Supplementary Methods

Data sources and identification of birth cohort

Birth notifications are reported by the attending midwife or other birth attendants within 36 hours of birth to the NHS[1]. They contain information about the newborn (e.g., birth weight and ethnicity) and mother's HES unique identifier (Token ID), through which mothers were linked to their babies in the birth cohort. HES APC is collated by NHS England and covers all hospital admissions paid for by the English NHS[2]. The HES mother-baby linked dataset, developed by Feng et al., based on birth and delivery records identified from HES APC[2,3], was used to identify mothers for births recorded solely in HES.

Birth admissions were determined using the criteria developed by Zylbersztejn et al.[4], based on diagnostic and procedure codes, healthcare resource group codes and administrative variables from hospital admissions within one month of life (Table A1). If more than one birth admission was identified for a child, the first one was seen as the sole birth record. Birth admissions were excluded from the outcome ascertainment.

Table A1. Criteria for identifying birth admission in HES

Variable used		Inclusion Criteria (value recorded in HES and explanation)
Diagnostic codes (ICD-10)		Z38: Liveborn infants according to place of birth and type of delivery Z37: Outcome of delivery
Healthcare Resource Group Codes	**Version 3.5**	N01: Neonates - Died <2 days old N02: Neonates with Multiple Minor Diagnoses N03: Neonates with one Minor Diagnosis N04: Neonates with Multiple Major Diagnoses N05: Neonates with one Major Diagnosis
	Version 4.0 (in use since financial year 2011/12)	PB01Z: Major Neonatal Diagnoses PB02Z: Minor Neonatal Diagnoses PB03Z: Healthy Baby
HES Specific Fields	**Episode type** *(epitype)*	3: Birth episode 6: Other birth event
	Patient classification *(classpat)*	5: Mothers and babies using only delivery facilities
	Admission method *(admimeth)*	82: Other: babies born in health care provider 83: Other: babies born outside the health care provider, except when born at home as intended 2C: Baby born at home as intended (available from 2013/14)
	Neonatal Care *(neocare)*	0: Normal care 1: Special care 2: Level 2 intensive care (high dependency intensive care 3: Level 1 intensive care (maximal intensive care)

HES, Hospital Episode Statistics; ICD-10, International Statistical Classification of Diseases and Related Health Problems. Financial years in England run from 1st April to 31st March the following year. Healthcare resource groups, developed by National Casemix Office, are standard grouping of clinically similar treatments which use common levels of healthcare resource.

Due to confidentiality restrictions, birth notifications contain the month of birth rather than the exact date. The date of birth was estimated by the birth admission date, the earliest admission date, or the 15th day of the recorded birth month. If a birth admission was identified in the HES APC using criteria listed in Table A1, the birth admission date was used as the estimated date of birth. If a birth admission was not identified but there is an admission in the same month of birth, the admission date was used as the estimated date of birth. If a birth admission was not identified in HES APC and there was no recorded admission in the same month of birth, the 15th day of the recorded birth month was used as the estimated date of birth.

In the study birth cohort, 97.4% of births appear in both HES and birth notifications, 2.4% appear in birth notification only, and 0.2% appear in HES only (Figure A1).

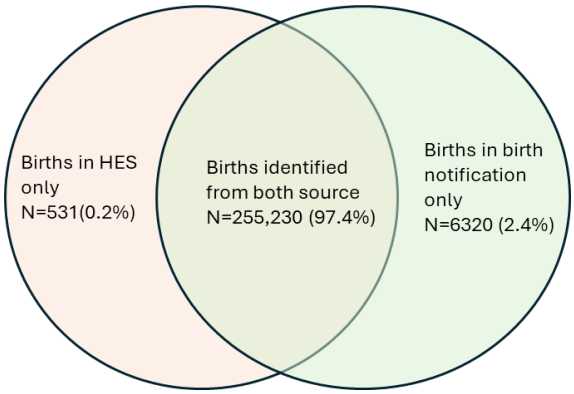

Figure A1. Source of births identified from Hospital Episode Statistics and birth notifications

Mothers were linked to their babies using the linkage in the birth notifications, and then the linkage developed by Feng et al. if the birth was identified in HES only[2,3]. Birth notifications contain a variable indicating the mother's TokenID (unique identifier). In the study cohort, the agreement between Qi's mother-baby link and birth notifications was 99.2%.

Death registrations are collected by the Office for National Statistics (ONS) as part of the national vital registration systems[5].

Cleaning and linking hospital admissions

We extracted all episodes of care for babies identified in the study birth cohort. We removed episodes with no clinical information recorded (e.g., unfinished episodes). We then cleaned and validated date variables (such as admission and discharge dates) which can contain recording errors (e.g., if the recorded admission date was after the discharge date). Finally, we de-duplicated the episodes. Details of data cleaning rules are described in Table A2.

We then linked episodes into admissions using an algorithm developed by Hardelid et al.[6] An admission was defined as a continuous period of time that a child spent under NHS hospital care. Hospital transfers and admissions within 1 day of each other were treated as one inpatient admission. Lastly, we derived the most commonly recorded value of region of residence, IMD score and post code per admissions. Stata codes are published on UCL Child Health Informatics Group GitHub site.

Table A2. Cleaning rules for HES longitudinal records

Criterion		Action
Drop episodes with no clinical information recorded	Unfinished episodes	Drop (as usually more complete record was available)
	Missing episode end date	Drop (as usually more complete record was available)
	Only clinical information recorded was diagnosis "R69" – "*Illness, unspecified*"	Drop (as usually more complete record was available)
	No recorded diagnoses	Drop (as usually more complete record was available)
Validate and correct date variables (admission and discharge dates, episode start and end dates)	Admission date missing	Replace to episode start date for the first episode of the admission (*epiorder*=1) Else, replace to admission date from episode with episode order smaller by 1 and closest episode start date Else, replace with episode start date
	Episode start date missing	Replace to admission date for the first episode of the admission (*epiorder*=1) Else, replace to episode end date from another episode with the same admission date and lower episode order
	Episode end date missing	Removed as part of exclusion criteria
	Episode start> episode end	Replace episode start with admission date if the issue is with the recording of episode start (episode start > episode end ≥ admission date) Replace episode end with episode start date if the issue is with the recording of episode end (episode start = admission date > episode end) Switch episode start with episode end, and admission date with discharge date if they were incorrectly recorded (episode start > episode end & admission date > discharge date where discharge date is not missing)
	Admission date > episode start	Replace episode start date with admission date
	Admission date > episode end	Replace episode end date with episode start date
Validate and correct date variables (admission and discharge dates, episode start and end dates)	Discharge date missing	Discharge date is recorded only on the last episode of care. Therefore, I generated a maximum discharge date by HESID and admission date as the "complete" discharge date. If "complete" discharge date was missing (when discharge date was not recorded for an admission), I replaced it with maximum episode end date by HESID and admission date. If "complete" discharge date was smaller than the maximum episode end date, I replaced it with the maximum episode end date.

	Episode ends in a different year than it starts	Drop if the difference is greater than or equal to two. It seems impossible to be seen by only one consultant while staying in the hospital for 2 years so it must be a data error.
	Missing episode start age	No such observations
	Missing episode end date	Generate an age using episode start and end dates for episodes with startage=7001 ("less than 1 day")
	Age at start of episode > age at end of episode	Switch age at start with age at end of episode
	Epistart – Epiend > 365	Episodes that lasted more than 1 year were assumed to be recording errors and dropped as it is unlikely that a patient would be seen by just one consultant for that long.
Drop duplicates	Exact duplicates	Drop duplicates in terms of: HESID, age at start and end of admission, month and year of birth, gender, post code, start and end date of the episode, episode order, admission and discharge dates, provider code,all diagnoses and operations and cause of injury

HES, Hospital Episode Statistics; IMD, Index of Multiple Deprivation.

