpha$                           | 7.802       | 35.48 to 200.6    | 11.84 to 406.9      | 73.54 to 507.3      | 1.020                         | 0.1178                 | 2.671                          | 0.3125                  |
| IL-12p70                               | 0.248       | 1.864 to 3.4      | 1.550 to 6.980      | 1.706 to 5.810      | 0.039                         | 0.0045                 | 0.365                          | 0.0427                  |
| IL-15                                  | 0.04819     | 76.48 to 163.5    | 86.02 to 155.2      | 82.52 to 147.5      | 0.141                         | 0.0163                 | 0.044                          | 0.0051                  |
| IL-18                                  | 1.807       | 171.1 to 724.5    | 104.5 to 130.8      | 97.70 to 123.7      | 0.719                         | 0.0830                 | 1.337                          | 0.1565                  |
| <b>C) Innate-like cytokines</b>        |             |                   |                     |                     |                               |                        |                                |                         |
| IL-1 $\beta$                           | 23.62       | 2.334 to 13.08    | 4.965 to 14.13      | 6.190 to 16.41      | 2.178                         | 0.2515                 | 4.757                          | 0.5570                  |
| IL-1 $\alpha$                          | 12.82       | 5.491 to 14.30    | 9.803 to 16.02      | 10.07 to 18.10      | 2.743                         | 0.3167                 | 3.508                          | 0.4104                  |
| GM-CSF                                 | 4.353       | 0.689 to 1.734    | 0.281 to 5.231      | 0.714 to 3.430      | 0.574                         | 0.0662                 | 1.215                          | 0.1422                  |
| <b>D) Regulatory cytokines</b>         |             |                   |                     |                     |                               |                        |                                |                         |
| IL-11                                  | 12.32       | 7.102 to 12.27    | 13.42 to 26.46      | 11.22 to 23.83      | 3.500                         | 0.4041                 | 2.386                          | 0.2793                  |
| IL-10                                  | 31.37       | 2.057 to 3.527    | 1.520 to 3.336      | 1.005 to 2.653      | 3.357                         | 0.3875                 | 5.598                          | 0.6548                  |
| IL-27                                  | 1.042       | 22.16 to 61.21    | 22.44 to 150.7      | 15.28 to 154.8      | 0.796                         | 0.0919                 | 0.996                          | 0.1166                  |
| <b>E) Th17-associated cytokines</b>    |             |                   |                     |                     |                               |                        |                                |                         |
| IL-12p40                               | 23.60       | 372.9 to 1039     | 668.8 to 1552       | 971.4 to 1770       | 2.570                         | 0.2969                 | 4.827                          | 0.5650                  |
| IL-22                                  | 10.85       | 3.690 to 10.03    | 2.573 to 8.689      | 2.100 to 4.996      | 2.058                         | 0.2376                 | 3.294                          | 0.3855                  |
| IL-23                                  | 17.74       | 5.104 to 19.11    | 8.923 to 18.35      | 9.395 to 21.46      | 1.536                         | 0.1774                 | 4.027                          | 0.4712                  |
| IL-17A                                 | 1.690       | 0.509 to 0.836    | 0.523 to 0.684      | 0.312 to 1.241      | 0.953                         | 0.1100                 | 1.285                          | 0.1504                  |
| IL-17F                                 | 0.102       | 1.076 to 7.284    | 0.330 to 11.07      | 1.384 to 6.477      | 0.313                         | 0.0362                 | 0.148                          | 0.0173                  |

**Supplementary Table 2.4 | Comparison of systemic cytokines and autoantibodies over the course of paediatric LC.** Related to Fig. 2, Fig. 3 and Supplementary Fig. 2. Serum cytokines and autoantibodies were analysed in paediatric LC patients with two visits per person. The upper table reports P values and numbers of observations from two-sided linear mixed-effects models (LMMs), with TsinceIndex entered as a binary fixed factor (LC < 1 yr versus LC 1–3 yr) and participant ID included as a random intercept. Multiple testing within functional families was controlled using the Holm–Bonferroni method; adjusted P values (Adj. P) are shown. Adj. P values > 1.0000 are reported as 1.0000. The lower table reports the corresponding model output, including F statistics, estimates, standard errors and 95% confidence intervals.

| Analyte                                             | P        | Adj. P        | obs (n) |
|-----------------------------------------------------|----------|---------------|---------|
| <b>a) SARS-CoV-2-related cytokines (see Fig. 2)</b> |          |               |         |
| IL-6                                                | 0.0353   | 0.0706        | 139     |
| IL-13                                               | < 0.0001 | <b>0.0003</b> | 139     |
| IL-33                                               | 0.5316   | 1.0000        | 139     |
| <b>b) Th1/2-related cytokines</b>                   |          |               |         |
| Ratio IL-4/IFN $\gamma$                             | 0.6099   | 0.6099        | 139     |
| <b>Th2-related cytokines</b>                        |          |               |         |
| IL-4                                                | 0.6781   | 1.0000        | 139     |
| IL-5                                                | 0.6051   | 1.0000        | 139     |
| IL-9                                                | 0.514    | 1.0000        | 139     |
| <b>Th1-related cytokines</b>                        |          |               |         |
| IL-2                                                | 0.3187   | 1.0000        | 139     |
| IFN $\gamma$                                        | 0.3683   | 1.0000        | 139     |
| TNF $\alpha$                                        | 0.4887   | 1.0000        | 139     |
| IL-12p70                                            | 0.4736   | 1.0000        | 139     |
| IL-15                                               | 0.1183   | 0.7098        | 139     |
| IL-18                                               | 0.5074   | 1.0000        | 139     |
| <b>c) Regulatory cytokines</b>                      |          |               |         |
| IL-11                                               | 0.0161   | <b>0.0322</b> | 139     |
| IL-10                                               | 0.0065   | <b>0.0195</b> | 139     |
| IL-27                                               | 0.1458   | 0.1458        | 139     |
| <b>d) Innate-like cytokines</b>                     |          |               |         |
| IL-1 $\beta$                                        | 0.2541   | 0.7623        | 139     |
| IL-1 $\alpha$                                       | 0.6328   | 1.0000        | 139     |
| GM-CSF                                              | 0.6087   | 1.0000        | 139     |
| <b>e) Th17/22-related cytokines</b>                 |          |               |         |
| IL-12p40                                            | 0.1290   | 0.5160        | 139     |
| IL-17A                                              | 0.7748   | 1.0000        | 139     |
| IL-17F                                              | 0.2297   | 0.6891        | 139     |
| IL-22                                               | 0.0044   | <b>0.0220</b> | 139     |
| IL-23                                               | 0.6879   | 1.0000        | 139     |
| <b>f) aAb (see Fig. 2, 3)</b>                       |          |               |         |
| Anti-Cardiolipin                                    | 0.0098   | 0.0686        | 139     |
| Anti- $\beta$ -2 GPI                                | 0.0306   | 0.1020        | 137     |
| Anti-Prothrombin                                    | 0.0138   | 0.0732        | 139     |
| Anti-MPO*                                           | 0.0122   | 0.0732        | 133     |
| Anti-PR3                                            | 0.0255   | 0.1020        | 138     |
| Anti-CCP                                            | 0.8388   | 0.8388        | 139     |
| Anti-TransG                                         | 0.1318   | 0.2636        | 139     |
| aAb per ID (Fig.3c)                                 | 0.5770   | unadjusted    | 139     |

| Analyte              | F (df1, df2)         | Estimate | SE       | 95% CI                |
|----------------------|----------------------|----------|----------|-----------------------|
| IL-6                 | 4.5645 (1, 91.5371)  | 9.1822   | 4.2978   | -17.1747 to -0.9613   |
| IL-13                | 29.2424 (1, 73.5456) | -16.3023 | 3.0147   | -22.4205 to -9.9889   |
| IL-33                | 0.3935 (1, 128.1152) | -14.2744 | 22.7546  | -61.2701 to 30.2500   |
| IL-4/IFN $\gamma$    | 0.2615 (1, 135.2056) | -0.0187  | 0.0365   | -0.0885 to 0.0474     |
| IL-4                 | 0.1735 (1, 84.6014)  | -2.1709  | 5.2117   | -12.2446 to 7.7826    |
| IL-5                 | 0.1819 (1, 129.2504) | 1.9539   | 4.5812   | -7.1686 to 10.5094    |
| IL-9                 | 0.2695 (1, 80.0390)  | -1.2108  | 2.3322   | -5.9688 to 3.0850     |
| IL-2                 | 1.0067 (1, 81.7885)  | 0.7194   | 0.7170   | -0.7447 to 2.1107     |
| IFN $\gamma$         | 0.8196 (1, 71.9630)  | -21.9319 | 24.2263  | -65.4031 to 29.4766   |
| TNF $\alpha$         | 0.4820 (1, 131.7864) | 90.9380  | 130.9835 | -163.8169 to 367.4913 |
| IL-12p70             | 0.5180 (1, 89.6848)  | -0.6800  | 0.9447   | -2.6584 to 1.1659     |
| IL-15                | 2.4784 (1, 109.1315) | -26.4264 | 16.7862  | -61.4815 to 9.1382    |
| IL-18                | 0.4417 (1, 135.3279) | -5.8488  | 8.8000   | -22.8599 to 11.6678   |
| IL-11                | 6.1318 (1, 89.5571)  | -5.8335  | 2.3558   | -10.2175 to -1.3949   |
| IL-10                | 7.7386 (1, 98.5442)  | -1.0698  | 0.3846   | -1.8105 to -0.2991    |
| IL-27                | 2.1601 (1, 75.6540)  | -25.4205 | 17.2961  | -59.1071 to 11.6122   |
| IL-1 $\alpha$        | 0.2296 (1, 100.7445) | -0.7987  | 1.6667   | -3.9619 to 2.3416     |
| IL-1 $\beta$         | 1.3204 (1, 77.5945)  | 1.5991   | 1.3917   | -0.8991 to 4.4210     |
| GM-CSF               | 0.2641 (1, 84.2039)  | -0.3600  | 0.7005   | -1.7576 to 0.9291     |
| IL-12p40             | 2.3463 (1, 91.8922)  | 263.0140 | 171.7084 | -71.3675 to 583.5334  |
| IL-17A               | 0.0822 (1, 126.8193) | 0.0593   | 0.2068   | -0.3612 to 0.4666     |
| IL-17F               | 1.4638 (1, 84.4674)  | -1.7680  | 1.4614   | -4.6962 to 1.0345     |
| IL-22                | 8.5028 (1, 94.6352)  | -2.9107  | 0.9982   | -4.9782 to -1.0066    |
| IL-23                | 0.1624 (1, 92.2683)  | 0.8976   | 2        | -3.4798 to 5.3329     |
| Anti-Cardiolipin     | 7.0677 (1, 88.9909)  | -0.9769  | 0.3675   | -1.6947 to -0.2955    |
| Anti- $\beta$ -2 GPI | 4.9779 (1, 128.1020) | 1.8438   | 0.8264   | 0.2884 to 3.4068      |

| Analyte                       | F (df1, df2)         | Estimate | SE     | 95% CI             |
|-------------------------------|----------------------|----------|--------|--------------------|
| Anti-Prothrombin              | 6.1623 (1, 91.3899)  | -1.5283  | 0.6156 | -2.7908 to -0.3558 |
| Anti-MPO                      | 6.3357 (1, 125.8138) | -0.2230  | 0.0886 | -0.4014 to -0.0646 |
| Anti-PR3                      | 5.0049 (1, 136.0000) | 0.5074   | 0.2268 | 0.0625 to 0.9525   |
| Anti-CCP                      | 0.0377 (1, 80.3247)  | 0.0959   | 0.4938 | -0.8992 to 1.0445  |
| Anti-TransG                   | 1.7493 (1, 95.0376)  | 1.4222   | 1.0753 | -0.6459 to 3.5138  |
| aAB reactivity per ID Fig. 3c | 0.3212(1;100.08)     | 0.0397   | 0.0701 | -0.0960 to 0.1700  |

### Supplementary Table 2.5a | Primary model predicting Bell score severity. Related to Fig. 2k.

A two-sided linear mixed-effects model (LMM) was used to relate Bell score to IL-12p40, mean corpuscular haemoglobin concentration (MCHC), absolute basophil granulocyte counts and anti-EBV EBNA titres in paediatric LC, with participant ID included as a random intercept to account for repeated measurements. All continuous variables were z-standardized. The model showed marginal and conditional  $R^2$  values of 0.2121 and 0.7858, respectively, and was significant by likelihood-ratio testing ( $P < 0.0001$ ); fixed effects were evaluated using Satterthwaite's method. No multiple-comparison adjustment was applied.

| Predictor                        | F (df1, df2)          | Estimate | 95% CI             | raw P   |
|----------------------------------|-----------------------|----------|--------------------|---------|
| IL-12p40                         | 16.8695 (1, 103.0928) | 7.6798   | 3.8605 to 11.1478  | <0.0001 |
| MCHC                             | 7.4328 (1, 109.7204)  | -4.9544  | -8.4997 to -1.5698 | 0.0075  |
| Basophil granulocytes (absolute) | 3.9514 (1, 109.5586)  | 3.5241   | 0.0279 to 6.7380   | 0.0493  |
| EBV EBNA IgG                     | 5.8558 (1, 67.8263)   | -5.5295  | -9.7982 to -0.8609 | 0.0182  |

### Supplementary Table 2.5b | Extended confounder-adjusted interaction model predicting Bell score severity. Related to Fig. 2k.

