Gestational age and hospital admissions during childhood, the TIGAR study: population-based, record linkage study in England

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Abstract

Objectives:

To explore the association between gestation at birth and hospital admissions to age 10 years and how admission rates change throughout childhood.

Design:

We used a population-based record-linkage cohort study design. Birth registration, birth notification and Hospital Episode Statistics were linked using a deterministic algorithm.

Setting:

National Health Service (NHS) hospitals in England, UK

Participants:

All live, singleton births in NHS hospitals occurring in England January 2005 to December 2006 (n=1,018,136).

Main outcome measures:

The primary outcome was all inpatient hospital admissions from birth to age 10 years, death or study end (March 2015) and the secondary outcome was the main cause of admission, which was defined as the first International Classification of Disease-10 (ICD10) code within each hospital admission record.

Results:

525,039 (52%) children experienced at least one hospital admission during the study period. Hospital admissions during childhood were strongly associated with gestational age at birth (<28, 28-29, 30-31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, and 42 weeks). Compared to children born full term (40 weeks' gestation), those born extremely preterm (<28 weeks) had the highest rate of hospital admission throughout childhood (adjusted RR, aRR=4·29, 95%CI: 4·58 to 5·30). Even children born at 38 weeks had a higher rate of hospital admission throughout childhood (aRR=1·19, 95%CI: 1·16 to 1·22). However, the association between gestational age and hospital admission decreased with increasing age (interaction p<0·001). Children born <28 weeks had an aRR of 6·38 (95%CI: 5.80 to 6.85) during infancy, declining to 3·28 (95%CI: 2.82 to 3.82) at ages 7-10, in comparison to those born full term; whilst in children born at 38 weeks, the aRRs were 1·29 (95%CI: 1.27 to 1.31) and 1·16 (95%CI: 1.13 to 1.19), during infancy and ages 7-10 respectively. Infection was the main cause of excess hospital admissions at all ages, but particularly during infancy. Respiratory and gastrointestinal conditions also accounted for a large proportion of admissions during the first two years of life.

Conclusions:

Whilst the association between gestational age and hospital admission rates decreased with age, an excess risk remained throughout childhood, even among children born at 38 and 39 weeks of gestation. Strategies aimed at the prevention and management of childhood infections should target children born preterm and those born a few weeks early.

Summary box

What is known?

Preterm birth is a major contributor to childhood morbidity.

There are few studies that have investigated the long-term health consequences in relation to the full spectrum of gestational age at birth in large, population-based studies in a UK context.

Existing evidence suggests that the risk of morbidity associated with preterm birth declines as children grow up, however it remains unclear at what age this begins to happen and how these changes vary by week of gestational age at birth.

What this study adds

Using a large, population-based, record linkage dataset, the findings from our study show that gestational age at birth is inversely associated with hospital admissions throughout childhood and that the effect of gestational age decreased over time, with the highest rates within the first two years after birth for all gestational ages.

Even though the excess risk of hospitalisation in those born at 37, 38 and 39 weeks was relatively small, 42% of children were born at these gestational ages in our cohort, representing a large number of potentially vulnerable children.

Infection-related hospital admissions were strongly associated with gestational age and were the main driver of excess hospital admissions at all ages, but particularly so during infancy.

Print abstract

Figure 2. Mean hospital admissions by gestational age over time, adjusted for maternal age at delivery, mother's country of birth, marital status, sex, SGA, parity, delivery method, IMD score, child's ethnicity and season of birth

Study question

What is the risk of hospital readmission from birth to 10 years of age in children born in England according to each week of gestational age, and how do these risks change over time?

Methods

Routinely-collected records from birth registration, birth notification and hospital admissions were linked for all live, singleton births occurring in England between 1st January 2005 and 31st December 2006. Children (n=1,018,136) were followed up from discharge after birth to age 10, death or censored at study end (31st March 2015). The primary outcome was all inpatient hospital admissions from birth to age 10 years, death or study end (March 2015). Generalised estimating equations were used to estimate adjusted rate ratios (RR) with 95% confidence intervals (CI).