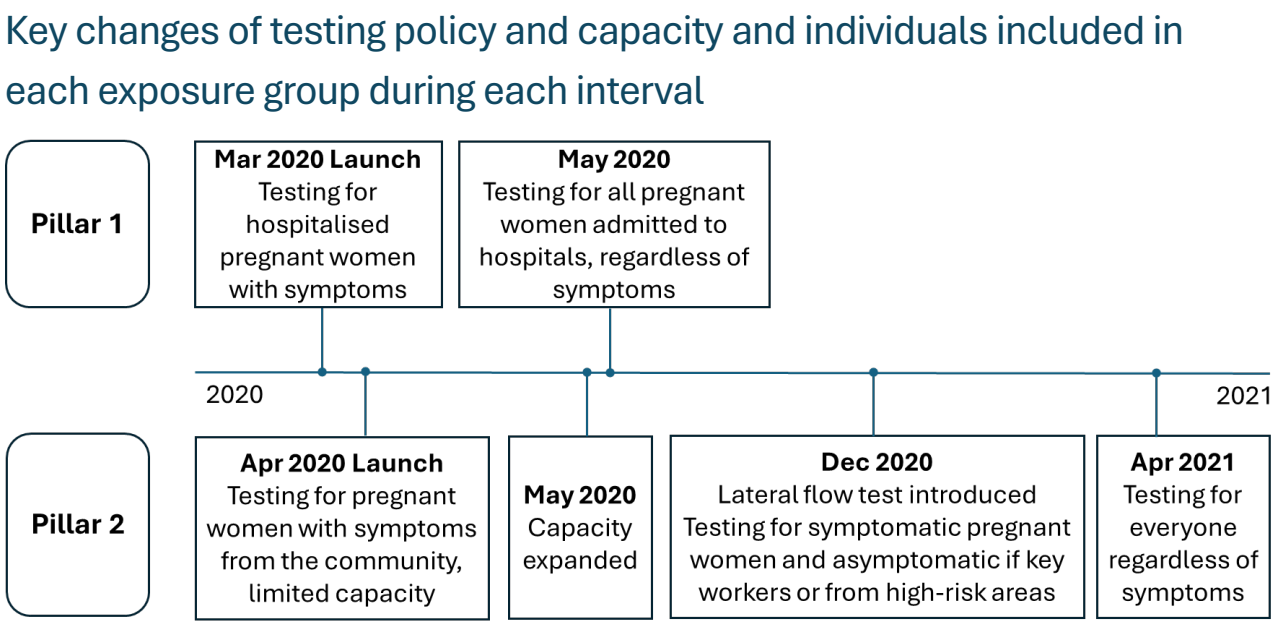

Figure A2. Key changes in Pillar 1 and Pillar 2 testing policy relevant to the exposure period

Table A3. Who are included in each exposure group over the study period

Exposure groups	Apr-Nov 2020	Dec 2020-Mar 2021	Apr-May 2021
Test-negative (all from community setting)	Symptomatic individuals	Symptomatic individuals, asymptomatic key workers or individuals from high-risk areas	Everyone, regardless of symptoms
Positive: Wild-type (Feb- mid-Dec 2020)	Hospital: Symptomatic or asymptomatic cases Community: Symptomatic cases	-	-
Positive: Alpha (mid-Dec 2020-May 2021)	-	Hospital: Symptomatic or asymptomatic cases Community: Symptomatic individuals, asymptomatic cases of key workers or individuals from high-risk areas	Hospital: Symptomatic or asymptomatic cases Community: Symptomatic or asymptomatic cases from any group of areas
No-recorded-result	Uninfected (not tested, or tested negative and not reported), or positive and not reported, or infected and not tested		

Identifying stillbirths and multiple births

Table A4. Rules for identifying stillbirths and multiple births in Hospital Episodes Statistics

Stillbirths	Rules
Multiple births	ICD-10 codes (diag_XX variables) include any of Z383, Z384, Z385, Z372, Z373, Z375, Z376, Z377, Z386, Z387
	Birth order ('birordr' variable)>1
	Number of babies ('numbaby' variable)>1
Still births	ICD-10 codes (diag_XX variables) include any of Z371, Z373, Z374, Z376, Z377, P95
	Discharge method ('dismeth' variable) is 5-stillbirth
	Birth status ('birstat' variable) is 2-still birth ante-partum, 3-still birth intra-partum, or 4-still birth indeterminate

Identifying planned and emergency admissions

The type of admissions was determined by the "admimeth" variable (method of admission) in HES APC, based on the classification in Table A4. The admission method of the first episode of each admission was considered the admission method of the admission. Transfer admission, birth admission, maternity admissions, and admissions with unclear admissions were excluded from the analysis.

Table A5. Definition, frequency, and inclusion of each type of admissions

Type of admission	Value in "Admimeth" variable in HES APC	Inclusion
Planned admission	11, 12, 13	Included in analysis of planned admission
Emergency admission	21, 22, 23, 24, 25, 28, 2A, 2D	Included in analysis of emergency admission
Transfer admission	2B,81	Excluded
Birth admission	2C, 82, 83	Excluded
Maternity admission	31, 32	Excluded
Unclear	98, 99	Excluded

Cleaning multiple SARS-CoV-2 tests on the same day

Pillar 1 data contains only positive PCR tests. Pillar 2 contains both PCR and rapid lateral flow tests with positive, negative, or unknown results. In Pillar 2, the variable "testresult" was used to determine the type of test and the results (Table A5). If there was more than one test result on the same day, rules in Table A6 were used to reduce them to one final result per day. Results from PCR tests were prioritised when test results were available in both PCR and lateral flow testing on the same day, as PCR has higher sensitivity than antigen tests[7,8].

Table A6. Determining the test type and results in Pillar 2 dataset

Value in "testresult" variable	**Type of test**	**Test result**
SCT: 1240581000000104	PCR	Positive
SCT: 1240591000000102	PCR	Negative
SCT: 1321691000000102	PCR	Unknown
SCT: 1322781000000102	LFT	Positive
SCT: 1322791000000100	LFT	Negative
SCT: 1322821000000105	LFT	Unknown

Table A7. Rules of reducing multiple SARS-CoV-2 tests on the same day to one final result per day

Scenarios	**SARS-CoV-2 test results for the day**
1) One test or multiple tests with consistent result	Use the consistent results
2) Multiple tests with inconsistent results but PCR test results are consistent	Use the consistent PCR results
3) Multiple LFT tests with inconsistent results and no PCR test result	If any of the LFT test result is positive, treat as positive; if LFT test results are either negative or unknown, treat as negative
4) Multiple PCR tests with inconsistent results	If any of the PCR tests is positive, treat as positive; if PCR test results are either negative or unknown, treat as negative

Calculating rate of emergency admission and planned admissions

All emergency and planned admissions (not just the first) were included in the calculation of admission rates, which were estimated separately for emergency and planned admissions. When calculating emergency admission rates, person-time at risk excluded periods of hospital stay during emergency admissions but included time spent in hospital for planned admissions; vice versa for planned admission rates. To account for multiple testing, 99% confidence intervals were reported alongside admission rates.