A two-sided linear mixed-effects model (LMM) was used to relate Bell score to IL-12p40, MCHC, absolute basophil granulocyte counts and anti-EBV EBNA titres in paediatric LC, adjusted for age, sex, comorbidity status and TsinceIndex, with additional interaction terms between anti-EBV EBNA and MCHC, vitamin B1, IL-12p40 and basophil counts. Participant ID was included as a random intercept. Model fit is reported as marginal and conditional  $R^2$  ( $R^2_m = 0.3328$ ,  $R^2_c = 0.8303$ ), with model significance confirmed by likelihood-ratio testing ( $P < 0.0001$ ); fixed effects were evaluated using Satterthwaite's method. No multiple-comparison adjustment was applied.

| Predictor                             | F (df1, df2)         | Estimate | 95% CI             | raw P  |
|---------------------------------------|----------------------|----------|--------------------|--------|
| Comorbidity                           | 0.4984 (1, 52.2331)  | -5.3258  | -20.3005 to 9.6488 | 0.4833 |
| Sex (M=1, F=0)                        | 0.3196 (1, 61.1489)  | 2.6716   | -6.7091 to 12.0523 | 0.5739 |
| Age                                   | 2.8688 (1, 54.3053)  | 3.7375   | -0.6426 to 8.1177  | 0.0960 |
| IL-12p40                              | 13.7416 (1, 93.0773) | 8.0414   | 3.7354 to 12.3474  | 0.0004 |
| MCHC                                  | 10.4664 (1, 97.8929) | -6.0036  | -9.6872 to -2.3200 | 0.0017 |
| Basophil granulocytes                 | 4.1279 (1, 97.1284)  | 3.5704   | 0.0822 to 7.0587   | 0.0449 |
| Anti-EBV EBNA                         | 2.5279 (1, 58.6863)  | -3.7304  | -8.3878 to 0.9269  | 0.1172 |
| Vitamin B1                            | 2.3614 (1, 78.3436)  | 2.4279   | -0.7083 to 5.5641  | 0.1284 |
| TsinceIndex                           | 0.3677 (1, 96.9658)  | -1.1746  | -5.0196 to 2.6704  | 0.5457 |
| Basophil granulocytes × Anti-EBV EBNA | 0.5291 (1, 97.4735)  | -1.3575  | -5.0621 to 2.3470  | 0.4687 |
| Anti-EBV EBNA × Vitamin B1            | 6.5743 (1, 66.3103)  | -3.6861  | -6.5398 to -0.8325 | 0.0126 |
| MCHC × Anti-EBV EBNA                  | 6.2641 (1, 97.9603)  | 4.4452   | 0.9197 to 7.9706   | 0.0140 |
| IL-12p40 × Anti-EBV EBNA              | 2.7041 (1, 97.9408)  | -2.9667  | -6.5478 to 0.6144  | 0.1033 |

**Supplementary Table 3.1 | No relevant correlations between G-protein-specific autoantibodies (aAb) and disease severity or cytokines. Additional information for the main text.** Two-sided linear mixed-effects models (LMM) were used to account for repeated patient visits. G-protein-specific autoantibodies (aAb, U mL<sup>-1</sup>) were used as dependent variables; predictors are listed in rows. Participant ID was included as a random intercept. Cytokines were selected based on significant differences between the Control and LC groups (Fig. 2c,f–h). Marginal R<sup>2</sup> (R<sup>2</sup>m) and the corresponding P value for the fixed effect are reported. No association was both statistically significant and associated with R<sup>2</sup>m > 0.20. Including age and time since index infection as covariates, and sex and vaccination status (Y/N) as factors, did not yield any model that was both statistically significant and associated with R<sup>2</sup>m > 0.20.

| Predictor   | β1-adrenergic receptor aAb | β2-adrenergic receptor aAb | M3 muscarinic receptor | M4 muscarinic receptor |                       |
|-------------|----------------------------|----------------------------|------------------------|------------------------|-----------------------|
| Bell score  | 0.0062<br>0.3056           | 0.0130<br>0.1779           | 0.0001<br>0.8994       | 0.0081<br>0.2477       | R <sup>2</sup> m<br>P |
| TsinceIndex | 0.0023<br>0.5215           | 0.0029<br>0.5284           | 0.0001<br>0.9548       | 0.0192<br>0.0684       | R <sup>2</sup> m<br>P |
| IL-6        | 0.0002<br>0.8752           | 0.0011<br>0.7117           | 0.0041<br>0.5086       | 0.0082<br>0.3013       | R <sup>2</sup> m<br>P |
| IL-13       | 0.0028<br>0.5900           | 0.0007<br>0.7983           | 0.0060<br>0.4493       | 0.0292<br>0.0843       | R <sup>2</sup> m<br>P |
| IFNγ        | 0.0000<br>0.9620           | 0.0008<br>0.7949           | 0.0018<br>0.6919       | 0.0034<br>0.5810       | R <sup>2</sup> m<br>P |
| IL-1α       | 0.0073<br>0.2556           | 0.0122<br>0.1837           | 0.0134<br>0.2004       | 0.0232<br>0.0551       | R <sup>2</sup> m<br>P |
| IL-1β       | 0.0161<br>0.1845           | 0.0520<br>0.0717           | 0.0268<br>0.1056       | 0.0080<br>0.3613       | R <sup>2</sup> m<br>P |
| GM-CSF      | 0.0026<br>0.5805           | 0.0100<br>0.2976           | 0.0137<br>0.2410       | 0.0012<br>0.7091       | R <sup>2</sup> m<br>P |
| IL-11       | 0.0023<br>0.5616           | 0.0028<br>0.5553           | 0.0177<br>0.1620       | 0.0230<br>0.0784       | R <sup>2</sup> m<br>P |
| IL-12p40    | 0.0056<br>0.3557           | 0.0179<br>0.1265           | 0.0233<br>0.0999       | 0.0011<br>0.6887       | R <sup>2</sup> m<br>P |
| IL-33       | 0.0058<br>0.2203           | 0.0137<br>0.0989           | 0.0120<br>0.1778       | 0.0050<br>0.2872       | R <sup>2</sup> m<br>P |

anti-β1-AdR aAb

| Predictor   | obs | F (df1, df2)         | Estimate | 95% CI            |
|-------------|-----|----------------------|----------|-------------------|
| Bell score  | 119 | 1.0618 (1, 97.2937)  | 1.0898   | -1.0051 to 3.1847 |
| TsinceIndex | 140 | 0.4061 (1, 126.7168) | -0.6625  | -2.7187 to 1.3936 |
| IL-6        | 137 | 0.0233 (1, 134.5209) | 0.1782   | -2.1523 to 2.5713 |
| IL-13       | 137 | 0.2919 (1, 119.9872) | 0.7299   | -1.9955 to 3.5498 |
| IFNγ        | 137 | 0.0022 (1, 102.6684) | 0.0674   | -2.7027 to 3.0731 |
| IL-1α       | 137 | 1.2846 (1, 128.5779) | 1.1822   | -0.8783 to 3.1463 |
| IL-1β       | 137 | 1.7522 (1, 120.2470) | 1.7545   | -0.7460 to 4.2830 |
| GM-CSF      | 137 | 0.3069 (1, 132.2081) | 0.6969   | -1.7108 to 3.1392 |
| IL-11       | 137 | 0.3293 (1, 134.6503) | 0.6598   | -1.5594 to 2.9780 |
| IL-12p40    | 137 | 0.8408 (1, 134.6275) | 1.0262   | -1.0468 to 3.2474 |
| IL-33       | 137 | 1.4879 (1, 103.5502) | 1.0437   | -0.7055 to 2.6174 |

anti-β2-AdR aAb

| Predictor   | obs | F (df1, df2)         | Estimate | 95% CI            |
|-------------|-----|----------------------|----------|-------------------|
| Bell score  | 120 | 1.8374 (1, 111.6144) | 1.7061   | -0.7868 to 4.1991 |
| TsinceIndex | 140 | 0.4279 (1, 136.5683) | 0.8061   | -1.6308 to 3.2430 |
| IL-6        | 138 | 0.1339 (1, 131.7679) | 0.5024   | -2.0579 to 2.8919 |
| IL-13       | 138 | 0.0641 (1, 105.2207) | 0.3856   | -2.5850 to 3.5281 |
| IFNγ        | 138 | 0.0680 (1, 91.5607)  | 0.4146   | -2.5795 to 3.5294 |
| IL-1α       | 138 | 1.7607 (1, 135.9993) | 1.6544   | -0.7283 to 4.0840 |
| IL-1β       | 138 | 3.2872 (1, 107.0304) | 2.7045   | -0.1645 to 5.5603 |
| GM-CSF      | 138 | 1.0761 (1, 120.3952) | 1.4985   | -1.3897 to 4.2823 |
| IL-11       | 138 | 0.3406 (1, 131.6819) | 0.7873   | -1.9664 to 3.2713 |

| Predictor | obs | F (df1, df2)         | Estimate | 95% CI            |
|-----------|-----|----------------------|----------|-------------------|
| IL-12p40  | 138 | 2.3177 (1, 132.2712) | 1.9943   | -0.5342 to 4.3968 |
| IL-33     | 138 | 2.7233 (1, 120.3719) | 1.7508   | -0.2745 to 3.9425 |

#### anti-M3-mAChR aAb

| Predictor     | obs | F (df1, df2)         | Estimate | 95% CI            |
|---------------|-----|----------------------|----------|-------------------|
| Bell score    | 120 | 0.0150 (1, 117.5213) | -0.1443  | -2.4757 to 2.1871 |
| TsinceIndex   | 140 | 0.0074 (1, 132.6103) | 0.0968   | -2.1321 to 2.3258 |
| IL-6          | 138 | 0.4335 (1, 113.8934) | 0.7982   | -1.6857 to 3.1956 |
| IL-13         | 138 | 0.5652 (1, 89.9698)  | 0.9668   | -1.5233 to 3.3499 |
| IFN $\gamma$  | 138 | 0.1594 (1, 80.8118)  | 0.5276   | -2.1654 to 3.1087 |
| IL-1 $\alpha$ | 138 | 1.6369 (1, 127.3435) | 1.4448   | -0.7266 to 3.5207 |
| IL-1 $\beta$  | 138 | 2.6287 (1, 91.8670)  | 2.0516   | -0.5288 to 4.5293 |
| GM-CSF        | 138 | 1.3751 (1, 101.6193) | 1.4646   | -1.0900 to 3.8232 |
| IL-11         | 138 | 1.9397 (1, 114.3462) | 1.6497   | -0.7011 to 4.0528 |
| IL-12p40      | 138 | 2.6913 (1, 116.8572) | 1.9003   | -0.3768 to 4.1429 |
| IL-33         | 138 | 1.8013 (1, 134.8442) | 1.3600   | -0.6851 to 3.5155 |

#### anti-M4-mAChR aAb

| Predictor     | obs | F (df1, df2)         | Estimate | 95% CI            |
|---------------|-----|----------------------|----------|-------------------|
| Bell score    | 120 | 1.3298 (1, 101.4168) | -1.0069  | -2.7364 to 0.7225 |
| TsinceIndex   | 140 | 3.3269 (1, 129.8961) | -1.5797  | -3.2924 to 0.1330 |
| IL-6          | 138 | 1.0607 (1, 135.5846) | 1.0322   | -0.9883 to 3.1290 |
| IL-13         | 138 | 3.0340 (1, 113.8515) | 1.9755   | -0.3771 to 4.2279 |
| IFN $\gamma$  | 138 | 0.3036 (1, 95.9690)  | 0.6622   | -1.7717 to 2.8883 |
| IL-1 $\alpha$ | 138 | 3.7494 (1, 134.0628) | 1.7368   | -0.0331 to 3.4683 |
| IL-1 $\beta$  | 138 | 0.8214 (1, 111.7070) | 1.0131   | -1.2164 to 3.2468 |
| GM-CSF        | 138 | 0.1357 (1, 127.2118) | 0.3951   | -1.7082 to 2.5099 |
| IL-11         | 138 | 3.0850 (1, 135.4435) | 1.7180   | -0.2835 to 3.7670 |
| IL-12p40      | 138 | 0.1574 (1, 135.4022) | 0.3835   | -1.5937 to 2.3573 |
| IL-33         | 138 | 1.1181 (1, 112.2391) | 0.8038   | -0.6704 to 2.2476 |

### Supplementary Table 3.2. GPCR autoantibodies across the course of paediatric long COVID.

Serum cytokines and functional G protein-coupled receptor (GPCR) autoantibodies (aAb) were analysed in paediatric long COVID (LC) patients at two visits per participant. Two-sided linear mixed models were fitted with time since index infection (TsinceIndex) as a binary factor (LC < 1 yr versus LC 1–3 yr). Shown are the number of observations (obs), marginal  $R^2$  ( $R^2_m$ ), F statistic with degrees of freedom, fixed-effect estimate, standard error (SE), 95% confidence interval (CI) and unadjusted and Holm–Bonferroni-adjusted P values. Confidence intervals were derived by percentile bootstrap (1,000 resamples). Adj. P values >1.0000 are reported as 1.0000. P < 0.05 was considered statistically significant.

| Analyte             | obs | $R^2_m$ | F (df1, df2)       | Estimate | 95% CI            | P      | Adj. P |
|---------------------|-----|---------|--------------------|----------|-------------------|--------|--------|
| anti-M3-mAChR       | 140 | 0.0016  | 0.2951 (1, 122.38) | 1.0043   | -2.6345 to 4.5513 | 0.5872 | 1.0000 |
| anti-M4-mAChR       | 140 | 0.0008  | 0.2471 (1, 93.71)  | -0.6454  | -3.2826 to 1.8761 | 0.415  | 1.0000 |
| anti- $\beta$ 1-AdR | 139 | 0.0015  | 0.4982 (1, 90.66)  | 1.0671   | -1.9083 to 3.9106 | 0.4821 | 1.0000 |
| anti- $\beta$ 2-AdR | 140 | 0.0005  | 0.1334 (1, 104.42) | 0.6916   | -3.1963 to 4.5657 | 0.7157 | 1.0000 |

### Supplementary Table 3.3 | Autoantibody (aAb) concentrations in paediatric LC and sensitivity analyses using stratified controls (see Fig. 2, 3 and Supplementary Fig. 4 for visualisation).

AAb were compared between controls and paediatric LC stratified by time since index infection (LC < 1 year; LC 1–3 yr) as additional information for Fig. 2e and Fig. 3b and c. a, Pooled controls (healthy + clinically stable cystic fibrosis (CF)) versus LC subgroups. b, Healthy controls versus LC subgroups (sensitivity analysis). c, CF controls versus LC subgroups (sensitivity analysis). Group medians and 95% confidence intervals are shown. Overall group differences were assessed using two-sided Kruskal–Wallis tests; H statistics are reported. Pairwise comparisons (control vs LC < 1 year; control vs LC 1–3 yr) were performed using Dunn's post hoc tests; exact P values, Dunn's Z statistics, effect sizes, and Holm–Bonferroni-adj. P values are shown; E, effect size. Significant entries are highlighted in bold; P values exceeding 1.0000 were set to 1.0000.