Study answer and limitations

Gestational age was strongly associated with hospitalisation, particularly for infections, throughout childhood in England and children had a consistently lower admission rate with each additional week of gestational age at birth. Whilst the relationship between gestational age and severe morbidity ameliorated over time, particularly in those born extremely preterm, the effect of gestational age persisted in later stages of childhood at all gestational ages. Key limitations of the study include: data quality and completeness issues within the datasets; no individual level markers of socio-economic status, lifestyle factors or underlying health issues associated with preterm birth or offspring outcomes; and a complete case analysis was used to address missing data.

What this study adds

Gestational age at birth is a strong predictor of severe morbidity, and infection accounts for the majority of hospital admissions across all gestational age and time points. Whilst the association between gestational age and hospital admission rates decreased with age, an excess risk remains throughout childhood until 7-10 years of age, even among children born a week or two early.

Introduction

The rates of preterm birth (<37 weeks' gestation) have been increasing since 2000, accounting for approximately 11% of births worldwide in 2014.[1] Complications arising from preterm birth are now the leading cause of infant mortality within high and middle-income countries.[2] Whilst significant advances in the care of preterm babies have resulted in higher survival rates,[3] those born preterm still remain at a higher risk of infant mortality and morbidity compared to those born at full-term. Evidence from studies exploring the long-term health consequences of preterm birth indicates that children born preterm are at higher risk of respiratory disease,[4–6] infections[7] and neurodevelopmental deficits[8] throughout childhood. There is growing evidence to suggest that even babies born at early term (37-38 weeks' gestation) have a higher risk of complications than those born at full-term (39-41 weeks' gestation).[6,9,10] Therefore, it is important to explore long-term health outcomes and to investigate effects by week of gestation at birth.

Approximately 8% of babies born in England and Wales were preterm in 2016.[11] Whilst the increased risk of childhood health complications following preterm or early term delivery is well established[12], there are few large, population-based studies that have investigated the long-term health consequences in relation to the full spectrum of gestational age conducted in UK populations. Previous studies have either analysed relatively small samples with broad categories of gestational age;[13] focused on narrow health outcomes;[4] or analysed data from older cohorts,[14] which means that results may not be generalisable to babies born in settings with more advanced medical care nor reflect increases in survival rates over the past 30 years for extremely preterm babies.[3]

In addition, there is evidence to suggest that the association between gestational age and hospitalisation rates ameliorate over time.[9,10,15] However, it remains unclear at what age this begins to happen and how these changes vary by week of gestational age at birth. This information is important to clinicians, policy makers and parents when assessing future health service utilisation, identifying populations at greatest risk of hospital admission and developing targeted interventions.

We present findings from the TIGAR study (Tracking the Impact of Gestational Age on Health, Educational and Economic outcomes: a Longitudinal Records Linkage Study), which is a population-based, record-linkage study using births and hospital admissions after hospital discharge from birth in England. The study objectives were to estimate the association between gestational age and hospital admissions from birth up to the age of 10 years, explore how rates of hospitalisation changed throughout childhood and describe the main causes of admission.

Methods

Data sources

We conducted a population-based data linkage cohort study in England using data from the Office for National Statistics (ONS) birth registration records linked to death registration records, birth notification records and Hospital Episode Statistics Admitted Patient Care records (HES APC).[16] HES APC contains details of all inpatient admissions to National Health Service (NHS) hospitals in England. Accident and Emergency (A & E) department

attendances and outpatient appointments are recorded in other HES databases, and were not linked due to poor quality data and incompleteness. The linkage was conducted by NHS Digital in collaboration with ONS and City, University of London, using deterministic algorithms as part of a previous National Institute for Health Research (NIHR) funded study, and a description of the datasets, linkage and quality assurance have been published elsewhere[17]. Details of additional quality assurance methods used for this study are included in supplementary information, section A.

Study population

All live, singleton births occurring in England between 1st January 2005 and 31st December 2006 were included in the study cohort and followed up from birth until 31st March 2015 (Figure 1). Children were not eligible for inclusion in the study population if they were born outside of a National Health Service (NHS) hospital in England (3·2%) or to mothers not living in England at the time of delivery (0·2%). Further exclusions from the analyses were: unlinked records (7·7%) and children whose parents had opted out of their data being used for research (1·3%); poor quality linkages (0·1%); gestational age of <23 weeks or >42 weeks (0·4%); missing gestational age or birthweight data (0·6%); implausible birthweight for gestational age [birthweight + or – 2 standard deviations from the median week of gestational age, sex and ethnicity][18] (1·3%); died before discharge (0·1%); or if records had data quality issues (0·7%) [e.g. discharge <34 weeks' corrected age[19]; discharge dates prior to admission; admission prior to date of birth (DOB); missing admission or discharge dates]. Children born >42 weeks' gestation were excluded due to gestational age data quality concerns.[20,21]