Directed Acyclic Graph

The exposure of this study is the recorded exposure to SARS-CoV-2 in utero, and the outcome of interest is child hospital admissions. Based on the directed acyclic graph[9] (Figure A1), the minimal sufficient adjustment sets contain area deprivation, ethnicity, maternal age, maternal chronic conditions, and the year-month of conception.

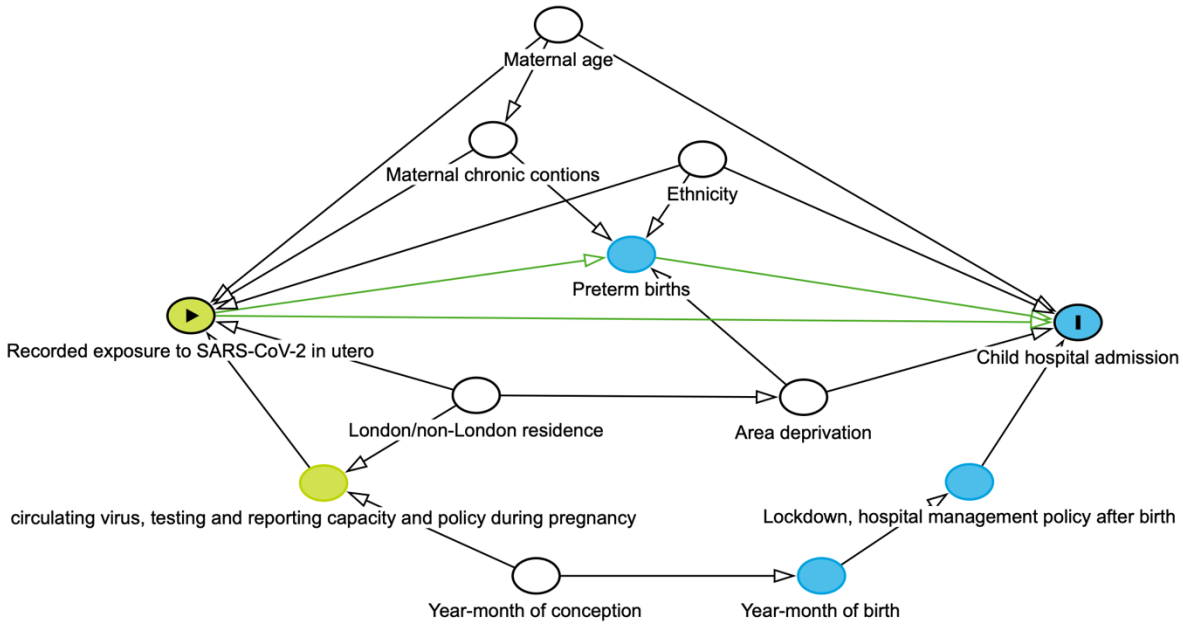

Figure A3. Directed Acyclic Graphs to identify cofounders
Note: Residence in London at birth was specifically adjusted for, as the transmission of SARS-CoV-2 was different in London[10–12], and hospital admission rates for young children are lower in London compared to the rest of England[13,14].

Categorisation of primary diagnosis

Table A7. Categorising primary diagnosis into disease groups

Disease group	ICD-10 codes in the primary diagnosis of the first episode of the admission
Certain infectious and parasitic diseases	
Bacterial infectious diseases	A00-A99
Non-bacterial infectious diseases	B00-B99
Neoplasms	
Malignant neoplasms	C00-C97
Benign neoplasms	D00-D49
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89
Endocrine, nutritional and metabolic diseases	E00-E90
Mental and behavioural disorders	F00-F99
Diseases of the nervous system	G00-G99
Diseases of the eye and adnexa	H00-H59
Diseases of the ear and mastoid process	H60-H95
Diseases of the circulatory system	
Heart diseases	I00-I52
Circulatory disease	I60-I99
Diseases of the respiratory system	J00-J99
Diseases of the digestive system	K00-K93
Diseases of the skin and subcutaneous tissue	L00-L99
Diseases of the musculoskeletal system and connective tissue	M00-M99
Diseases of the genitourinary system	N00-N99
Certain conditions originating in the perinatal period	P00-P96
Congenital malformations, deformations and chromosomal abnormalities	Q00-Q99
Injury, poisoning and certain other consequences of external causes	S00-S99, T00-T98

Note: Disease categorisation was developed by Hviid et al.[21] based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision

Supplementary Tables and Figures

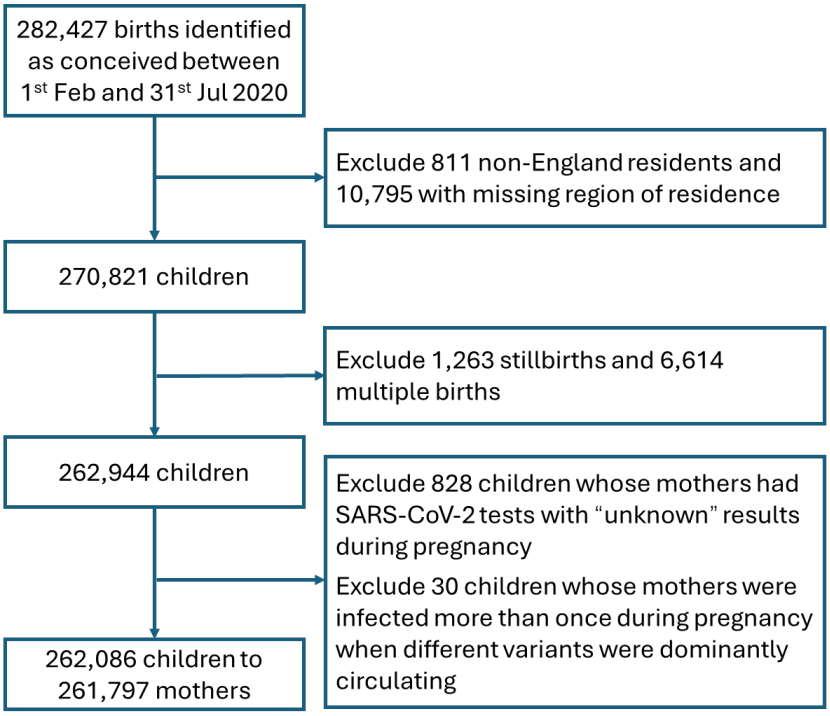

Figure B1. Flow chart showing the inclusion of births in the birth cohort

Testing policy and criteria for Pillar 1 and Pillar 2

Number of SARS-CoV-2 tests and COVID-19 diagnoses over study period

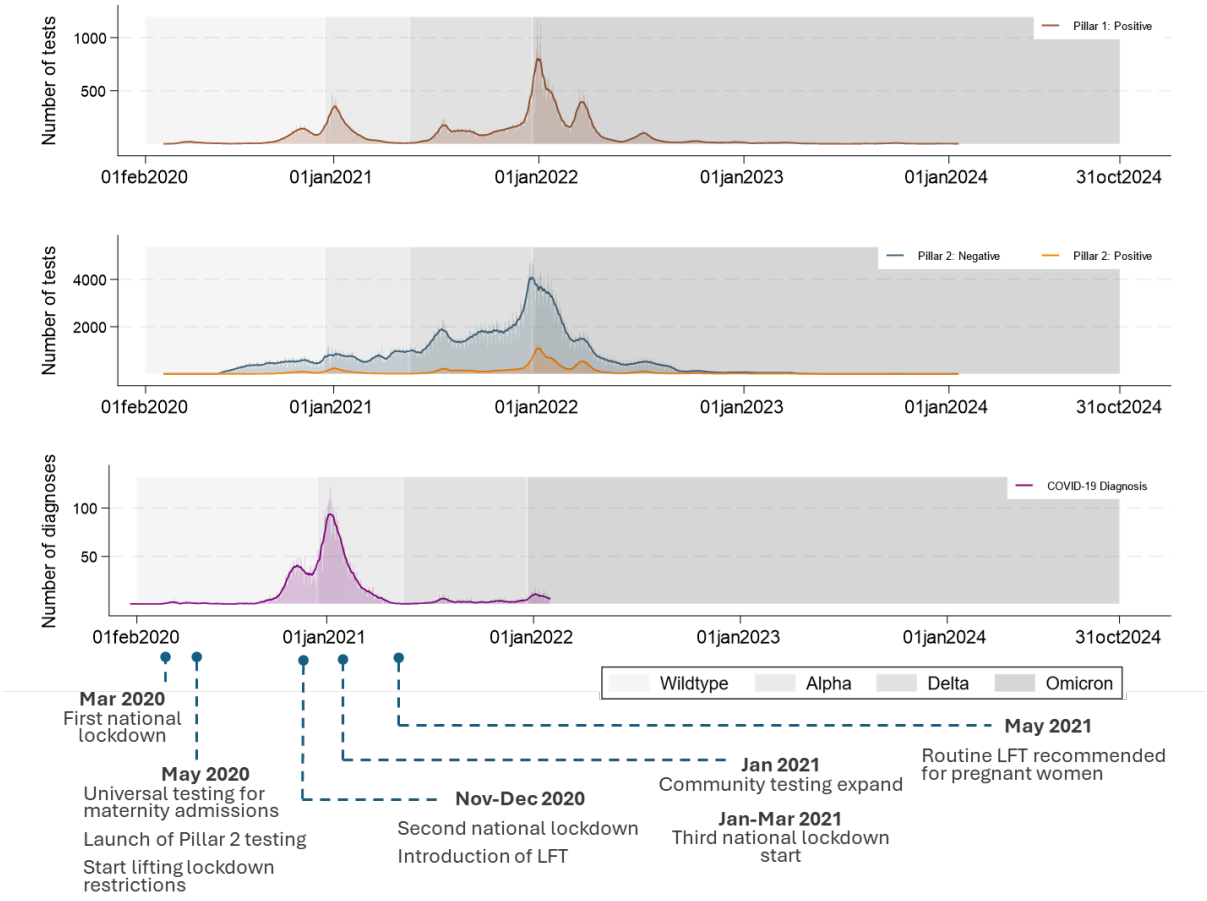

Figure B2. Distribution of SARS-CoV-2 tests and COVID-19 diagnosis among mothers of the study cohort. From top panel to bottom panel: positive tests from Pillar 1; positive and negative tests from Pillar 2; positive diagnosis in HES. Transparent bars show daily counts, and solid lines show the 15-day rolling average of daily counts (a week before + the index day + a week after). All recorded tests from mothers of the birth cohorts were included (including those taken postnatally) to illustrate changes in testing uptake over calendar time.

Kaplan-Meier curves

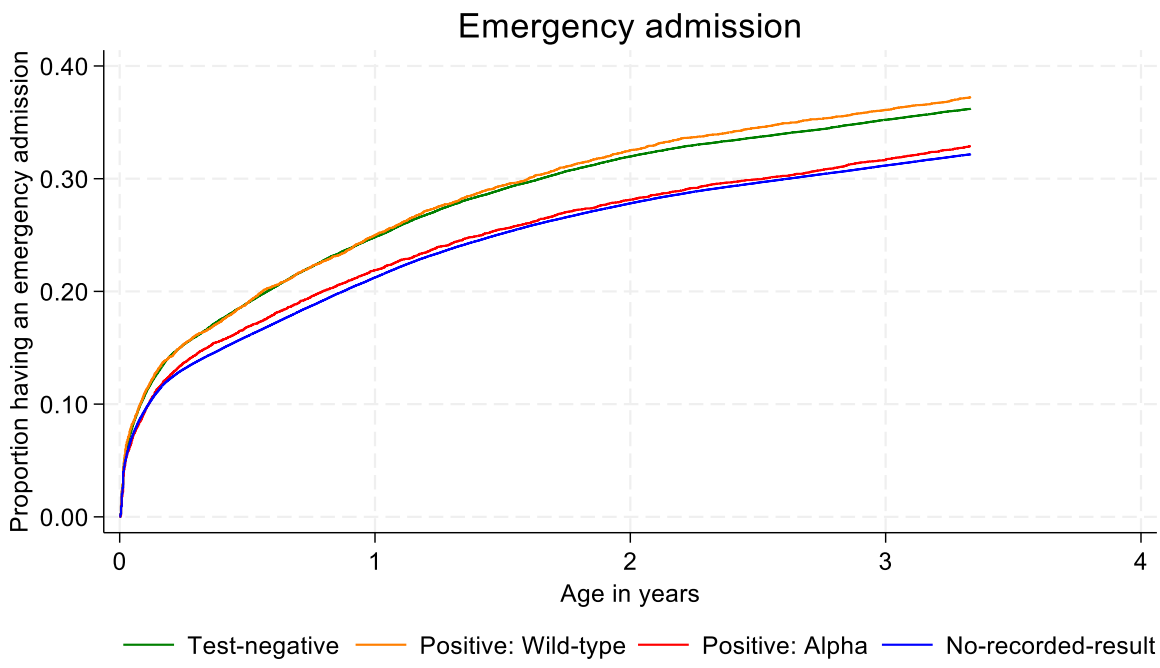

Figure B3. Kaplan-Meier plot for children's first emergency admissions up to 40 months old by SARS-CoV-2 exposure in utero

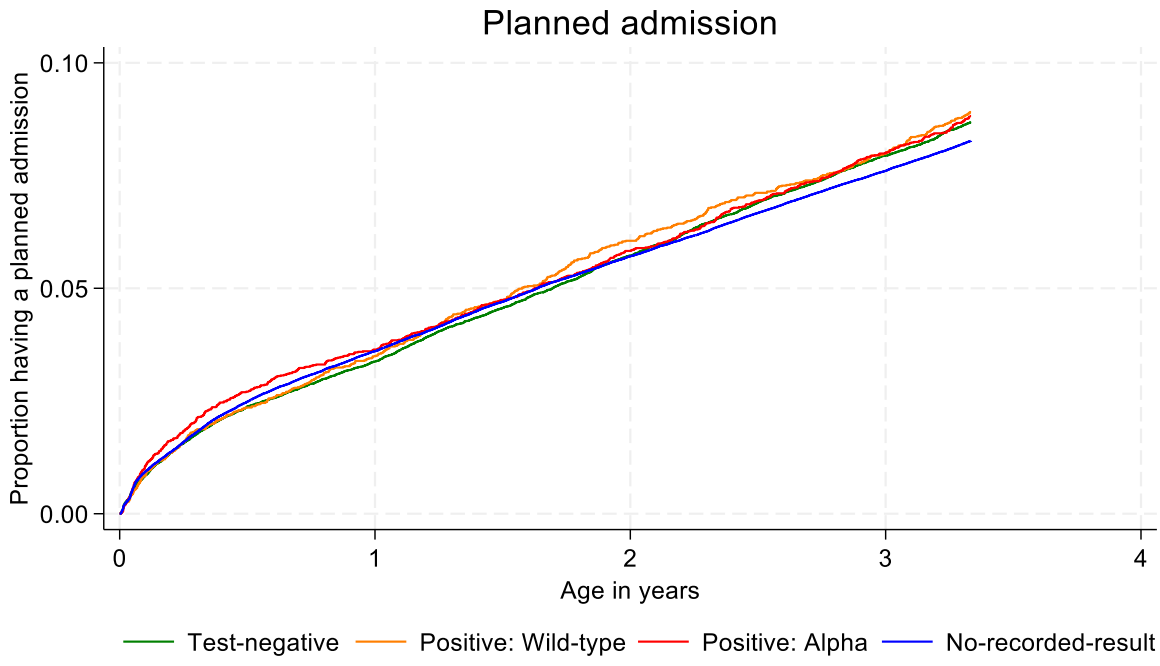

Figure B4. Kaplan-Meier plot for children's first planned admission up to 40 months years old by SARS-CoV-2 exposure in utero