### a) Pooled controls versus LC subgroups (sensitivity); (see Fig. 2, 3; Supplementary Fig. 4)

| aAb<br>(see Fig. 2, 3) | H statistic | 95% CI control | 95% CI<br>LC < 1 yr | 95% CI<br>LC 1–3 yr |
|------------------------|-------------|----------------|---------------------|---------------------|
| Anti-Cardiolipin       | 2.177       | 3.3 to 7.0     | 3.5 to 4.65         | 3.35 to 4.35        |
| Anti-β-2 GPI           | 3.621       | 2.4 to 3.9     | 2.2 to 3.4          | 2.6 to 4.3          |
| Anti-Prothrombin       | 5.701       | 3.0 to 6.3     | 4.25 to 6.8         | 3.5 to 5.75         |
| Anti-MPO*              | 21.24       | 0.8 to 1.2     | 0.5 to 0.8          | 0.3 to 0.7          |
| Anti-PR3               | 26.0        | 0.2 to 1.0     | 0.025 to 0.0695     | 0.562 to 1.3        |
| Anti-CCP               | 0.2465      | 2.2 to 6.9     | 2.8 to 4.65         | 3.1 to 5.1          |
| Anti-TransG            | 2.790       | 2.8 to 8.0     | 2.65 to 4.4         | 3.0 to 5.3          |
| aAB reactivity per ID  | 0.2210      | 0.0 to 1.0     | 0.0                 | 0.0 to 1.0          |

| aAb<br>(see Fig 2,3)  | P             | Dunn's Z  | E         | Adj. P        | P                 | Dunn's Z  | E         | Adj. P        |
|-----------------------|---------------|-----------|-----------|---------------|-------------------|-----------|-----------|---------------|
|                       | LC < 1 yr     | LC < 1 yr | LC < 1 yr | LC < 1 yr     | LC 1–3 yr         | LC 1–3 yr | LC 1–3 yr | LC 1–3 yr     |
| Anti-Cardiolipin      | 0.6209        | 1.014     | 0.1179    | 1.0000        | 0.2822            | 1.472     | 0.1723    | 1.0000        |
| Anti-β-2 GPI          | 0.1521        | 1.774     | 0.2062    | 0.6395        | 1.0000            | 0.5893    | 0.0690    | 1.0000        |
| Anti-Prothrombin      | 0.1279        | 1.853     | 0.2154    | 0.6395        | 1.0000            | 0.0054    | 0.0006    | 1.0000        |
| Anti-MPO*             | <b>0.0020</b> | 3.288     | 0.3822    | <b>0.0140</b> | <b>&lt;0.0001</b> | 4.581     | 0.5362    | <b>0.0007</b> |
| Anti-PR3              | <b>0.0041</b> | 3.086     | 0.3587    | <b>0.0246</b> | 0.4664            | 1.192     | 0.1395    | 1.0000        |
| Anti-CCP              | 1.0           | 0.2081    | 0.0242    | 1.0000        | 1.0000            | 0.2175    | 0.0255    | 1.0000        |
| Anti-TransG           | 0.1915        | 1.666     | 0.1937    | 0.6395        | 0.6765            | 0.9576    | 0.1121    | 1.0000        |
| aAB reactivity per ID | 1.0           | 0.1520    | 0.022     | 1.0000        | 1.0000            | 0.4407    | 0.0516    | unadjusted    |

### b) Healthy controls versus LC subgroups (sensitivity); (see Fig. 2, 3; Supplementary Fig. 4)

| aAb<br>(see Fig. 2, 3) | H statistic | 95% CI control | 95% CI<br>LC < 1 yr | 95% CI<br>LC 1–3 yr |
|------------------------|-------------|----------------|---------------------|---------------------|
| Anti-Cardiolipin       | 0.9352      | 2.8-9.0        | 3.5 to 4.65         | 3.35 to 4.35        |
| Anti-β-2 GPI           | 4.212       | 2.3-7.6        | 2.2 to 3.4          | 2.6 to 4.3          |
| Anti-Prothrombin       | 4.708       | 2.7-10.2       | 4.25 to 6.8         | 3.5 to 5.75         |
| Anti-MPO*              | 14.78       | 0.6-1.4        | 0.5 to 0.8          | 0.3 to 0.7          |
| Anti-PR3               | 23.91       | 0.027-1.0      | 0.025 to 0.0695     | 0.5620 to 1.3       |
| Anti-CCP               | 2.104       | 2.2-15.6       | 2.8 to 4.65         | 3.1 to 5.1          |
| Anti-TransG            | 2.755       | 2.1-26.6       | 2.65 to 4.4         | 3.0 to 5.3          |

| aAb<br>(see Fig 2,3) | P             | Dunn's Z | E         | Adj.P     | P             | Dunn's Z  | E         | Adj.P         |
|----------------------|---------------|----------|-----------|-----------|---------------|-----------|-----------|---------------|
|                      | C < 1 yr      | C < 1 yr | LC < 1 yr | LC < 1 yr | LC 1–3 yr     | LC 1–3 yr | LC 1–3 yr | LC 1–3 yr     |
| Anti-Cardiolipin     | 1.0000        | 0.5960   | 0.0763    | 1.0000    | 0.6890        | 0.9453    | 0.1220    | 1.0000        |
| Anti-β-2 GPI         | 0.1051        | 1.9390   | 0.2483    | 0.63006   | 0.5791        | 1.0590    | 0.1367    | 1.0000        |
| Anti-Prothrombin     | 1.0000        | 0.3585   | 0.0459    | 1.0000    | 0.5483        | 1.0940    | 0.1412    | 1.0000        |
| Anti-MPO*            | <b>0.0108</b> | 2.783    | 0.3563    | 0.0756    | <b>0.0003</b> | 3.8350    | 0.4951    | <b>0.0021</b> |
| Anti-PR3             | 0.1719        | 1.7170   | 0.2198    | 0.8595    | 0.2149        | 1.6100    | 0.2079    | 1.0000        |
| Anti-CCP             | 0.2939        | 1.4500   | 0.1857    | 0.8817    | 0.5421        | 1.1010    | 0.1421    | 1.0000        |
| Anti-TransG          | 0.2030        | 1.6380   | 0.2097    | 0.8595    | 0.5554        | 1.0860    | 0.1402    | 1.0000        |

### c) CF controls versus LC subgroups (sensitivity); (see Fig. 2, 3; Supplementary Fig. 4)

| aAb<br>(see Fig. 2, 3) | H statistic | 95% CI control | 95% CI<br>LC < 1 yr | 95% CI<br>LC 1–3 yr |
|------------------------|-------------|----------------|---------------------|---------------------|
| Anti-Cardiolipin       | 1.869       | 3.2 to 7.2     | 3.5 to 4.65         | 3.35 to 4.35        |
| Anti-β-2 GPI           | 2.058       | 2.4 to 3.9     | 2.2 to 3.4          | 2.6 to 4.3          |
| Anti-Prothrombin       | 8.6883      | 2.8 to 4.6     | 4.25 to 6.8         | 3.5 to 5.75         |
| Anti-MPO*              | 11.40       | 0.6 to 1.6     | 0.5 to 0.8          | 0.3 to 0.7          |
| Anti-PR3               | 26.77       | 0.2 to 1.5     | 0.025 to 0.0695     | 0.5620 to 1.3       |
| Anti-CCP               | 2.275       | 1.3 to 6.1     | 2.8 to 4.65         | 3.1 to 5.1          |
| Anti-TransG            | 1.208       | 2.8 to 8.0     | 2.65 to 4.4         | 3.0 to 5.3          |

| aAb<br>(see Fig. 2, 3) | H statistic   |          | 95% CI control |               | 95% CI<br>LC < 1 yr |           | 95% CI<br>LC 1–3 yr |               |
|------------------------|---------------|----------|----------------|---------------|---------------------|-----------|---------------------|---------------|
| aAb<br>(see Fig 2.3)   | P             | Dunn's Z | E              | Adj. P        | P                   | Dunn's Z  | E                   | Adj. P        |
|                        | C < 1 yr      | C < 1 yr | C < 1 yr       | C < 1 yr      | LC 1–3 yr           | LC 1–3 yr | LC 1–3 yr           | LC 1–3 yr     |
| Anti-Cardiolipin       | 0.6307        | 1.004    | 0.1296         | 1.0           | 0.3455              | 1.363     | 0.1774              | 1.0           |
| Anti-β-2 GPI           | 0.8668        | 0.7834   | 0.1011         | 1.0           | 1.0                 | 1.376     | 0.1791              | 1.0           |
| Anti-Prothrombin       | <b>0.0191</b> | 2.591    | 0.3345         | 0.1146        | 0.5003              | 1.15      | 0.1497              | 1.0           |
| Anti-MPO*              | <b>0.0394</b> | 2.332    | 0.3011         | 0.1970        | <b>0.0016</b>       | 3.346     | 0.4356              | <b>0.0112</b> |
| Anti-PR3               | <b>0.0040</b> | 3.09     | 0.3989         | <b>0.0280</b> | 1.0                 | 0.1751    | 0.0228              | 1.0           |
| Anti-CCP               | 0.4785        | 1.177    | 0.1520         | 1.0           | 0.2629              | 1.508     | 0.1963              | 1.0           |
| Anti-TransG            | 0.6836        | 0.9506   | 0.1227         | 1.0           | 1.0                 | 0.3988    | 0.0519              | 1.0           |

**Supplementary Table 3.4 | Association of anti-DFS70 positivity with coagulation factors, complement components, EBV serostatus, and receptor autoantibodies in paediatric LC. Additional information for Fig. 3e of the main text and Supplementary Fig. 3c–e.**

Analysis of coagulation factors, components of the complement system and EBV-status were analysed in paediatric LC patients with two visits per person. The table reports P values from two-sided LMMs (n = 139 observations), with anti-DFS70<sup>pos</sup> vs. anti-DFS70<sup>neg</sup> entered as a bivariate factor and participant ID as a cluster variable. Family-wise multiplicity was controlled using the Holm–Bonferroni (listed as “adjusted P value”). Adjusted P values greater than 1.0000 are reported as and those <0.05 were considered significant. Significant entries are shown in bold. Receptors (anti-M-mAChR) and β-adrenergic receptors (anti-β-AdrR). Lower panels report the full model output.

**Anti-DFS70<sup>pos</sup> vs. anti-DFS70<sup>neg</sup> and coagulation factors, complement system, and EBV-status (see Fig. 3c–e)**

| Analyte        | obs (n) | R <sup>2</sup> m | F (df1, df2)         | Estimate | 95% CI                | P      | Adj. P |
|----------------|---------|------------------|----------------------|----------|-----------------------|--------|--------|
| vWF%           | 139     | 0.1384           | 13.6020 (1, 72.8142) | -42.8349 | -65.8046 to 19.8652   | 0.0003 | 0.0039 |
| vWF Activity%  | 139     | 0.1421           | 14.2924 (1, 73.7543) | -38.0280 | -57.9214 to 18.1346   | 0.0003 | 0.0039 |
| F VIII%        | 139     | 0.1249           | 13.9225 (1, 76.1260) | -34.8917 | -53.3853 to 16.3981   | 0.0003 | 0.0039 |
| aPTT           | 139     | 0.0983           | 9.7138 (1, 70.8476)  | 2.9947   | 1.0944 to 4.8950      | 0.0022 | 0.0220 |
| Antithrombin   | 133     | 0.0507           | 4.6834 (1, 67.0093)  | 8.2020   | 0.7034 to 15.7005     | 0.0311 | 0.2799 |
| Fibrinogen     | 139     | 0.0099           | 0.8834 (1, 69.0565)  | -0.1660  | -0.5152 to 0.1833     | 0.3442 | 1.0000 |
| D-Dimer        | 139     | 0.0070           | 0.9371 (1, 76.3026)  | -27.2135 | -82.8094 to 28.3824   | 0.3304 | 1.0000 |
| Protein C      | 138     | 0.0233           | 1.9886 (1, 72.5387)  | -9.5804  | -23.0174 to 3.8566    | 0.1566 | 1.0000 |
| Free Protein S | 138     | 0.0163           | 1.2370 (1, 72.0504)  | -7.1281  | -19.1019 to 4.5006    | 0.2633 | 1.0000 |
| Anti-EBV EBNA  | 138     | 0.0071           | 0.5563 (1, 71.1154)  | -63.9302 | -230.5483 to 107.8559 | 0.4543 | 1.0000 |
| IgG EBV VCA    | 138     | 0.0026           | 0.2076 (1, 71.0883)  | -37.6163 | -200.9171 to 125.6846 | 0.6520 | 1.0000 |
| C3             | 135     | 0.0121           | 1.0244 (1, 72.2856)  | -0.0667  | -0.1971 to 0.0637     | 0.3084 | 1.0000 |
| C4             | 135     | 0.0004           | 0.0301 (1, 71.4311)  | 0.0031   | -0.0325 to 0.0387     | 0.8858 | 1.0000 |

### Related to Supplementary Fig. 3e

| Analyte       | obs (n) | R <sup>2</sup> m | F (df1, df2)        | Estimate | 95% CI              | P      | Adj. P |
|---------------|---------|------------------|---------------------|----------|---------------------|--------|--------|
| anti-M3-mAChR | 140     | 0.0000           | 0.0021 (1, 70.3001) | 0.2004   | -8.3500 to 8.7509   | 0.9268 | 1.0000 |
| anti-M4-mAChR | 140     | 0.0000           | 0.0015 (1, 70.5383) | 0.1619   | -8.0076 to 8.3314   | 0.9250 | 1.0000 |
| anti-β1-AdrR  | 139     | 0.0007           | 0.0579 (1, 71.9224) | 1.2121   | -8.7488 to 11.1730  | 0.8243 | 1.0000 |
| anti-β2-AdrR  | 140     | 0.0000           | 0.0000 (1, 72.1047) | -0.0054  | -10.5810 to 10.5702 | 0.9209 | 1.0000 |

**Supplementary Table 4 | EBV-experienced paediatric LC patients show elevated cytokine and aAb concentrations but no enhanced SARS-CoV-2-specific responses.** This table provides detailed results for the two-sided LMMs shown in Table 2 and Fig. 4 of the main text. Associations of clinical scores, aAb concentrations, and cytokine concentrations with EBV exposure status were analysed in paediatric LC patients using LMMs with repeated measurements clustered by participant ID. The number of observations was  $n = 138$  for clinical scores, anti-S Ab, and IgG CoV-2 Liaison (spike);  $n = 137$  for anti-M3-mAChR, anti-M4-mAChR, and granulocyte subtypes; and  $n = 136$  for anti-CCP, anti-TransG, anti- Prothrombin, and cytokine concentrations. EBV exposure status was modelled as a binary factor, distinguishing EBV-naïve patients (anti-EBV EBNA < 50 U mL<sup>-1</sup>) from EBV-experienced patients (anti-EBV EBNA > 50 U mL<sup>-1</sup>). Sex, vaccination status, and comorbidity were included as categorical factors, whereas time since index infection preceding LC onset and age were included as covariates. The dependent variable is indicated above each section. Holm–Bonferroni-adjusted P values are reported in Table 1 of the main text. Significant associations with EBV exposure are marked by bold numbers of the corresponding P values when the overall model fit was significant; observation (obs).