Outcomes

The primary outcome was the total number of NHS inpatient hospital admissions during childhood, reported during the following periods: <1, 1-2, 3-4, 5-6, and 7-10 years. Admissions occurring at least one day after discharge from the birth admission were included in the analysis. We define the 'birth admission' as the initial hospital admission relating to the baby's birth; it began when the baby was born and ended when the baby was discharged from an NHS hospital. We define a (subsequent) 'admission' as a period of continued care within an NHS hospital, which ends when the child was discharged. Hospital records with transfer codes (see supplementary information [S3]) and ≤2 days between admission and discharge dates were considered part of the same admission. Further details on HES data are described in supplementary information, section B.

Hospital diagnoses are coded in HES using the World Health Organisation's (WHO) International Classification of Diseases, 10th revision (ICD-10). Admissions involving healthy babies admitted alongside a sick mother were excluded (Z76·3). The primary diagnosis code within the first episode of each admission was used to define the cause of each admission; they were then grouped into the following broad categories[5]: infection; non-infection respiratory; non-infection gastrointestinal; oral cavity; perinatal; congenital anomalies; social issues; mental health; injury; renal and genitourinary; neoplasm; central nervous system (CNS); and other. See supplementary information, section G.

Exposures

Gestational age was recorded in the birth notification record by the midwife or doctor attending the birth and estimated using the date of the mother's last menstrual period (LMP), ultrasound dating scan and the baby's date of birth. Whilst the LMP is calculated, it is common practice to use the ultrasound scan in early pregnancy to estimate gestational age, as this is generally accepted to be more accurate. There is no method of assessment recorded in birth notification; however, a dating ultrasound is part of routine antenatal care in the NHS, and almost all women will receive one.[22] Gestational age was analysed in weeks, using the following categories: <28, 28-29, 30-31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, and 42. Where numbers were small, gestational ages were grouped (e.g. <28, 28-29 and 30-31) to ensure sufficient power to estimate rate ratios. In models with interaction terms, gestational age was grouped using the following categories: <28, 28-31, 32-33, 34-36, 37-38, 39-41 and 42. Because gestational age is strongly correlated with birthweight, we investigated fetal growth using sex and gestation specific birthweight centiles and identified those born small for gestational age (SGA) (defined as a birthweight below the 10th percentile for all births).

Statistical analysis

Chi-squared tests were performed to compare the distribution of all categorical variables in children with and without an admission during childhood. Person-years-at-risk (PYR) for each child were calculated as time from discharge from birth admission up to the age of 10 years, death or the study end (31st March 2015). Crude hospital admission rates per 100 person years (PY) were calculated for each category of gestational age within each age band (<1, 1-2, 3-4, 5-6, and 7-10) by dividing the number of subsequent admissions by the PYR and multiplying by 100. This was repeated for each cause of admission category. Because rates were so similar for 39-41 and 42 weeks, these categories of gestational age were combined for brevity.

Generalized estimating equations (GEE) with a negative binomial distribution and log link were used to estimate rate ratios (RRs) for hospital admissions and 95% confidence intervals (CIs) for each week of gestational age compared with a referent of birth at 40 weeks' gestation. GEEs were used to account for the correlation between repeated readmissions within and across different age bands (<1, 1-2, 3-4, 5-6, and 7-10), and a negative binomial distribution accounted for the over-dispersed data. The models were fitted first to explore the association between gestational age and hospital admission rates, and second to explore whether the association changed over time. For the latter, an interaction term was included for gestational age category (<28, 28-31, 32-33, 34-36, 37-38, 39-41, 42) and age at admission in years (<1, 1-2, 3-4, 5-6, and 7-10); this was assessed using the Wald test. Finally, an age-stratified analysis was conducted using negative binomial regression models to estimate unadjusted and adjusted RRs for admissions by gestational age categories, which were repeated for each of the following age bands (<1, 1-2, 3-4, 5-6, and 7-10). Population attributable fractions (PAF) were estimated for each band of gestational age as: (proportion of cases exposed) x (RR-1/RR), where RR is the adjusted RR from the GEE model.