Table B1. Time to child's first emergency and planned admission up to 40 months old: crude and adjusted hazard ratio (99% confidence interval) by in utero exposure to SARS-CoV-2 during pregnancy, based on 257,241 children conceived between February and July 2020 in England

Exposure and covariates	Emergency admissions (99% CI)		Planned admissions (99% CI)	
	Crude	Adjusted	Crude	Adjusted
In-utero SARS-CoV-2 exposure				
Test-negative	1	1	1	1
Positive: Wild-type	1.04 (0.98,1.09)	1.03 (0.97,1.09)	1.04 (0.93,1.16)	1.05 (0.93,1.17)
Positive: Alpha	0.89 (0.84,0.94)	0.92 (0.87,0.97)	1.01 (0.91,1.13)	1.00 (0.90,1.12)
No-recorded-result	0.86 (0.84,0.88)	0.88 (0.86,0.90)	0.95 (0.91,1.00)	0.95 (0.90,0.99)
Ethnicity				
White		1 (1.00,1.00)		1 (1.00,1.00)
Asian		0.98 (0.95,1.00)		0.89 (0.84,0.94)
Black		0.84 (0.80,0.88)		1.06 (0.97,1.15)
Mixed		0.91 (0.86,0.97)		0.93 (0.83,1.04)
Other		0.90 (0.86,0.95)		0.97 (0.89,1.06)
Area deprivation				
Most deprived 10%		1		1
More deprived 10-20%		0.99 (0.95,1.02)		0.99 (0.92,1.06)
More deprived 20-30%		0.95 (0.91,0.98)		0.97 (0.91,1.04)
More deprived 30-40%		0.94 (0.91,0.98)		0.98 (0.91,1.05)
More deprived 40-50%		0.96 (0.92,0.99)		0.96 (0.89,1.04)
Less deprived 40-50%		0.92 (0.88,0.95)		0.92 (0.85,1.00)
Less deprived 30-40%		0.92 (0.89,0.96)		0.95 (0.88,1.03)
Less deprived 20-30%		0.93 (0.90,0.97)		0.95 (0.88,1.03)
Less deprived 10-20%		0.93 (0.90,0.97)		0.92 (0.88,0.99)
Least deprived 10%		0.86 (0.83,0.90)		0.95 (0.87,1.03)
Mother's history of chronic disease				
No		1		1
Yes		1.33 (1.28,1.39)		1.34 (1.24,1.46)
Maternal age (years)				
<25		1		1
25-29		0.91 (0.89,0.94)		1.00 (0.94,1.06)
30-34		0.84 (0.82,0.86)		0.98 (0.93,1.04)
35-39		0.80 (0.77,0.82)		1.00 (0.94,1.07)
≥40		0.81 (0.77,0.85)		0.98 (0.89,1.08)
London residence				
No		1		1
Yes		0.71 (0.69,0.73)		1.19 (1.13,1.25)
Month of conception				
Feb 2020		1		1
Mar 2020		1.03 (1.00,1.06)		1.01 (0.95,1.08)
Apr 2020		1.04 (1.01,1.08)		0.96 (0.90,1.02)
May 2020		1.03 (1.00,1.06)		0.94 (0.89,1.00)
Jun 2020		1.03 (1.00,1.06)		0.98 (0.92,1.04)
Jul 2020		1.05 (1.02,1.08)		1.00 (0.94,1.07)

Check for the proportional hazard assumption

The proportional hazard assumption has been assessed by including an interaction term between the exposure status to SARS-CoV-2 in utero and the time variable in the Cox proportional hazard model (age of the child), with adjustment for maternal ethnicity, area deprivation decile, mother's history of chronic conditions, maternal age, London residence, and month of conception. Likelihood ratio tests were used to compare the models with and without the interaction.

Table B2. P-value from tests for the proportional hazard assumption

Interaction with age	Emergency admissions	Planned admissions
Positive: Wild-type	0.401	0.974
Positive: Alpha	0.261	0.178
No-recorded-result	0.533	<0.001
Likelihood ratio test comparing with the model without the interaction between exposure status and time variable	0.627	<0.001

Number of children and hospital admissions by trimesters

Table B3. Emergency and planned admissions by trimester of in utero exposure to SARS-CoV-2

Trimester of in utero exposure	**Positive: Wild-type**		**Positive: Alpha**	
	N children	**N children with a hospital admission (%)**	**N children[#]**	**N children with a hospital admission (%)**
Emergency admission				
First trimester	603	213 (35.3)	-	-
Second trimester	3,035	1,066 (35.1)	1,308	396 (30.3)
Third trimester	3,333	1,124 (33.7)	6,592	1,973 (29.9)
Planned admission				
First trimester	603	47 (7.8)	-	-
Second trimester	3,035	206 (6.8)	1,308	96 (7.3)
Third trimester	3,333	232(7.0)	6,592	442 (6.7)

[#] As this study includes children conceived between Feb and Jul 2020 and the Alpha period starts in Dec 2020, no child in this study would have in utero exposure in the first trimester during the Alpha period.

Supplementary Sensitivity Analysis

Excluding SARS-CoV-2-related admissions

We identified SARS-CoV-2-related admissions using criteria defined by Hardelid et al in a previous study[22]: (i) an individual had tested positive for SARS-CoV-2 up to 14 days prior to hospital admission, on the day of admission, or in between the hospital admission and discharge date, and/or (ii) an International Classification of Disease-version 10 (ICD-10) diagnostic code for COVID-19 (U07.1-U07.2) had been recorded during admission as primary or secondary diagnosis. We cleaned and identified children's SARS-CoV-2 positive tests in the same way as the mother's SARS-CoV-2 tests, described in the method section of the main text.