### a. Anti-SARS-response

| Analyte    | obs (n) | Predictor      | F (df1, df2)         | Estimate   | 95% CI                   | raw P  |
|------------|---------|----------------|----------------------|------------|--------------------------|--------|
| Anti-Spike | 138     | TsinceIndex    | 0.8615 (1, 121.7985) | -312.1596  | -977.5812 to 353.2621    | 0.3552 |
|            |         | Comorbidity    | 0.3674 (1, 68.9239)  | -856.5714  | -3652.6417 to 1939.4989  | 0.5464 |
|            |         | Vaccination    | 12.4864 (1, 71.1589) | -2739.8675 | -4273.9623 to -1205.7727 | 0.0007 |
|            |         | Age            | 2.0782 (1, 76.8479)  | 573.3736   | -213.5502 to 1360.2975   | 0.1535 |
|            |         | Sex (M=1, F=0) | 0.0642 (1, 76.5592)  | -197.6976  | -1741.9398 to 1346.5446  | 0.8007 |
|            |         | EBV            | 0.0209 (1, 90.9542)  | 107.4303   | -1362.5037 to 1577.3643  | 0.8853 |
| CH50       | 131     | TsinceIndex    | 1.9549 (1, 123.9267) | -1.2383    | -2.9211 to 0.5924        | 0.1646 |
|            |         | Comorbidity    | 0.0581 (1, 68.5294)  | -0.9781    | -8.8457 to 6.8657        | 0.8102 |
|            |         | Vaccination    | 2.2468 (1, 70.2857)  | 3.3254     | -0.5415 to 7.7925        | 0.1384 |
|            |         | Age            | 0.8657 (1, 78.3766)  | 1.0344     | -1.0761 to 3.1948        | 0.355  |
|            |         | Sex (M=1, F=0) | 0.9845 (1, 76.9654)  | 2.1822     | -2.1306 to 6.1515        | 0.3242 |
|            |         | EBV            | 0.0890 (1, 100.3094) | 0.6073     | -3.2431 to 4.6126        | 0.7661 |
| C3         | 133     | TsinceIndex    | 0.0663 (1, 125.7775) | 0.0041     | -0.0256 to 0.0359        | 0.7973 |
|            |         | Comorbidity    | 0.3501 (1, 67.8980)  | -0.0451    | -0.1923 to 0.0981        | 0.556  |
|            |         | Vaccination    | 2.1032 (1, 69.7707)  | 0.0604     | -0.0230 to 0.1489        | 0.1515 |
|            |         | Age            | 1.3327 (1, 78.8728)  | 0.0241     | -0.0155 to 0.0661        | 0.2518 |
|            |         | Sex (M=1, F=0) | 0.1940 (1, 76.9539)  | 0.0182     | -0.0576 to 0.1026        | 0.6609 |
|            |         | EBV            | 0.0003 (1, 102.1705) | 0.0007     | -0.0765 to 0.0728        | 0.986  |
| C4         | 133     | TsinceIndex    | 0.9302 (1, 119.8654) | -0.0038    | -0.0115 to 0.0040        | 0.3368 |
|            |         | Comorbidity    | 0.0132 (1, 67.2889)  | -0.0024    | -0.0410 to 0.0373        | 0.9088 |
|            |         | Vaccination    | 0.3544 (1, 70.1166)  | 0.0067     | -0.0153 to 0.0277        | 0.5535 |
|            |         | Age            | 0.9285 (1, 82.1063)  | 0.0053     | -0.0049 to 0.0159        | 0.3381 |
|            |         | Sex (M=1, F=0) | 0.0115 (1, 78.5566)  | 0.0012     | -0.0202 to 0.0215        | 0.9147 |
|            |         | EBV            | 0.3596 (1, 110.8580) | 0.0059     | -0.0128 to 0.0257        | 0.5499 |

### b. SARS-CoV-2 related cytokines

| Analyte   | obs (n) | Predictor   | F (df1, df2)          | Estimate | 95% CI              | raw P   |
|-----------|---------|-------------|-----------------------|----------|---------------------|---------|
| IFN-alpha | 136     | TsinceIndex | 30.9665 (1, 102.9725) | -8.3157  | -11.2389 to -5.5041 | <0.0001 |
|           |         | Comorbidity | 1.5207 (1, 59.8338)   | -11.3253 | -29.1557 to 5.7932  | 0.2223  |
|           |         | Vaccination | 0.0532 (1, 59.4833)   | -1.1925  | -11.4569 to 9.2811  | 0.8184  |
|           |         | Age         | 1.3826 (1, 61.3045)   | 3.0644   | -2.1685 to 8.3407   | 0.2442  |

| Analyte | obs (n) | Predictor      | F (df1, df2)          | Estimate | 95% CI               | raw P         |
|---------|---------|----------------|-----------------------|----------|----------------------|---------------|
|         |         | Sex (M=1, F=0) | 3.5246 (1, 59.0509)   | 9.8955   | -0.5504 to 20.0692   | 0.0654        |
|         |         | EBV            | 4.2148 (1, 119.5967)  | 8.7201   | 0.7356 to 17.0552    | <b>0.0423</b> |
| IL-6    | 136     | TsincelIndex   | 13.5014 (1, 108.4902) | -10.2454 | -15.8166 to -4.4073  | 0.0004        |
|         |         | Comorbidity    | 0.0455 (1, 64.9710)   | -3.57    | -35.8117 to 29.6540  | 0.8318        |
|         |         | Vaccination    | 0.5641 (1, 64.5790)   | -7.0814  | -26.1728 to 12.1061  | 0.4554        |
|         |         | Age            | 1.4500 (1, 66.4771)   | 5.7238   | -3.7619 to 15.7567   | 0.2328        |
|         |         | Sex (M=1, F=0) | 3.2903 (1, 64.1705)   | 17.4285  | -0.7679 to 35.7653   | 0.0744        |
|         |         | EBV            | 3.6340 (1, 118.9562)  | 14.9338  | -0.1224 to 29.7869   | 0.0590        |
| IL-13   | 136     | TsincelIndex   | 117.4069 (1, 68.7002) | -17.3693 | -20.3142 to -14.3255 | <0.0001       |
|         |         | Comorbidity    | 0.8535 (1, 64.5963)   | -18.6482 | -58.1815 to 18.6766  | 0.3590        |
|         |         | Vaccination    | 0.0575 (1, 64.7193)   | 2.7269   | -19.0886 to 25.4233  | 0.8112        |
|         |         | Age            | 3.0718 (1, 65.1245)   | 9.9769   | -0.8063 to 20.8195   | 0.0844        |
|         |         | Sex (M=1, F=0) | 3.0299 (1, 64.2325)   | 20.2407  | -2.1534 to 42.8667   | 0.0865        |
|         |         | EBV            | 0.5342 (1, 96.9720)   | 4.2162   | -6.6451 to 15.1540   | 0.4666        |

### c. Innate-associated cytokines

| Analyte | obs (n) | Predictor      | F (df1, df2)          | Estimate | 95% CI                | raw P         |
|---------|---------|----------------|-----------------------|----------|-----------------------|---------------|
| IL-1α   | 136     | TsincelIndex   | 7.6888 (1, 120.8035)  | -2.8818  | -5.1918 to -0.9054    | 0.0064        |
|         |         | Comorbidity    | 1.5327 (1, 61.9656)   | -6.8186  | -18.2807 to 4.2099    | 0.2204        |
|         |         | Vaccination    | 1.9113 (1, 61.3236)   | -4.2843  | -10.3878 to 1.7345    | 0.1718        |
|         |         | Age            | 0.5073 (1, 63.5930)   | 1.116    | -1.6963 to 4.2778     | 0.4789        |
|         |         | Sex (M=1, F=0) | 2.1687 (1, 61.1038)   | 4.6484   | -1.8231 to 10.8158    | 0.1460        |
|         |         | EBV            | 7.7586 (1, 104.5994)  | 7.6022   | 2.4221 to 12.8164     | 0.0063        |
| IL-1β   | 136     | TsincelIndex   | 0.1188 (1, 92.7449)   | 0.3426   | -1.4428 to 2.4099     | 0.7311        |
|         |         | Comorbidity    | 0.7581 (1, 65.3465)   | -6.2087  | -20.6272 to 7.8925    | 0.3871        |
|         |         | Vaccination    | 0.9042 (1, 65.2089)   | -3.8197  | -12.1567 to 4.0530    | 0.3452        |
|         |         | Age            | 0.9261 (1, 66.5921)   | 1.9431   | -1.9111 to 5.6236     | 0.3394        |
|         |         | Sex (M=1, F=0) | 4.1613 (1, 64.6493)   | 8.358    | 0.8431 to 16.1785     | 0.0454        |
|         |         | EBV            | 4.9895 (1, 128.6919)  | 6.7727   | 1.1255 to 12.9422     | <b>0.0272</b> |
| GM-CSF  | 136     | TsincelIndex   | 1.5054 (1, 105.1694)  | -0.5996  | -1.4708 to 0.3649     | 0.2226        |
|         |         | Comorbidity    | 0.7454 (1, 66.8187)   | -2.6483  | -8.7871 to 3.1248     | 0.3910        |
|         |         | Vaccination    | 0.0022 (1, 66.5008)   | -0.0813  | -3.7401 to 3.1774     | 0.9626        |
|         |         | Age            | 1.7027 (1, 68.2624)   | 1.1354   | -0.6896 to 2.8915     | 0.1963        |
|         |         | Sex (M=1, F=0) | 3.4213 (1, 66.0435)   | 3.2568   | -0.0945 to 6.7086     | 0.0688        |
|         |         | EBV            | 4.0249 (1, 122.8621)  | 2.8157   | 0.0909 to 5.4269      | 0.0470        |
| TNF-α   | 136     | TsincelIndex   | 0.6789 (1, 116.2504)  | 62.6191  | -96.1807 to 211.8993  | 0.4116        |
|         |         | Comorbidity    | 0.7576 (1, 67.9638)   | -270.606 | -872.2837 to 340.5532 | 0.3872        |
|         |         | Vaccination    | 0.0307 (1, 66.5121)   | -30.5149 | -394.6246 to 304.4905 | 0.8614        |
|         |         | Age            | 0.6550 (1, 69.1902)   | 72.0439  | -99.1294 to 246.0072  | 0.4211        |
|         |         | Sex (M=1, F=0) | 5.7729 (1, 67.0318)   | 426.4619 | 65.2576 to 781.8016   | 0.0191        |
|         |         | EBV            | 7.0555 (1, 81.8964)   | 449.8793 | 99.9196 to 750.3758   | 0.0095        |
| IL-15   | 136     | TsincelIndex   | 15.0291 (1, 125.9663) | -38.9436 | -59.4189 to -20.3002  | 0.0002        |
|         |         | Comorbidity    | 1.4488 (1, 59.0952)   | -60.3926 | -158.5127 to 34.2072  | 0.2335        |
|         |         | Vaccination    | 1.2952 (1, 58.3144)   | -32.1115 | -88.2833 to 23.0183   | 0.2597        |
|         |         | Age            | 0.8648 (1, 60.7310)   | 13.2916  | -16.2765 to 41.0003   | 0.3561        |
|         |         | Sex (M=1, F=0) | 3.7595 (1, 58.2136)   | 55.7179  | -1.0961 to 110.4158   | 0.0574        |
|         |         | EBV            | 8.5183 (1, 95.5353)   | 74.367   | 20.8550 to 122.7316   | <b>0.0044</b> |
| IL-18   | 136     | TsincelIndex   | 2.3730 (1, 94.5713)   | -7.0125  | -15.3152 to 1.9495    | 0.1268        |
|         |         | Comorbidity    | 0.3103 (1, 67.6355)   | 9.5835   | -22.8161 to 43.4613   | 0.5793        |

| Analyte | obs (n) | Predictor      | F (df1, df2)        | Estimate | 95% CI              | raw P         |
|---------|---------|----------------|---------------------|----------|---------------------|---------------|
|         |         | Vaccination    | 0.6618 (1, 65.7913) | 7.8074   | -10.1133 to 25.2900 | 0.4188        |
|         |         | Age            | 1.7347 (1, 68.3066) | -6.5027  | -16.3122 to 3.3653  | 0.1922        |
|         |         | Sex (M=1, F=0) | 5.5901 (1, 66.7272) | 23.168   | 3.6273 to 42.5224   | 0.0210        |
|         |         | EBV            | 4.2814 (1, 74.4913) | 19.8455  | 0.8662 to 39.9876   | <b>0.0420</b> |

### d.Th1/Th2 Balance (IL-4/IFN $\gamma$ )

| Analyte                   | obs (n) | Predictor      | F (df1, df2)         | Estimate | 95% CI            | raw P  |
|---------------------------|---------|----------------|----------------------|----------|-------------------|--------|
| IL-4 / IFN $\gamma$ ratio | 136     | TsincerIndex   | 0.0492 (1, 116.6014) | 0.0048   | -0.0406 to 0.0486 | 0.8248 |
|                           |         | Comorbidity    | 0.3641 (1, 66.3096)  | 0.054    | -0.1154 to 0.2217 | 0.5483 |
|                           |         | Vaccination    | 0.2045 (1, 64.8755)  | 0.0227   | -0.0737 to 0.1214 | 0.6527 |
|                           |         | Age            | 0.3032 (1, 67.5614)  | 0.0141   | -0.0336 to 0.0686 | 0.5837 |
|                           |         | Sex (M=1, F=0) | 0.2634 (1, 65.3759)  | -0.0262  | -0.1264 to 0.0686 | 0.6095 |
|                           |         | EBV            | 1.5071 (1, 80.7721)  | -0.0598  | -0.1475 to 0.0351 | 0.2231 |

### e.Th17/22-associated cytokines

| Analyte  | obs (n) | Predictor      | F (df1, df2)          | Estimate  | 95% CI                 | raw P         |
|----------|---------|----------------|-----------------------|-----------|------------------------|---------------|
| IL-12p40 | 136     | TsincerIndex   | 0.1997 (1, 122.2443)  | 51.1136   | -170.3487 to 276.7515  | 0.6557        |
|          |         | Comorbidity    | 1.0906 (1, 66.0406)   | -629.4195 | -1799.5231 to 584.8103 | 0.3002        |
|          |         | Vaccination    | 0.4986 (1, 65.3846)   | -239.4511 | -897.3348 to 417.9618  | 0.4826        |
|          |         | Age            | 0.2428 (1, 67.6700)   | 84.5142   | -251.8513 to 420.6164  | 0.6238        |
|          |         | Sex (M=1, F=0) | 6.5154 (1, 65.1746)   | 881.675   | 236.2351 to 1592.6432  | 0.0130        |
|          |         | EBV            | 11.0355 (1, 106.4001) | 994.594   | 415.1102 to 1568.7524  | <b>0.0012</b> |
| IL-17A   | 136     | TsincerIndex   | 0.2722 (1, 124.8386)  | -0.0661   | -0.3194 to 0.1860      | 0.6028        |
|          |         | Comorbidity    | 0.2876 (1, 67.3414)   | -0.2934   | -1.4294 to 0.7755      | 0.5935        |
|          |         | Vaccination    | 1.4324 (1, 66.1084)   | -0.3674   | -0.9452 to 0.2547      | 0.2356        |
|          |         | Age            | 0.0218 (1, 68.7851)   | -0.0231   | -0.3560 to 0.2662      | 0.8830        |
|          |         | Sex (M=1, F=0) | 1.3595 (1, 66.4126)   | 0.3646    | -0.2558 to 0.9710      | 0.2478        |
|          |         | EBV            | 3.2645 (1, 86.4924)   | 0.5294    | -0.0376 to 1.1244      | 0.0743        |
| IL-17F   | 136     | TsincerIndex   | 3.4153 (1, 105.0353)  | -1.8705   | -3.9718 to -0.0158     | 0.0674        |
|          |         | Comorbidity    | 0.8539 (1, 66.7503)   | -5.8766   | -18.0163 to 6.3702     | 0.3588        |
|          |         | Vaccination    | 0.0342 (1, 66.4340)   | 0.662     | -5.7798 to 7.9637      | 0.8539        |
|          |         | Age            | 1.4463 (1, 68.1928)   | 2.1695    | -1.1854 to 5.9102      | 0.2333        |
|          |         | Sex (M=1, F=0) | 4.4687 (1, 65.9756)   | 7.7169    | 0.1193 to 15.5337      | 0.0383        |
|          |         | EBV            | 3.8468 (1, 122.9180)  | 5.7041    | 0.1220 to 11.4545      | 0.0521        |
| IL-22    | 136     | TsincerIndex   | 10.0375 (1, 116.8028) | -2.1017   | -3.4260 to -0.8201     | 0.0020        |
|          |         | Comorbidity    | 0.2455 (1, 64.9347)   | -1.824    | -8.3211 to 5.3329      | 0.6219        |
|          |         | Vaccination    | 0.0797 (1, 64.3917)   | 0.585     | -3.5076 to 4.7117      | 0.7786        |
|          |         | Age            | 0.9407 (1, 66.5286)   | 1.0149    | -0.8921 to 2.9798      | 0.3356        |
|          |         | Sex (M=1, F=0) | 5.1208 (1, 64.0930)   | 4.7765    | 0.4507 to 9.0213       | 0.0270        |
|          |         | EBV            | 4.1788 (1, 111.3021)  | 3.6543    | 0.0342 to 7.1583       | <b>0.0433</b> |

### f. Regulatory cytokines

| Analyte | obs (n) | Predictor      | F (df1, df2)          | Estimate | 95% CI              | raw P         |
|---------|---------|----------------|-----------------------|----------|---------------------|---------------|
| IL-11   | 136     | TsincerIndex   | 24.0098 (1, 101.6221) | -7.1604  | -10.0351 to -4.2351 | <0.0001       |
|         |         | Comorbidity    | 1.8030 (1, 62.4370)   | -12.4124 | -32.1264 to 6.7767  | 0.1842        |
|         |         | Vaccination    | 0.4367 (1, 62.1314)   | -3.4405  | -13.4011 to 7.7214  | 0.5112        |
|         |         | Age            | 2.3446 (1, 63.8723)   | 4.0149   | -1.1453 to 9.3585   | 0.1307        |
|         |         | Sex (M=1, F=0) | 1.5238 (1, 61.6666)   | 6.5506   | -3.7196 to 16.3599  | 0.2217        |
|         |         | EBV            | 6.5693 (1, 122.6172)  | 10.7974  | 2.5200 to 17.9975   | <b>0.0116</b> |

| Analyte | obs (n) | Predictor      | F (df1, df2)         | Estimate | 95% CI                | raw P         |
|---------|---------|----------------|----------------------|----------|-----------------------|---------------|
| IL-10   | 136     | TsinceIndex    | 5.5922 (1, 124.6465) | -0.6048  | -1.0728 to -0.1105    | 0.0196        |
|         |         | Comorbidity    | 0.2155 (1, 66.6375)  | -0.6091  | -3.1476 to 1.8004     | 0.6440        |
|         |         | Vaccination    | 0.1111 (1, 65.9183)  | -0.246   | -1.6054 to 1.1069     | 0.7400        |
|         |         | Age            | 1.3472 (1, 68.2758)  | 0.4336   | -0.2981 to 1.1660     | 0.2498        |
|         |         | Sex (M=1, F=0) | 3.9642 (1, 65.7602)  | 1.4966   | -0.0937 to 2.9599     | 0.0506        |
|         |         | EBV            | 6.1582 (1, 103.8895) | 1.6356   | 0.3592 to 2.8537      | <b>0.0147</b> |
| IL-27   | 136     | TsinceIndex    | 9.8878 (1, 84.0096)  | -37.6827 | -61.2812 to -15.1229  | 0.0023        |
|         |         | Comorbidity    | 0.8600 (1, 64.5455)  | -90.1409 | -293.8003 to 101.5830 | 0.3572        |
|         |         | Vaccination    | 0.8985 (1, 64.5236)  | -51.911  | -158.6306 to 45.8202  | 0.3467        |
|         |         | Age            | 0.8235 (1, 65.6047)  | 24.947   | -26.3503 to 77.3958   | 0.3675        |
|         |         | Sex (M=1, F=0) | 2.6664 (1, 63.9236)  | 91.2703  | -27.7403 to 198.6589  | 0.1074        |
|         |         | EBV            | 4.8595 (1, 127.4497) | 84.5259  | 9.3582 to 154.8435    | <b>0.0293</b> |

## 377 g. Autoantibodies

| Analyte          | obs (n) | Predictor      | F (df1, df2)          | Estimate | 95% CI             | raw P   |
|------------------|---------|----------------|-----------------------|----------|--------------------|---------|
| Anti-Prothrombin | 136     | TsinceIndex    | 20.1861 (1, 109.0069) | -1.7558  | -2.5502 to -0.9580 | <0.0001 |
|                  |         | Comorbidity    | 0.0014 (1, 67.5455)   | 0.089    | -4.8482 to 4.6129  | 0.9701  |
|                  |         | Vaccination    | 0.2838 (1, 67.1689)   | 0.7101   | -1.9337 to 3.2386  | 0.5959  |
|                  |         | Age            | 0.8251 (1, 69.0360)   | 0.6102   | -0.6623 to 2.0265  | 0.3669  |
|                  |         | Sex (M=1, F=0) | 2.2601 (1, 66.7510)   | -2.0418  | -4.6059 to 0.5632  | 0.1375  |
|                  |         | EBV            | 3.2898 (1, 120.3521)  | 2        | -0.2226 to 4.2796  | 0.0722  |
| Anti-CCP         | 136     | TsinceIndex    | 0.7553 (1, 98.4492)   | -0.3022  | -0.9598 to 0.3871  | 0.3869  |
|                  |         | Comorbidity    | 5.7271 (1, 67.9234)   | 5.6897   | 1.2613 to 10.3561  | 0.0195  |
|                  |         | Vaccination    | 0.7368 (1, 67.7283)   | 1.1496   | -1.5218 to 3.6657  | 0.3937  |
|                  |         | Age            | 0.4190 (1, 69.2384)   | 0.436    | -0.8210 to 1.7495  | 0.5196  |
|                  |         | Sex (M=1, F=0) | 1.5040 (1, 67.1988)   | -1.6748  | -4.3746 to 0.8563  | 0.2243  |
|                  |         | EBV            | 0.0779 (1, 127.4979)  | 0.29     | -1.7653 to 2.3843  | 0.7806  |
| Anti-TransG      | 136     | TsinceIndex    | 1.6355 (1, 74.9042)   | 0.3846   | -0.2069 to 1.0107  | 0.2049  |
|                  |         | Comorbidity    | 0.7110 (1, 66.6326)   | -2.6865  | -8.8466 to 3.3709  | 0.4021  |
|                  |         | Vaccination    | 3.1556 (1, 66.7357)   | 3.1882   | -0.2688 to 6.5978  | 0.0802  |
|                  |         | Age            | 0.0587 (1, 67.3368)   | -0.2179  | -1.9283 to 1.4759  | 0.8093  |
|                  |         | Sex (M=1, F=0) | 0.0179 (1, 66.1736)   | -0.2456  | -3.5136 to 3.3990  | 0.8939  |
|                  |         | EBV            | 1.3903 (1, 110.9859)  | -1.2293  | -3.2905 to 0.7120  | 0.2409  |
| M3-mAChR AAK     | 137     | TsinceIndex    | 0.6821 (1, 126.2062)  | 0.918    | -1.2678 to 3.2187  | 0.4104  |
|                  |         | Comorbidity    | 1.4000 (1, 67.2511)   | 5.7304   | -4.1050 to 14.9778 | 0.2409  |
|                  |         | Vaccination    | 0.5997 (1, 70.1476)   | -2.0544  | -7.5731 to 3.2095  | 0.4413  |
|                  |         | Age            | 0.2943 (1, 77.2695)   | 0.7351   | -1.9160 to 3.4406  | 0.5890  |
|                  |         | Sex (M=1, F=0) | 0.7065 (1, 76.8778)   | 2.2374   | -3.5251 to 7.4931  | 0.4032  |
|                  |         | EBV            | 8.3462 (1, 94.3314)   | 7.2379   | 1.9072 to 12.0500  | 0.0048  |
| M4-mAChR AAK     | 137     | TsinceIndex    | 1.8083 (1, 123.1557)  | -1.1688  | -2.7845 to 0.5206  | 0.1812  |
|                  |         | Comorbidity    | 0.6186 (1, 66.2147)   | 3.6252   | -5.3600 to 12.6264 | 0.4344  |
|                  |         | Vaccination    | 0.0656 (1, 70.3677)   | -0.6401  | -5.4490 to 4.1419  | 0.7986  |
|                  |         | Age            | 0.5322 (1, 83.2956)   | 0.9073   | -1.5916 to 3.4968  | 0.4677  |
|                  |         | Sex (M=1, F=0) | 0.0201 (1, 80.0846)   | 0.3475   | -4.7364 to 5.0171  | 0.8877  |
|                  |         | EBV            | 6.5382 (1, 113.0733)  | 4.7318   | 1.1452 to 7.8124   | 0.0119  |

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## h. Granulocytes

| Analyte     | obs (n) | Predictor      | F (df1, df2)         | Estimate | 95% CI             | raw P         |
|-------------|---------|----------------|----------------------|----------|--------------------|---------------|
| Neutrophils | 137     | TsincelIndex   | 0.8522 (1, 85.9325)  | 0.1015   | -0.1179 to 0.3219  | 0.3585        |
|             |         | Comorbidity    | 2.0040 (1, 62.5503)  | -0.5834  | -1.3339 to 0.2628  | 0.1618        |
|             |         | Vaccination    | 10.5684 (1, 63.4130) | 0.7415   | 0.3017 to 1.2319   | 0.0018        |
|             |         | Age            | 8.8916 (1, 66.4799)  | 0.3548   | 0.1190 to 0.5897   | 0.0040        |
|             |         | Sex (M=1, F=0) | 0.2970 (1, 66.8155)  | 0.127    | -0.3244 to 0.5933  | 0.5876        |
|             |         | EBV            | 5.4935 (1, 71.8285)  | 0.5331   | 0.0775 to 0.9657   | <b>0.0219</b> |
|             |         |                |                      |          |                    |               |
| Eosinophils | 137     | TsincelIndex   | 3.3267 (1, 114.5374) | 0.0255   | -0.0027 to 0.0531  | 0.0708        |
|             |         | Comorbidity    | 0.0710 (1, 66.2732)  | 0.0152   | -0.0962 to 0.1320  | 0.7908        |
|             |         | Vaccination    | 0.7027 (1, 68.6584)  | -0.0264  | -0.0881 to 0.0340  | 0.4048        |
|             |         | Age            | 9.0526 (1, 74.0629)  | -0.0489  | -0.0798 to -0.0183 | 0.0036        |
|             |         | Sex (M=1, F=0) | 0.7077 (1, 73.8811)  | 0.0268   | -0.0292 to 0.0906  | 0.4029        |
|             |         | EBV            | 0.0025 (1, 85.8172)  | -0.0015  | -0.0623 to 0.0540  | 0.9604        |
|             |         |                |                      |          |                    |               |
| Basophils   | 137     | TsincelIndex   | 0.4621 (1, 128.3612) | 0.0012   | -0.0024 to 0.0045  | 0.4979        |
|             |         | Comorbidity    | 0.0716 (1, 67.4922)  | -0.002   | -0.0170 to 0.0119  | 0.7899        |
|             |         | Vaccination    | 4.2184 (1, 70.9290)  | 0.0085   | -0.0002 to 0.0165  | 0.0437        |
|             |         | Age            | 0.0654 (1, 78.9578)  | -0.0005  | -0.0047 to 0.0039  | 0.7988        |
|             |         | Sex (M=1, F=0) | 0.4704 (1, 77.8546)  | -0.0029  | -0.0113 to 0.0056  | 0.4948        |
|             |         | EBV            | 0.0067 (1, 97.0784)  | -0.0003  | -0.0079 to 0.0068  | 0.9351        |
|             |         |                |                      |          |                    |               |