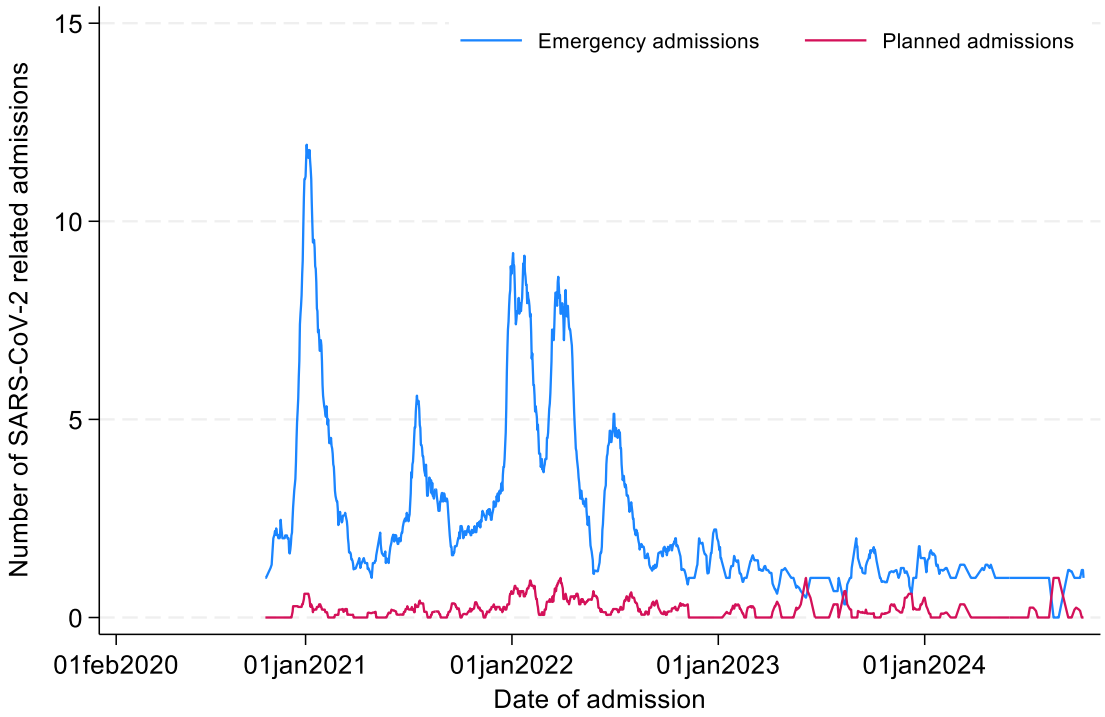

Figure C1. The 15-day rolling average count (a week before + the index day + a week after) of SARS-CoV-2-related emergency admissions and planned admissions in the study cohort

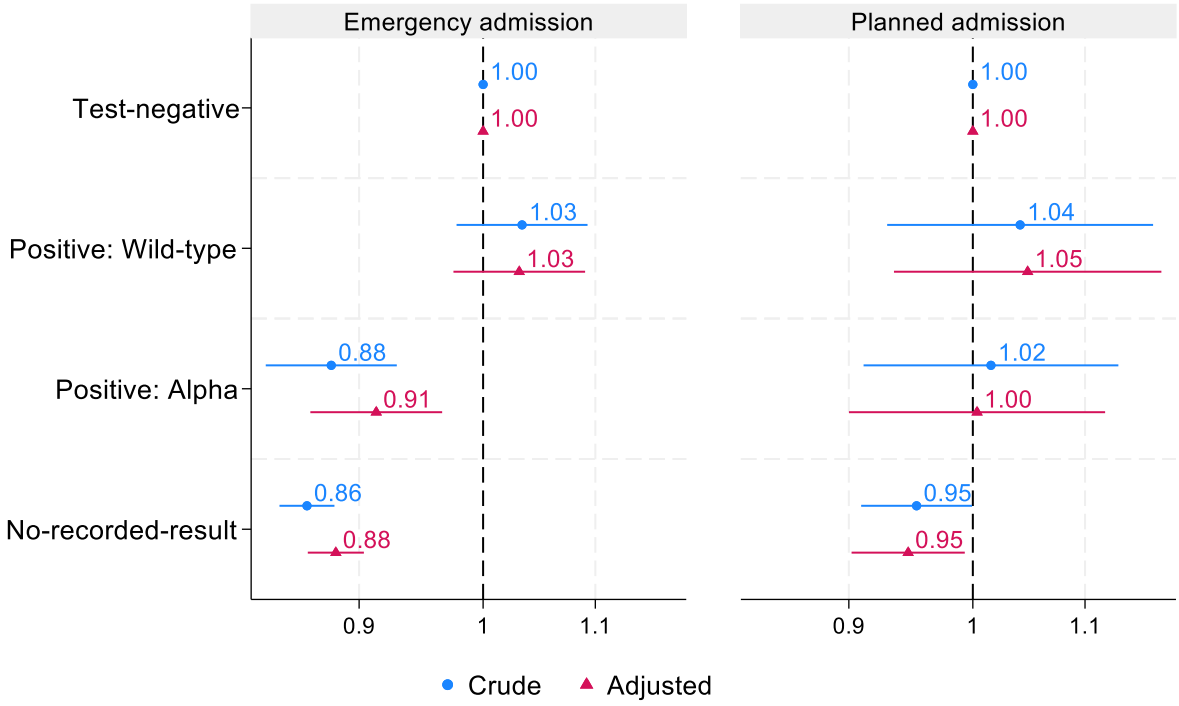

Figure C2. Time to child's first non-COVID-19-related emergency and planned admission up to 40 months old: hazard ratio and 99% confidence interval by in utero exposure to SARS-CoV-2 during pregnancy, children conceived between February and July 2020 in England. Reference=Test-negative group

Note: Results based on Cox proportional hazard regression models adjusted for maternal ethnicity, area deprivation decile, maternal chronic conditions, maternal age, London residence, and month of conception. A total of 257,241 children with complete data for all covariates were used.

Excluding admissions and deaths within the first 7 days of life, and starting follow-up from day 8

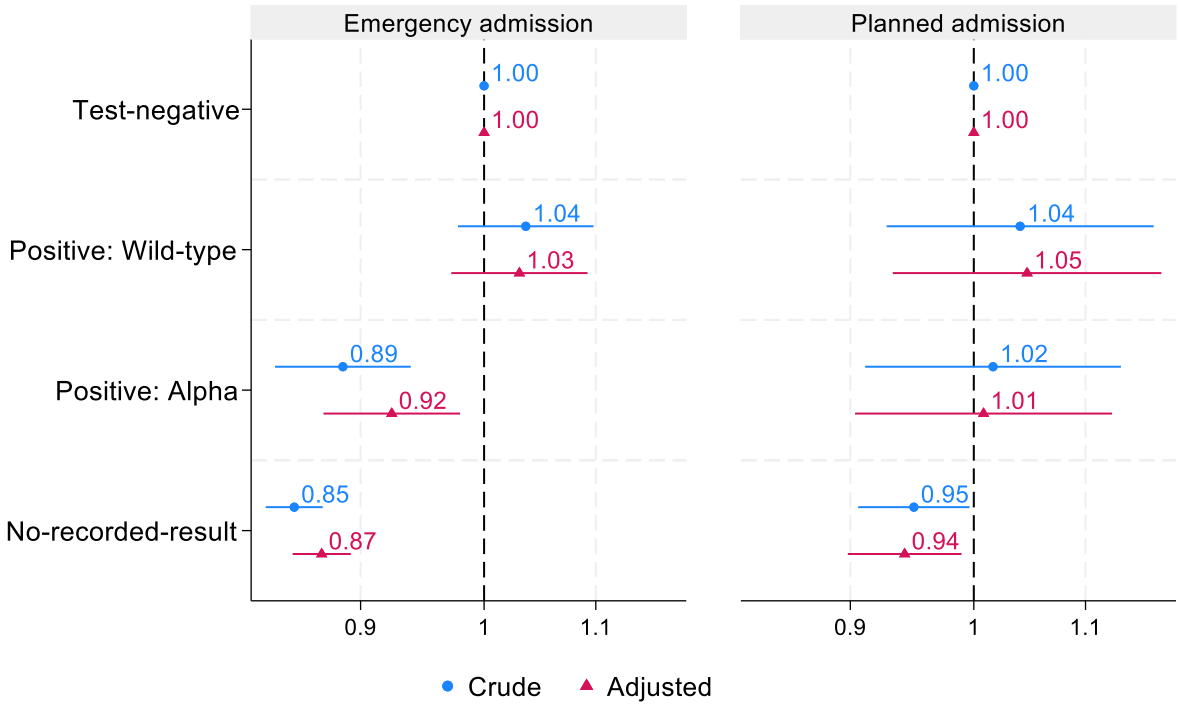

Figure C3. Time to child's first emergency and planned admission between day 8 of life and 40 months old: hazard ratio and 99% confidence interval by in utero SARS-CoV-2 exposure status, children conceived and born between February 2020 and April 2021 in England. Reference=Test-negative group

Note: Admissions and deaths within the first 7 days of life were excluded. Follow-up starts from day 8. Models adjusted for maternal ethnicity, area deprivation decile, maternal chronic conditions, maternal age, London residence, and month of conception. A total of 257,241 children with complete data for all covariates were used.