## i. Mental Health

| Analyte   | obs (n) | Predictor      | F (df1, df2)          | Estimate | 95% CI             | raw P  |
|-----------|---------|----------------|-----------------------|----------|--------------------|--------|
| SF-12 PCS | 137     | TsincelIndex   | 0.4621 (1, 128.3612)  | 0.0012   | -0.0024 to 0.0045  | 0.4979 |
|           |         | Comorbidity    | 0.0716 (1, 67.4922)   | -0.002   | -0.0170 to 0.0119  | 0.7899 |
|           |         | Vaccination    | 4.2184 (1, 70.9290)   | 0.0085   | -0.0002 to 0.0165  | 0.0437 |
|           |         | Age            | 0.0654 (1, 78.9578)   | -0.0005  | -0.0047 to 0.0039  | 0.7988 |
|           |         | Sex (M=1, F=0) | 0.4704 (1, 77.8546)   | -0.0029  | -0.0113 to 0.0056  | 0.4948 |
|           |         | EBV            | 0.0067 (1, 97.0784)   | -0.0003  | -0.0079 to 0.0068  | 0.9351 |
|           |         |                |                       |          |                    |        |
| PHQ-9     | 138     | TsincelIndex   | 11.5632 (1, 128.1644) | -1.6381  | -2.5975 to -0.7016 | 0.0009 |
|           |         | Comorbidity    | 0.2100 (1, 65.8572)   | 0.9767   | -3.2592 to 5.5588  | 0.6483 |
|           |         | Vaccination    | 0.3915 (1, 68.7232)   | -0.7298  | -3.0585 to 1.7432  | 0.5336 |
|           |         | Age            | 1.3805 (1, 76.0060)   | 0.6987   | -0.3869 to 1.8441  | 0.2437 |
|           |         | Sex (M=1, F=0) | 0.3534 (1, 75.2205)   | -0.694   | -2.9546 to 1.6545  | 0.5540 |
|           |         | EBV            | 0.9549 (1, 94.0475)   | 1.0709   | -1.0301 to 3.3019  | 0.3310 |
|           |         |                |                       |          |                    |        |
| GAD-7     | 138     | TsincelIndex   | 5.3317 (1, 128.9848)  | -0.9675  | -1.8107 to -0.1759 | 0.0225 |
|           |         | Comorbidity    | 0.0804 (1, 66.0600)   | 0.5305   | -2.9041 to 4.1941  | 0.7777 |
|           |         | Vaccination    | 0.0621 (1, 69.0227)   | 0.2551   | -1.6112 to 2.2032  | 0.8040 |
|           |         | Age            | 0.2566 (1, 76.5817)   | 0.2641   | -0.7210 to 1.3336  | 0.6139 |
|           |         | Sex (M=1, F=0) | 0.1677 (1, 75.6958)   | -0.4192  | -2.2688 to 1.4859  | 0.6833 |
|           |         | EBV            | 2.2725 (1, 95.2333)   | 1.5834   | -0.2178 to 3.9955  | 0.1350 |
|           |         |                |                       |          |                    |        |

**Supplementary Table 5a | LMM screening of 43 metabolic and biomarker parameters.** Related to Table 3. Two-sided linear mixed-effects models (LMMs) were fitted separately for each of 43 blood-based clinical laboratory parameters, with participant ID included as a random intercept. Fixed effects comprised TsincelIndex (LC ≤1 year versus LC 1–3 yr), anti-EBV EBNA serostatus, anti-DFS70 aAb status, and all two-way and three-way interaction terms. P values were estimated using Satterthwaite's approximation and validated by non-parametric percentile bootstrap (1,000 iterations). Raw and Holm–Bonferroni-adjusted P values are reported across all 43 parameters; adjusted P < 0.05 was considered significant. R<sup>2</sup>m indicates the variance explained by the fixed

effects. Effect-specific P values for the main effects and interaction terms are shown only for analytes whose overall model remained significant after Holm–Bonferroni correction; corresponding cells for all other analytes were left blank by design. Full effect-level summaries across all 43 analytes are provided in Supplementary Table 5b. Abbreviations: aAb, autoantibody; ACTH, adrenocorticotrophic hormone; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase myocardial band; DFS70, dense fine speckled 70; EBV, Epstein–Barr virus; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; hs-CRP, high-sensitivity C-reactive protein; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LC, long COVID; LDH, lactate dehydrogenase; LMM, linear mixed-effects model; Lp(a), lipoprotein(a); obs, observations; RDW, red cell distribution width; TSH, thyroid-stimulating hormone.

| Analyte            | P                | obs (n) | R <sup>2</sup> Mag | Adj. P        | Time (T)                             | EBV (E) | DFS70 (D) | Interaction T*D | Interaction E*D | Interaction T*E | Interaction T*E*D |
|--------------------|------------------|---------|--------------------|---------------|--------------------------------------|---------|-----------|-----------------|-----------------|-----------------|-------------------|
| TSH                | <b>&lt;.0001</b> | 137     | 0.4141             | <b>0.0043</b> | <.0001                               | <.0001  | <.0001    | <.00001         | <.0001          | <.0001          | <.0001            |
| aPTT               | <b>&lt;.0001</b> | 138     | 0.2477             | <b>0.0043</b> | 0.0004                               | 0.0025  | 0.0056    | 0.0003          | 0.051           | 0.2716          | 0.0003            |
| Lp(a)              | <b>0.0003</b>    | 131     | 0.1816             | <b>0.0123</b> | 0.0015                               | 0.0753  | 0.0078    | 0.0022          | 0.0146          | 0.0053          | 0.0022            |
| RDW                | <b>0.0016</b>    | 137     | 0.1636             | 0.064         |                                      |         |           |                 |                 |                 |                   |
| IgA                | <b>0.0018</b>    | 138     | 0.1875             | 0.0702        |                                      |         |           |                 |                 |                 |                   |
| Vitamin D          | <b>0.0039</b>    | 136     | 0.1721             | 0.1482        |                                      |         |           |                 |                 |                 |                   |
| CRP HS mg/l        | 0.0095           | 111     | 0.1379             | 0.3515        |                                      |         |           |                 |                 |                 |                   |
| Factor VIII        | 0.0171           | 138     | 0.1522             | 0.6156        |                                      |         |           |                 |                 |                 |                   |
| Zinc               | 0.0545           | 137     | 0.1071             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Selenium           | 0.0591           | 136     | 0.0942             | 1.0000        | <b>Holm–Bonferroni Adj. P ≥ 0.05</b> |         |           |                 |                 |                 |                   |
| Bicarbonate        | 0.0635           | 127     | 0.0941             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Chloride           | 0.0644           | 137     | 0.0935             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Holotranscobalamin | 0.1731           | 73      | 0.1339             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Creatinine         | 0.2347           | 137     | 0.0875             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Vitamin B12        | 0.257            | 133     | 0.0466             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Lipase             | 0.2655           | 137     | 0.0517             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| LDH                | 0.2696           | 137     | 0.0625             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| D-dimer            | 0.2702           | 138     | 0.0591             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Fibrinogen         | 0.3118           | 138     | 0.0604             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Potassium          | 0.3141           | 137     | 0.0677             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Free proteinS      | 0.3221           | 137     | 0.0611             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Ferritin           | 0.3262           | 137     | 0.0475             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| CK                 | 0.4264           | 137     | 0.0531             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Vitamin B6         | 0.4592           | 136     | 0.0577             | 1.0000        | <b>Holm–Bonferroni Adj. P ≥ 0.05</b> |         |           |                 |                 |                 |                   |
| Folate             | 0.4755           | 137     | 0.0364             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Glucose            | 0.511            | 127     | 0.0455             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Lactate            | 0.5453           | 131     | 0.0438             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Phosphate          | 0.55             | 137     | 0.0478             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| hs-cTnT            | 0.5537           | 137     | 0.0474             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| IgM                | 0.5729           | 138     | 0.0366             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| IgG                | 0.5746           | 138     | 0.0353             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| CK-MB              | 0.6354           | 137     | 0.0361             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Oxygen             | 0.6761           | 127     | 0.0381             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| ACTH               | 0.7157           | 137     | 0.0416             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| AST                | 0.7509           | 137     | 0.0299             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Blood pH           | 0.7893           | 127     | 0.0314             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Calcium            | 0.8242           | 137     | 0.0278             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Urine pH           | 0.8628           | 127     | 0.0251             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Triglycerides      | 0.8764           | 135     | 0.0243             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| ALT                | 0.908            | 137     | 0.0131             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| eGFR               | 0.9322           | 138     | 0.0166             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Vitamin B1         | 0.9594           | 134     | 0.0171             | 1.0000        |                                      |         |           |                 |                 |                 |                   |
| Uric acid          | 0.9776           | 111     | 0.0119             | 1.0000        |                                      |         |           |                 |                 |                 |                   |

**Supplementary Table 5b |** Effect-level model output for the three parameters remaining significant after multiple-testing correction, plus effect-specific summaries across all 43 parameters. Related to Table 3. Two-sided linear mixed-effects models (LMMs) are shown for the three parameters that remained significant after Holm–Bonferroni adjustment across 43 tested parameters. Models included TsinceIndex as a binary variable (LC ≤1 year versus LC 1–3 yr), anti-EBV EBNA status,

anti-DFS70 aAb status, and all relevant two-way and three-way interaction terms, with participant ID included as a random intercept. For each fixed effect, F statistics with numerator and residual degrees of freedom, parameter estimates, 95% confidence intervals, and raw P values are reported. Degrees of freedom were estimated using Satterthwaite's approximation, and 95% confidence intervals were obtained by percentile bootstrap (1,000 resamples). Model fit showed marginal and conditional R<sup>2</sup> values of 0.1816 and 0.9416 for LP(a), 0.2477 and 0.7023 for aPTT, and 0.4141 and 0.6991 for TSH, respectively; all models were significant by likelihood-ratio testing (all P < 0.0001, except LP(a), P = 0.0003). Lower panels summarize the fixed effects of TsinclIndex, anti-DFS70 status, and anti-EBV EBNA status across all 43 analytes.

#### LP(a)

| Predictor                 | F (df1, df2)         | Estimate  | 95% CI                | raw P  |
|---------------------------|----------------------|-----------|-----------------------|--------|
| TsinclIndex               | 10.8515 (1, 70.7058) | -90.5793  | -140.6564 to -37.9835 | 0.0015 |
| DFS70                     | 7.5063 (1, 69.4132)  | 77.8142   | 19.9763 to 130.9512   | 0.0078 |
| EBV                       | 3.2562 (1, 72.0769)  | 50.2246   | -8.0446 to 104.6886   | 0.0753 |
| TsinclIndex × DFS70       | 10.1337 (1, 70.7058) | -175.0643 | -277.2893 to -72.6404 | 0.0022 |
| TsinclIndex × EBV         | 8.2854 (1, 70.9029)  | -158.4385 | -268.2688 to -51.7122 | 0.0053 |
| DFS70 × EBV               | 6.2645 (1, 72.0769)  | 139.3277  | 26.2671 to 251.1839   | 0.0146 |
| TsinclIndex × DFS70 × EBV | 7.9643 (1, 70.9029)  | -310.6771 | -527.0259 to -99.8924 | 0.0062 |

#### aPTT

| Predictor                 | F (df1, df2)         | Estimate | 95% CI              | raw P  |
|---------------------------|----------------------|----------|---------------------|--------|
| TsinclIndex               | 13.3700 (1, 83.8713) | -3.9609  | -6.0473 to -1.7776  | 0.0004 |
| DFS70                     | 8.1085 (1, 79.6957)  | 3.1320   | 0.9880 to 5.2495    | 0.0056 |
| EBV                       | 9.7016 (1, 81.4417)  | 3.4109   | 1.3755 to 5.4691    | 0.0025 |
| TsinclIndex × DFS70       | 14.3897 (1, 83.8713) | -8.2183  | -12.5283 to -3.6742 | 0.0003 |
| TsinclIndex × EBV         | 1.2246 (1, 83.7277)  | -2.4016  | -6.5191 to 2.1265   | 0.2716 |
| DFS70 × EBV               | 3.9234 (1, 81.4417)  | 4.3382   | 0.1020 to 8.6903    | 0.0510 |
| TsinclIndex × DFS70 × EBV | 2.2544 (1, 83.7277)  | -6.5169  | -15.0383 to 2.4404  | 0.1370 |

#### TSH

| Predictor                 | F (df1, df2)         | Estimate | 95% CI            | raw P   |
|---------------------------|----------------------|----------|-------------------|---------|
| TsinclIndex               | 23.0038 (1, 93.0667) | 2.0647   | 1.2128 to 2.9165  | <0.0001 |
| DFS70                     | 40.0124 (1, 88.8778) | 2.7532   | 1.8919 to 3.6145  | <0.0001 |
| EBV                       | 23.6385 (1, 90.2590) | 2.1102   | 1.2514 to 2.9691  | <0.0001 |
| TsinclIndex × DFS70       | 28.6769 (1, 93.0667) | 4.6105   | 2.9068 to 6.3141  | <0.0001 |
| TsinclIndex × EBV         | 30.3013 (1, 92.7434) | 4.7462   | 3.0401 to 6.4524  | <0.0001 |
| DFS70 × EBV               | 25.1040 (1, 90.2590) | 4.3493   | 2.6316 to 6.0671  | <0.0001 |
| TsinclIndex × DFS70 × EBV | 25.9706 (1, 92.7434) | 8.7880   | 5.3756 to 12.2003 | <0.0001 |

#### TsinclIndex effect across all 43 analytes

| Analyte | F (df1, df2)         | Estimate | 95% CI lower to upper | raw P  |
|---------|----------------------|----------|-----------------------|--------|
| TSH     | 23.0038 (1, 93.0667) | 2.0647   | 1.1913 to 2.8685      | <.0001 |
| aPTT    | 13.3700 (1, 83.8713) | -3.9609  | -6.1676 to -1.7687    | 0.0004 |
| Lp(a)   | 10.8515 (1, 70.7058) | -90.5793 | -143.8749 to -35.9046 | 0.0015 |
| ACTH    | 0.0472 (1, 84.9612)  | -1.1777  | -11.6833 to 9.7447    | 0.8285 |
| ALT     | 0.0814 (1, 71.7088)  | 0.0516   | -0.3037 to 0.3812     | 0.7763 |
| AST     | 0.4251 (1, 77.8481)  | -0.0714  | -0.2833 to 0.1597     | 0.5163 |

| Analyte              | F (df1, df2)             | Estimate | 95% CI lower to upper | raw P  |
|----------------------|--------------------------|----------|-----------------------|--------|
| Blood pH             | 0.0320 (1, 91.5232)      | 0.0020   | -0.0189 to 0.0256     | 0.8585 |
| CK                   | 0.0051 (1, 115.2715)     | -0.1037  | -2.9407 to 2.7649     | 0.9433 |
| CK-MB                | 0.2850 (1, 79.4893)      | -0.2475  | -1.1130 to 0.7443     | 0.5949 |
| Calcium              | 0.1368 (1, 101.9214)     | -0.0131  | -0.0835 to 0.0567     | 0.7122 |
| Chloride             | 0.8824 (1, 111.7689)     | 0.7254   | -0.7760 to 2.2398     | 0.3496 |
| Creatinine           | 0.0001 (1, 78.6462)      | 0.0683   | -9.9409 to 11.3401    | 0.9903 |
| D-dimer              | 0.2316 (1, 120.1178)     | 19.4825  | -58.8297 to 99.7768   | 0.6312 |
| Factor VIII          | 2.3492 (1, 92.0462)      | 18.7727  | -5.5424 to 42.2800    | 0.1288 |
| Ferritin             | 0.3004 (1, 76.8874)      | -10.4783 | -48.4507 to 27.8592   | 0.5852 |
| Fibrinogen           | 0.9793 (1, 77.5560)      | 0.2168   | -0.2136 to 0.6296     | 0.3254 |
| Folate               | 0.2752 (1, 74.4616)      | -1.5865  | -7.2925 to 4.1967     | 0.6014 |
| Free protein S       | 5.3227 (1, 81.5742)      | -18.5697 | -35.3476 to -2.8059   | 0.0236 |
| Glucose              | 0.4001 (1, 119.0000)     | 0.1652   | -0.3773 to 0.6786     | 0.5283 |
| Holotranscobalamin   | 1.1657 (1.0000, 43.0867) | 15.0760  | -11.1751 to 38.6771   | 0.2863 |
| IgA                  | 0.8850 (1, 105.6613)     | -0.5419  | -1.6253 to 0.5437     | 0.3490 |
| IgG                  | 1.0169 (1, 73.4721)      | 0.9679   | -0.9109 to 2.8971     | 0.3166 |
| IgM                  | 0.5230 (1, 70.5523)      | 0.1474   | -0.2331 to 0.5689     | 0.4720 |
| LDH                  | 3.2929 (1, 86.2536)      | -0.4948  | -0.9999 to 0.0234     | 0.0731 |
| Lactate              | 0.3159 (1, 109.8061)     | -0.0904  | -0.4223 to 0.2079     | 0.5752 |
| Lipase               | 0.0650 (1, 74.0014)      | -0.0153  | -0.1289 to 0.0888     | 0.7994 |
| Oxygen               | 0.1442 (1, 101.2408)     | -0.3562  | -2.2876 to 1.4061     | 0.7049 |
| Phosphate            | 0.9725 (1, 84.2751)      | -0.0908  | -0.2675 to 0.0933     | 0.3269 |
| Potassium            | 0.0164 (1, 92.9724)      | 0.0140   | -0.2028 to 0.2182     | 0.8983 |
| RDW                  | 9.8620 (1, 76.3516)      | 0.8855   | 0.2936 to 1.4722      | 0.0024 |
| Selenium             | 0.1909 (1, 84.0881)      | -0.0263  | -0.1480 to 0.0897     | 0.6633 |
| Standard bicarbonate | 0.5950 (1, 85.7801)      | 0.3418   | -0.4564 to 1.1522     | 0.4426 |
| Triglycerides        | 0.3641 (1, 100.5375)     | -0.1473  | -0.5973 to 0.3396     | 0.5476 |
| Uric acid            | 0.5203 (1.0000, 64.8662) | 26.3469  | -44.9953 to 92.4289   | 0.4733 |
| Urine pH             | 0.0048 (1, 93.0272)      | -0.0293  | -0.8727 to 0.8179     | 0.9447 |
| Vitamin B1           | 0.3248 (1, 94.9403)      | 8.4384   | -21.1339 to 38.5476   | 0.5701 |
| Vitamin B12          | 0.0096 (1, 79.4277)      | -12.2694 | -249.7698 to 231.7737 | 0.9220 |
| Vitamin B6           | 0.3450 (1, 95.9158)      | -27.7940 | -118.2831 to 63.0868  | 0.5583 |
| Vitamin D            | 5.5840 (1, 104.3312)     | -30.1484 | -54.6478 to -4.7638   | 0.0200 |
| Zinc                 | 0.2454 (1, 99.8496)      | 0.4402   | -1.3016 to 2.2542     | 0.6215 |
| eGFR                 | 0.0937 (1, 84.4070)      | 2.0194   | -12.0537 to 14.2052   | 0.7602 |
| hs-CRP               | 0.0694 (1.0000, 62.7000) | 0.0222   | -0.8981 to 0.9363     | 0.7930 |
| hs-cTnT              | 0.0001 (1, 106.0523)     | -0.0083  | -1.6178 to 1.6876     | 0.9921 |

### Anti-DFS70 effect across all 43 analytes

| Analyte | F (df1, df2)         | Estimate | 95% CI lower to upper | raw P   |
|---------|----------------------|----------|-----------------------|---------|
| TSH     | 40.0124 (1, 88.8778) | 2.7532   | 1.8972 to 3.6084      | <0.0001 |
| aPTT    | 8.1085 (1, 79.6957)  | 3.1320   | 1.0089 to 5.2095      | 0.0056  |
| Lp(a)   | 7.5063 (1, 69.4132)  | 77.8142  | 22.8854 to 129.7002   | 0.0078  |

| Analyte              | F (df1, df2)             | Estimate | 95% CI lower to upper | raw P  |
|----------------------|--------------------------|----------|-----------------------|--------|
| ACTH                 | 0.7416 (1, 80.7035)      | -4.7334  | -16.0995 to 6.6062    | 0.3917 |
| ALT                  | 0.0549 (1, 69.4927)      | -0.0436  | -0.4118 to 0.3154     | 0.8154 |
| AST                  | 0.0185 (1, 74.2611)      | -0.0152  | -0.2310 to 0.2086     | 0.8923 |
| Blood pH             | 0.0190 (1, 87.6316)      | 0.0016   | -0.0220 to 0.0241     | 0.8908 |
| CK                   | 0.1140 (1, 112.7367)     | -0.4919  | -3.4540 to 2.1155     | 0.7363 |
| CK-MB                | 0.1500 (1, 76.0751)      | 0.1834   | -0.7273 to 1.1735     | 0.6996 |
| Calcium              | 0.0022 (1, 98.0940)      | 0.0017   | -0.0654 to 0.0708     | 0.9623 |
| Chloride             | 1.1476 (1, 108.7816)     | -0.8292  | -2.3447 to 0.5624     | 0.2864 |
| Creatinine           | 3.9026 (1, 75.5412)      | -11.3212 | -22.1574 to -0.4652   | 0.0519 |
| D-dimer              | 0.2982 (1, 118.1216)     | -22.1102 | -100.5071 to 52.0413  | 0.5860 |
| Factor VIII          | 4.4219 (1, 87.8222)      | -26.0576 | -49.7055 to -4.4284   | 0.0383 |
| Ferritin             | 1.0882 (1, 74.1216)      | -20.4442 | -58.3147 to 18.2591   | 0.3003 |
| Fibrinogen           | 0.0401 (1, 73.9674)      | -0.0448  | -0.4546 to 0.3930     | 0.8419 |
| Folate               | 0.0273 (1, 71.6603)      | 0.5119   | -5.3712 to 6.3992     | 0.8693 |
| Free protein S       | 1.2296 (1, 77.9114)      | -9.0976  | -24.9615 to 6.9686    | 0.2709 |
| Glucose              | 1.6154 (1, 119.0000)     | -0.3320  | -0.8280 to 0.1832     | 0.2062 |
| Holotranscobalamin   | 6.0054 (1.0000, 50.1273) | -37.1303 | -64.5938 to -10.5638  | 0.0178 |
| IgA                  | 1.7587 (1, 102.0481)     | 0.7682   | -0.3961 to 1.9107     | 0.1877 |
| IgG                  | 0.1254 (1, 71.5830)      | 0.3500   | -1.5481 to 2.2409     | 0.7242 |
| IgM                  | 1.1236 (1, 69.5196)      | 0.2233   | -0.1992 to 0.6351     | 0.2928 |
| LDH                  | 0.5093 (1, 82.0020)      | 0.1973   | -0.3395 to 0.7434     | 0.4775 |
| Lactate              | 0.9219 (1, 107.4702)     | -0.1546  | -0.4683 to 0.1741     | 0.3391 |
| Lipase               | 0.0400 (1, 71.4106)      | -0.0124  | -0.1294 to 0.1156     | 0.8420 |
| Oxygen               | 0.1319 (1, 98.0970)      | -0.3414  | -2.2508 to 1.5842     | 0.7173 |
| Phosphate            | 2.4912 (1, 80.4493)      | 0.1480   | -0.0129 to 0.3209     | 0.1184 |
| Potassium            | 1.2534 (1, 88.8066)      | 0.1233   | -0.1182 to 0.3346     | 0.2659 |
| RDW                  | 5.1704 (1, 73.3183)      | 0.6563   | 0.1302 to 1.2562      | 0.0259 |
| Selenium             | 0.7941 (1, 80.0757)      | 0.0546   | -0.0556 to 0.1723     | 0.3755 |
| Standard bicarbonate | 1.8998 (1, 81.9510)      | 0.6185   | -0.1689 to 1.4937     | 0.1719 |
| Triglycerides        | 0.0002 (1, 96.6661)      | -0.0033  | -0.5007 to 0.4748     | 0.9892 |
| Uric acid            | 0.0029 (1.0000, 68.0557) | -9.6728  | -81.4099 to 62.6226   | 0.9575 |
| Urine pH             | 0.0114 (1, 89.0717)      | 0.0453   | -0.7236 to 0.8399     | 0.9153 |
| Vitamin B1           | 0.0005 (1, 91.0869)      | 0.3310   | -28.6974 to 27.1305   | 0.9823 |
| Vitamin B12          | 0.0368 (1, 76.2819)      | 24.4868  | -225.0885 to 282.6802 | 0.8484 |
| Vitamin B6           | 0.2913 (1, 92.1420)      | -25.7481 | -111.4605 to 71.9683  | 0.5907 |
| Vitamin D            | 0.3105 (1, 100.7160)     | 7.1494   | -19.5092 to 31.7942   | 0.5786 |
| Zinc                 | 0.2824 (1, 95.7632)      | 0.4753   | -1.2775 to 2.2847     | 0.5964 |
| eGFR                 | 0.6003 (1, 80.5674)      | -5.2003  | -17.5935 to 7.3043    | 0.4407 |
| hs-CRP               | 6.6581 (1.0000, 85.1250) | 1.6469   | 0.5441 to 2.7155      | 0.0116 |
| hs-cTnT              | 1.6800 (1, 102.4996)     | -1.0951  | -2.7431 to 0.4993     | 0.1978 |

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**Anti-EBV EBNA effect across all 43 analytes**

| Analyte              | F (df1, df2)              | Estimate | 95% CI lower to upper | raw P   |
|----------------------|---------------------------|----------|-----------------------|---------|
| TSH                  | 23.6385 (1, 90.2590)      | 2.1102   | 1.2610 to 2.9207      | <0.0001 |
| aPTT                 | 9.7016 (1, 81.4417)       | 3.4109   | 1.2863 to 5.5022      | 0.0025  |
| Lp(a)                | 3.2562 (1, 72.0769)       | 50.2246  | -0.7104 to 105.1451   | 0.0753  |
| ACTH                 | 0.2702 (1, 82.3635)       | -2.8460  | -13.3096 to 8.4591    | 0.6046  |
| ALT                  | 0.0879 (1, 72.1790)       | 0.0544   | -0.3138 to 0.4227     | 0.7677  |
| AST                  | 0.4959 (1, 76.3805)       | 0.0781   | -0.1439 to 0.2707     | 0.4834  |
| Blood pH             | 0.4264 (1, 88.5215)       | -0.0075  | -0.0308 to 0.0131     | 0.5155  |
| CK                   | 0.4701 (1, 113.2732)      | 0.9987   | -1.8696 to 3.8103     | 0.4943  |
| CK-MB                | 1.8194 (1, 78.2270)       | 0.6339   | -0.2874 to 1.4917     | 0.1813  |
| Calcium              | 0.0386 (1, 99.1273)       | -0.0070  | -0.0708 to 0.0635     | 0.8446  |
| Chloride             | 4.0421 (1, 109.4381)      | -1.5554  | -3.0113 to -0.0702    | 0.0468  |
| Creatinine           | 0.0006 (1, 77.8299)       | 0.1410   | -10.7770 to 12.3390   | 0.9803  |
| D-dimer              | 0.3859 (1, 118.5217)      | 25.1489  | -55.6401 to 106.0314  | 0.5357  |
| Factor VIII          | 0.0756 (1, 89.2583)       | -3.3959  | -27.0752 to 20.7620   | 0.7840  |
| Ferritin             | 0.0434 (1, 76.5686)       | 4.0432   | -32.8657 to 42.9783   | 0.8354  |
| Fibrinogen           | 2.6211 (1, 76.0916)       | 0.3594   | -0.0805 to 0.8070     | 0.1096  |
| Folate               | 0.1976 (1, 74.1388)       | 1.3632   | -4.5033 to 7.0192     | 0.6580  |
| Free protein S       | 0.0365 (1, 79.9028)       | 1.5567   | -14.5745 to 17.9132   | 0.8491  |
| Glucose              | 2.7900 (1, 119.0000)      | -0.4364  | -0.9276 to 0.0847     | 0.0975  |
| Holotranscobalamin   | 2.0638 (1.0000, 47.7606)  | -24.7643 | -56.4857 to 8.7000    | 0.1574  |
| IgA                  | 0.6447 (1, 102.9670)      | -0.4645  | -1.6246 to 0.6318     | 0.4239  |
| IgG                  | 0.2144 (1, 74.3096)       | 0.4508   | -1.4742 to 2.3131     | 0.6447  |
| IgM                  | 3.0582 (1, 72.0825)       | 0.3604   | -0.0409 to 0.7701     | 0.0846  |
| LDH                  | 3.4870 (1, 83.6339)       | 0.5143   | -0.0342 to 1.0657     | 0.0654  |
| Lactate              | 1.2338 (1, 107.9070)      | -0.1788  | -0.4856 to 0.1654     | 0.2691  |
| Lipase               | 0.4533 (1, 73.9627)       | -0.0411  | -0.1553 to 0.0737     | 0.5029  |
| Oxygen               | 1.7183 (1, 98.7227)       | -1.2317  | -3.1884 to 0.6528     | 0.1930  |
| Phosphate            | 0.0001 (1, 82.3127)       | -0.0008  | -0.1819 to 0.1761     | 0.9935  |
| Potassium            | 0.0344 (1, 90.2013)       | 0.0204   | -0.2012 to 0.2254     | 0.8533  |
| RDW                  | 1.6961 (1, 75.6758)       | 0.3724   | -0.2064 to 0.9920     | 0.1967  |
| Selenium             | 1.7191 (1, 81.8357)       | 0.0799   | -0.0407 to 0.1958     | 0.1935  |
| Standard bicarbonate | 1.6346 (1, 83.0570)       | 0.5721   | -0.2749 to 1.4308     | 0.2046  |
| Triglycerides        | 0.6313 (1, 97.6918)       | 0.1950   | -0.2583 to 0.6711     | 0.4288  |
| Uric acid            | 0.2650 (1.0000, 67.7699)  | -26.3601 | -117.0929 to 73.9953  | 0.6084  |
| Urine pH             | 0.2256 (1, 90.1663)       | 0.2012   | -0.6716 to 1.0217     | 0.6360  |
| Vitamin B1           | 0.0754 (1, 92.2604)       | -4.0892  | -34.6370 to 24.8809   | 0.7843  |
| Vitamin B12          | 0.0139 (1, 78.4484)       | 14.9343  | -223.7406 to 259.8407 | 0.9064  |
| Vitamin B6           | 0.3188 (1, 93.3667)       | -26.8751 | -123.6076 to 69.9630  | 0.5737  |
| Vitamin D            | 0.2076 (1, 101.6375)      | -5.8396  | -30.9824 to 22.0119   | 0.6496  |
| Zinc                 | 0.7783 (1, 96.8353)       | 0.7878   | -0.9024 to 2.5863     | 0.3799  |
| eGFR                 | 0.3693 (1, 82.4299)       | -4.0572  | -16.6607 to 9.0015    | 0.5450  |
| hs-CRP               | 10.4840 (1.0000, 79.0623) | 2.1774   | 0.8598 to 3.4374      | 0.0018  |
| hs-cTnT              | 0.2300 (1, 103.3637)      | 0.4048   | -1.2588 to 2.0551     | 0.6325  |