Logistic regression

Logistic regression shows similar results to those from Cox proportion hazard models.

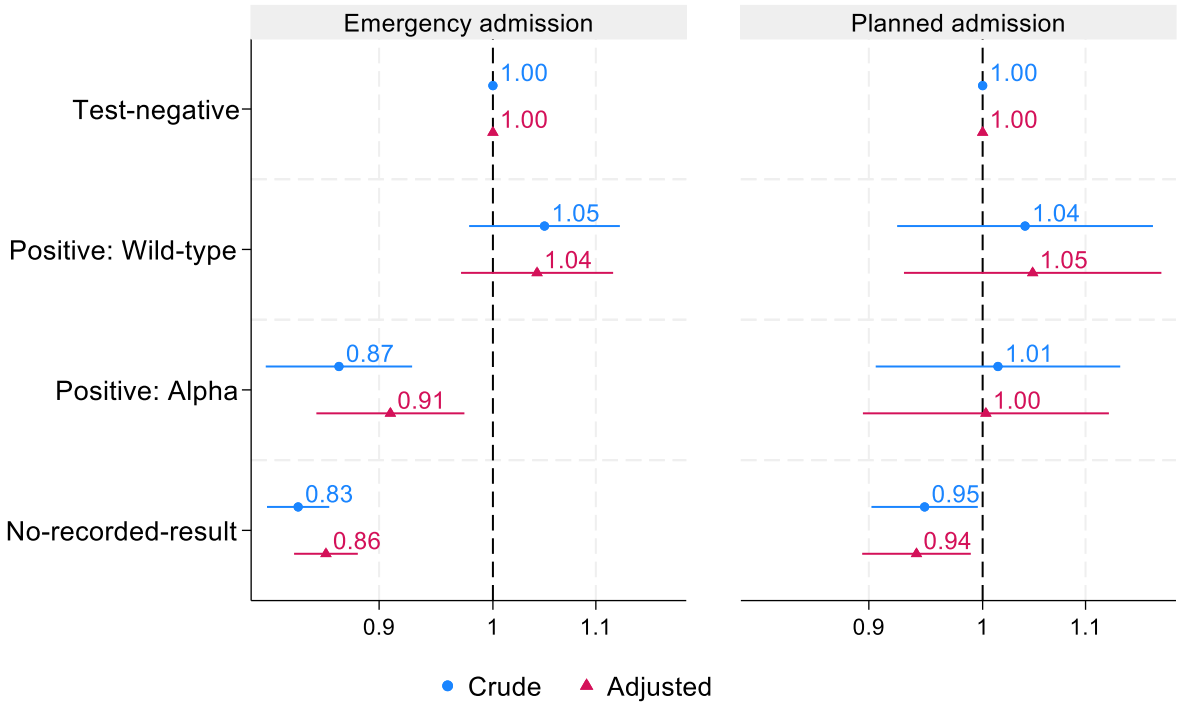

Figure C4. Odds ratio (99% CI) for children's hospital admissions up to 40 months old according to SARS-CoV-2 exposure in utero, children conceived between February and July 2020 in England. Reference=Test-negative group

Note: Results based on Logistic regression models adjusted for maternal ethnicity, area deprivation decile, maternal chronic conditions, maternal age, London residence, and month of conception. A total of 257,241 children with complete data for all covariates were used.