**Supplementary Table 5c** | Extended age- and sex-adjusted linear mixed-effects models for the three significant metabolic parameters. Related to Table 3. Two-sided linear mixed-effects models (LMMs) are shown for the three parameters that remained significant after Holm–Bonferroni adjustment across 43 tested parameters and were subsequently adjusted for age and sex. Models included TsinceIndex as a binary variable (LC ≤1 year versus LC 1–3 yr), anti-EBV EBNA status, anti-DFS70 aAb status, age, sex, and all relevant two-way and three-way interaction terms, with participant ID included as a random intercept. For each fixed effect, F statistics with numerator and residual degrees of freedom, parameter estimates, 95% confidence intervals, and raw P values are reported. Degrees of freedom were approximated using Satterthwaite’s method, and 95% confidence intervals were obtained by percentile bootstrap (1,000 resamples). Model fit showed marginal and conditional R<sup>2</sup> values of 0.1974 and 0.9483 for LP(a), 0.4103 and 0.7030 for TSH, and 0.3315 and 0.7010 for PTT, respectively; all models were significant by likelihood-ratio testing (all P < 0.0001, except LP(a), P = 0.0001).

#### LP(a)

| Predictor                 | F (df1, df2)         | Estimate  | 95% CI                | P      |
|---------------------------|----------------------|-----------|-----------------------|--------|
| TsinceIndex               | 9.7488 (1, 68.5364)  | -88.1301  | -147.2162 to -31.4292 | 0.0026 |
| DFS70                     | 4.7260 (1, 69.7187)  | 63.8682   | 2.5483 to 119.9772    | 0.0331 |
| EBV                       | 3.3634 (1, 69.2425)  | 51.8133   | -2.5382 to 102.6204   | 0.0710 |
| Age                       | 0.7332 (1, 104.4184) | -5.5298   | -18.8421 to 6.9046    | 0.3938 |
| Sex (M=1, F=0)            | 4.4148 (1, 93.5943)  | -26.8969  | -51.0523 to -2.6589   | 0.0383 |
| TsinceIndex × DFS70       | 9.6389 (1, 68.1568)  | -174.8017 | -288.5638 to -63.1781 | 0.0028 |
| TsinceIndex × EBV         | 6.6270 (1, 69.6622)  | -144.8688 | -261.4848 to -34.2957 | 0.0122 |
| DFS70 × EBV               | 5.3457 (1, 68.9234)  | 130.1968  | 26.2134 to 233.3846   | 0.0238 |
| TsinceIndex × DFS70 × EBV | 6.5638 (1, 68.9242)  | -287.6749 | -531.5525 to -64.2164 | 0.0126 |

#### TSH

| Predictor                 | F (df1, df2)         | Estimate | 95% CI            | P       |
|---------------------------|----------------------|----------|-------------------|---------|
| TsinceIndex               | 21.9692 (1, 89.0897) | 2.0740   | 1.1492 to 2.8758  | <0.0001 |
| DFS70                     | 37.0779 (1, 85.9752) | 2.7892   | 1.9579 to 3.7230  | <0.0001 |
| EBV                       | 23.3001 (1, 87.1400) | 2.1272   | 1.3099 to 2.9694  | <0.0001 |
| Age                       | 0.0016 (1, 78.8126)  | -0.0046  | -0.2287 to 0.2121 | 0.9681  |
| Sex (M=1, F=0)            | 0.2557 (1, 77.1997)  | 0.1099   | -0.3189 to 0.5389 | 0.6145  |
| TsinceIndex × DFS70       | 27.6908 (1, 89.6669) | 4.6446   | 2.8629 to 6.3048  | <0.0001 |
| TsinceIndex × EBV         | 27.7979 (1, 91.1534) | 4.7208   | 2.9137 to 6.4059  | <0.0001 |
| DFS70 × EBV               | 24.6561 (1, 87.4050) | 4.3589   | 2.7259 to 6.0689  | <0.0001 |
| TsinceIndex × DFS70 × EBV | 24.8342 (1, 89.1156) | 8.7834   | 5.2275 to 12.0876 | <0.0001 |

#### PTT

| Predictor                 | F (df1, df2)         | Estimate | 95% CI              | P      |
|---------------------------|----------------------|----------|---------------------|--------|
| TsinceIndex               | 11.5179 (1, 82.4730) | -3.5271  | -5.6399 to -1.5209  | 0.0011 |
| DFS70                     | 8.8946 (1, 79.5097)  | 3.2125   | 1.2692 to 5.1778    | 0.0038 |
| EBV                       | 13.0787 (1, 80.3806) | 3.7457   | 1.8334 to 5.7379    | 0.0005 |
| Age                       | 2.9309 (1, 74.8700)  | -0.4572  | -0.9847 to 0.0670   | 0.0910 |
| Sex (M=1, F=0)            | 5.8391 (1, 74.3584)  | 1.2390   | 0.2853 to 2.2249    | 0.0181 |
| TsinceIndex × DFS70       | 12.3303 (1, 83.0105) | -7.2777  | -11.4968 to -3.3310 | 0.0007 |
| TsinceIndex × EBV         | 0.8817 (1, 84.3503)  | -1.9693  | -6.0649 to 2.0775   | 0.3504 |
| DFS70 × EBV               | 4.8845 (1, 80.5413)  | 4.5576   | 0.6375 to 8.3423    | 0.0299 |
| TsinceIndex × DFS70 × EBV | 2.1056 (1, 82.1251)  | -5.9978  | -14.3958 to 1.9957  | 0.1506 |

**Supplementary Table 6a** | Linear mixed-effects model (LMM) of Bell score in the EBV-naïve/low paediatric LC subgroup. Related to Fig. 4. A two-sided LMM was applied to the anti-EBV EBNA-negative/low subgroup of paediatric LC patients to assess associations of Bell score with IL-12p40, MCHC, absolute basophil granulocyte counts and vitamin B1, with participant ID included as a random intercept. Model fit shows marginal and conditional R<sup>2</sup> (R<sup>2</sup><sub>m</sub> = 0.318, R<sup>2</sup><sub>c</sub> = 0.853);

model significance was confirmed by likelihood-ratio testing ( $P < 0.0001$ ). Degrees of freedom were approximated using Satterthwaite's method, and confidence intervals were derived by percentile bootstrap (1,000 resamples). No multiple-comparison adjustment was applied.

| Bell score    |                      |          |                     |        |
|---------------|----------------------|----------|---------------------|--------|
| Predictor     | F (1, df2)           | Estimate | 95% CI              | P      |
| IL-12p40      | 6.8321 (1, 35.5107)  | 3.7157   | 0.9739 to 6.6601    | 0.0130 |
| MCHC          | 12.4870 (1, 62.7262) | -8.3943  | -12.9761 to -3.4395 | 0.0008 |
| Baso. Granul. | 6.0902 (1, 56.6442)  | 4.7450   | 0.9319 to 8.7520    | 0.0166 |
| Vitamin B1    | 8.0014 (1, 50.8157)  | 5.9728   | 1.7207 to 10.2134   | 0.0067 |

**Supplementary Table 6b | Confounder-adjusted Bell score model in the EBV-naïve/low paediatric LC subgroup.** Related to Fig. 4. A two-sided linear mixed-effects model (LMM) was applied to the anti-EBV EBNA-negative/low subgroup of paediatric LC patients to assess associations of Bell score with IL-12p40, MCHC, absolute basophil granulocyte counts and vitamin B1 after adjustment for vaccination status, comorbidity, age, sex and TsinceIndex, with participant ID included as a random intercept. Model fit showed marginal and conditional  $R^2$  values of 0.3169 and 0.8562, respectively, and was significant by likelihood-ratio testing ( $P < 0.0001$ ). Degrees of freedom were approximated using Satterthwaite's method, and confidence intervals were derived by percentile bootstrap (1,000 resamples). No multiple-comparison adjustment was applied.

| Bell score     |                      |          |                     |        |
|----------------|----------------------|----------|---------------------|--------|
| Predictor      | F (1, df2)           | Estimate | 95% CI              | P      |
| Comorbidity    | 0.0445 (1, 34.2564)  | 2.8304   | -24.0452 to 29.7060 | 0.8342 |
| Sex (M=1, F=0) | 0.0931 (1, 39.6282)  | -1.8934  | -14.3175 to 10.5307 | 0.7618 |
| Age            | 1.9037 (1, 38.5456)  | 4.1271   | -1.8626 to 10.1167  | 0.1756 |
| IL-12p40       | 7.9696 (1, 32.4347)  | 4.1284   | 1.2000 to 7.0568    | 0.0081 |
| MCHC           | 10.5361 (1, 58.9073) | -8.0269  | -12.9788 to -3.0750 | 0.0019 |
| Baso. Granul.  | 5.7484 (1, 54.4877)  | 4.7005   | 0.7746 to 8.6263    | 0.0200 |
| Vitamin B1     | 7.4327 (1, 47.2095)  | 5.9910   | 1.5906 to 10.3914   | 0.0090 |
| TsinceIndex    | 0.1406 (1, 51.1670)  | -0.7568  | -4.7985 to 3.2849   | 0.7092 |

**Supplementary Table 7 | Pre-existing conditions in paediatric LC: cohort prevalence versus reported population benchmarks.** Pre-existing conditions recorded at enrolment among participants with paediatric LC ( $n = 74$ ). Data are shown as  $n$  (%) unless stated otherwise. Published prevalence estimates are provided for contextual comparison only and should be interpreted with caution given heterogeneity in age strata, case definitions, data sources (population-based surveys vs clinical cohorts), and ascertainment; they were not used for statistical inference in this study. Benchmark estimates were obtained from population-based German health surveys, international systematic reviews, and disease-specific registries (e.g., Robert Koch Institute; KiGGS Wave 2, 2014–2017, published 2018). Participants could report more than one pre-existing condition; therefore, counts across conditions are not mutually exclusive and may sum to  $> 74$ . “Atopy” reflects questionnaire-based self-report and was not necessarily physician-diagnosed.

| Group                                  | Condition                                       | Cohort $n$ (%) | Population benchmark (context only)              |
|----------------------------------------|-------------------------------------------------|----------------|--------------------------------------------------|
| Neurodevelopmental / Neurological      | ADHD (Attention Deficit Hyperactivity Disorder) | 4 (5.4%)       | ~4.4 % (diagnosed cases, DE)                     |
|                                        | Dyslexia                                        | 2 (2.7%)       | 1.9–2.6 % strict, up to 7–15 % broadly defined   |
|                                        | Migraine                                        | 4 (5.4%)       | ~10 % (children/adolescents)                     |
|                                        | Other (each $n=1$ ; 1.4%)                       | 2 (2.7%)       | variable / referral-based (see note)             |
|                                        | Lactose Malabsorption                           | 7 (9.5%)       | ~20–40% in clinical groups, lower overall        |
| Gastrointestinal Metabolic / Endocrine | Obesity                                         | 2 (2.7%)       | 5.9 % (obesity), 15.4 % including overweight     |
|                                        | Other (each $n=1$ ; 1.4%)                       | 2 (2.7%)       | study-dependent (see note)                       |
| Cardiac Respiratory–Allergic           | Other (each $n=1$ ; 1.4%)                       | 2 (2.7%)       | study-dependent (see note)                       |
|                                        | Bronchial Asthma                                | 3 (4.1%)       | 3.5–4 % (12-month prevalence)                    |
|                                        | Self-reported atopy (questionnaire-based)       | 27 (36%)       | ≥16 % with ≥1 atopic disease                     |
| Other / rare conditions                | Other (each $n=1$ ; 1.4%)                       | 9 (12.2%)      | variable / often no robust prevalence (see note) |

| Group   | Condition        | Cohort n (%) | Population benchmark (context only) |
|---------|------------------|--------------|-------------------------------------|
| Overall | Cystic Fibrosis  | 0 (0%)       | 1:3,300–1:4,800 newborns in Germany |
|         | No Prior Illness | 37 (50.0%)   | n/a                                 |

Notes (what is included in “Other (each n=1; 1.4%)”)

- **Neurodevelopmental / Neurological (2× n=1):** Sensory processing disorder; psychogenic gait disorder.
- **Metabolic / Endocrine (2× n=1):** NAFLD; Hashimoto’s thyroiditis.
- **Cardiac (3× n=1):** Coronary fistula; bicuspid aortic valve; mild mitral regurgitation.
- **Other / rare (6× n=1):** Gilbert’s syndrome (Gilbert–Meulengracht syndrome); FASD; Loeys–Dietz syndrome; scoliosis; acne; visual disorders (amblyopia); divergent strabismus; myofascial pain syndrome; chromosome 13 anomaly (Trisomy 13).