Separate control (test-negative group) by variant period

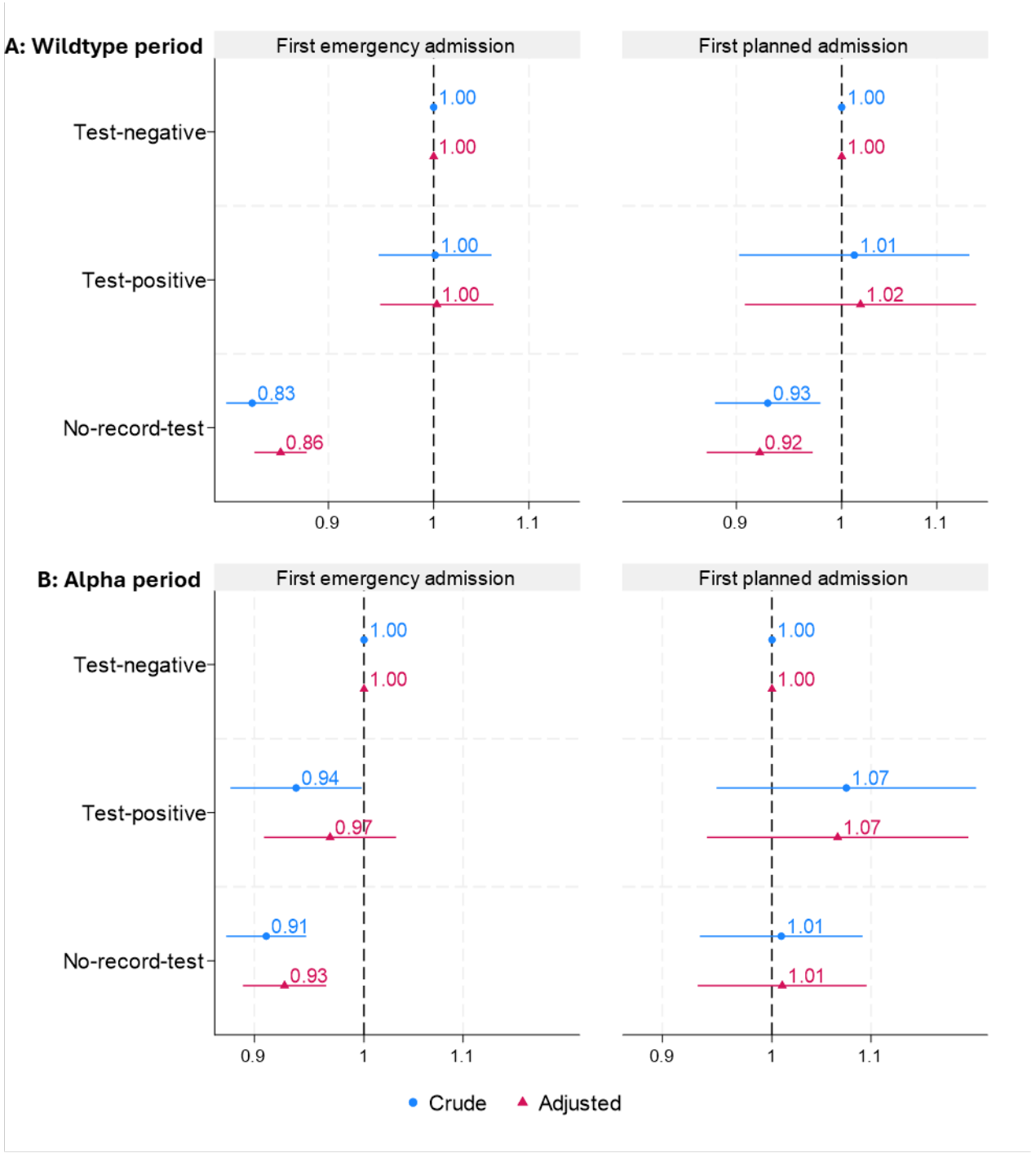

Figure C5. Time to child's first emergency and planned admission up to 40 months old: crude and adjusted hazard ratio and 99% confidence interval by in utero SARS-CoV-2 exposure status. In Panel A, the test-negative and test-positive groups are defined based on test results during the wildtype period, and in Panel B, based on results during the Alpha period. The no-recorded-result group is the same in both panel A and panel B and comprises children whose mother had no recorded SARS-CoV-2 test result during pregnancy in either wildtype or Alpha period. Adjusted models include maternal ethnicity, deprivation decile, maternal chronic conditions, maternal age, London residence, and month of conception.

Table C1. Admission rates per 1,000 child-years (99% CI) by primary diagnosis, including all emergency and planned admissions up to 40 months old. The test-negative and positive groups under the "wild-type period" and "Alpha period" columns are defined based on test results during the wild-type period and Alpha period, respectively. The no-recorded-result group comprises children whose mothers had no recorded SARS-CoV-2 test result during pregnancy in both the wild-type and Alpha period.

Disease group	Number of disease cases	Number of admissions	Wild-type period		Alpha period		No-recorded-result	Total
			Test-negative	Positive	Test-negative	Positive		
Certain infectious and parasitic diseases								
Bacterial infectious diseases	7,692	8,880	11.9 (11.0,12.7)	14.1 (12.2,16.2)	11.4 (10.2,12.7)	9.9 (8.4,11.6)	9.8 (9.5,10.1)	10.2 (9.9,10.5)
Non-bacterial infectious diseases	13,955	19,337	25.1 (23.9,26.4)	27.6 (24.9,30.6)	21.4 (19.8,23.2)	20.7 (18.6,23.2)	21.7 (21.2,22.1)	22.2 (21.8,22.6)
Neoplasms								
Malignant neoplasms	193	4,420	5.7 (5.2,6.4)	11.0 (9.3,12.9)	5.1 (4.4,6.1)	-[#]	5.0 (4.8,5.2)	5.1 (4.9,5.3)
Benign neoplasms	906	1,501	2.7 (2.3,3.2)	1.1 (0.7,1.8)	1.7 (1.3,2.3)	1.9 (1.3,2.8)	1.6 (1.5,1.7)	1.7 (1.6,1.8)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	806	2,502	2.2 (1.9,2.6)	4.4 (3.4,5.7)	0.99 (0.7,1.4)	2.8 (2.0,3.7)	3.0 (2.9,3.2)	2.9 (2.7,3.0)
Endocrine, nutritional and metabolic diseases	1,228	2,373	3.3 (2.9,3.88)	2.2 (1.5,3.1)	2.4 (1.9,3.0)	2.7 (1.9,3.6)	2.7 (2.5,2.8)	2.7 (2.6,2.9)
Mental and behavioural disorders	330	360	0.4 (0.3,0.6)	0.2 (0.0,0.6)	0.4 (0.2,0.7)	0.3 (0.1,0.7)	0.4 (0.4,0.5)	0.4 (0.4,0.5)
Diseases of the nervous system	1,902	3,435	4.5 (4.0,5.1)	5.0 (4.0,6.4)	3.8 (3.1,4.6)	3.8 (3.0,5.0)	3.9 (3.7,4.1)	3.9 (3.8,4.1)
Diseases of the eye and adnexa	1,596	1,907	2.4 (2.1,2.9)	2.6 (1.9,3.7)	2.2 (1.7,2.8)	2.0 (1.4,2.8)	2.1 (2.0,2.3)	2.2 (2.1,2.3)
Diseases of the ear and mastoid process	2,258	2,626	3.9 (3.4,4.4)	3.9 (3.0,5.2)	3.2 (2.6,3.9)	2.7 (1.9,3.6)	2.9 (2.7,3.0)	3.0 (2.9,3.2)
Diseases of the circulatory system								
Heart diseases	268	461	0.5 (0.4,0.8)	0.4 (0.2,0.9)	0.5 (0.3, 0.9)	0.3 (0.1,0.8)	0.5 (0.5,0.6)	0.5 (0.5,0.6)
Circulatory diseases	290	358	0.5 (0.4,0.7)	0.4 (0.2,0.9)	0.5 (0.3, 0.8)	0.6 (0.3,1.1)	0.4 (0.3,0.4)	0.4 (0.4,0.5)
Diseases of the respiratory system	31,816	45,898	66.5 (64.5,68.5)	59.7 (55.7,64.0)	59.3 (56.5, 62.2)	55.3 (51.6,59.1)	50.0 (49.3,50.7)	52.7 (52.1, 53.3)
Diseases of the digestive system	7,534	9,762	12.9 (12.0,13.8)	12.8 (11.1,14.9)	11.6 (10.4,13.0)	10.8 (9.2,12.6)	10.9 (10.6,11.2)	11.2 (10.9,11.5)
Diseases of the skin and subcutaneous tissue	3,330	3,954	4.9 (4.3,5.4)	5.7 (4.6,7.2)	4.3 (3.6,5.1)	4.5 (3.5,5.7)	4.5 (4.3,4.7)	4.5 (4.4,4.7)
Diseases of the musculoskeletal system and connective tissue	805	1,040	1.1 (0.8,1.4)	1.3 (0.8,2.1)	1.1 (0.8,1.5)	1.5 (1.0,2.3)	1.2 (1.1,1.3)	1.2 (1.1,1.3)
Diseases of the genitourinary system	3,482	5,436	6.5 (5.9,7.1)	6.0 (4.8,7.5)	5.6 (4.8, 6.6)	5.6 (4.6,7.0)	6.3 (6.0,6.5)	6.2 (6.0,6.5)
Certain conditions originating in the perinatal period	19,576	22,541	27.7 (26.4,29.1)	28.2 (25.5,31.2)	25.9 (24.1, 27.8)	24.5 (22.1,27.1)	25.4 (24.9,25.9)	25.8 (25.3,26.2)
Congenital malformation, deformations and chromosomal abnormalities	7,247	11,366	14.3 (13.4,15.3)	12.8 (11.1,14.9)	12.6 (11.4,14.0)	12.1 (10.4,13.9)	12.9 (12.6,13.3)	13.0 (12.7,13.4)
Injury, poisoning, and certain other consequences of external causes	8,608	9,990	11.9 (11.0,12.8)	14.3 (12.4,16.5)	10.8 (9.6,12.0)	10.2 (8.7,12.0)	11.4(11.1,11.7)	11.5(11.2,11.8)
Total	95,715	197,735	261.7 (257.7,265.8)	263.9 (255.3,272.8)	234.0 (228.4,239.8)	215.0 (207.9,222.7)	220.8 (219.3,222.2)	226.8 (225.5,228.1)

Supplementary STROBE Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-9
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14-16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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