Models were determined a priori and were adjusted for the following variables based on existing evidence: Maternal age at delivery[23] (<20; 20-24; 25-29; 30-34; 35-39; 40+yrs); marital status at birth registration[24] (married, partner, single); area deprivation based on quintiles of Index of Multiple Deprivation (IMD) score[25,26] (for babies born in 2005 and 2006, IMD scores from 2004 and 2007 were used respectively); child's ethnicity based on the 2001 census classification (white British; white other; Bangladeshi; Indian; Pakistani; black African; black

Caribbean; other); mother's country of birth[27] (UK or non-UK born); mode of delivery[28] (vaginal, caesarean section); parity[29,30] (nulliparous, parous); month of birth[31] (Jan-Mar, Apr-Jun, Jul-Sept, Oct-Dec), sex[26] (male, female) and SGA[30] (yes, no).

A number of sensitivity analyses were performed to explore how stable the estimates were: [1] Children considered 'high-risk' were excluded (defined as a diagnosis of at least one of the following: malignant neoplasm; a blood disorder; chronic kidney disease; cystic fibrosis; immune dysfunction; or a congenital anomaly) [Table S3 in supplementary information]; [2] due to data quality concerns for the variable parity, a hospital was defined as an 'unreliable reporter' of parity if it reported <20% or >70% women as nulliparous in 2005 or 2006.[17] (see supplementary information, section F); [3] the analysis was restricted to emergency hospital admissions only (see supplementary information, section D); [4] baseline model further adjusted for labour induction; (5) to account for correlation between children born to the same mother, the analysis was restricted to first born babies during the study period; [6] because very preterm (<32 weeks' gestation) babies are likely to have long birth admission lengths of stay (LOS), they have a shorter period at risk of subsequent admission and their rates may appear lower. Therefore a z-score for LOS was created for each week of gestational age, then categorised (<1, 0-1, >1) and added to the model in an attempt to adjust for this;[28] and [7] the analysis was restricted to children who were not SGA.

With the exception of labour induction (23% missing), all variables had between 0% and 5.8% missing data (Table 1). A complete case analysis (CCA) was conducted. This was deemed a sensible approach because some data was likely to be missing not at random (MNAR). For example, parity was only missing for unmarried women (see supplementary file F for more detail) and a sensitivity analysis was undertaken to explore the impact of this. All analyses were conducted using Stata 14[32].

Patient and Public Involvement

The TIGAR study was supported by a patient, parent and public advisory group, which provided input to different aspects of the study. This group met at the start of the study and gave input into the study protocol and the lay summary of the project.

Results

There were 1,170,970 live, singleton births in NHS hospitals, born to mothers living in England between 1st January 2005 and 31st December 2006. After linking and cleaning the datasets, a total of 1,018,136 children remained, with a total of 9,372,105 person years of follow up and an average of 9.2 years of follow up per child. There was a total of 1,315,338 admissions between 1st January 2005 and 31st March 2015, and 831,729 (63%) were emergency admissions. There were 525,039 (52%) children who experienced ≥1 admissions up to the age of 10 years (Table 1), including 262,606 (26%) who experienced one, 123,583 (12%) who experienced two, 89,293 (9%) who experienced 3-4 and 49,555 (5%) who experienced ≥5 admissions (Table S4).

Table 1· Socio-demographic characteristics of sample population (n=1,018,136)

	Total (n=1,018,136) n (%)	No admission (n=493,097) n (%)	Any admission (n=525,039) n (%)
Mother's age at birth			
<20	44,486 (4.4)	17,127 (3.5)	27,359 (5.2)
20-24	181,633 (17.8)	76,351 (15.5)	105,282 (20.1)
25-29	253,055 (24.9)	119,340 (24.2)	133,715 (25.5)
30-34	293,741 (28.9)	150,816 (30.6)	142,925 (27.2)
35-39	193,622 (19.0)	102,276 (20.7)	91,346 (17.4)
40+	51,599 (5.1)	27,187 (5.5)	24,412 (4.6)
Parity			
Nulliparous	480,616 (47.2)	230,947 (46.8)	249,669 (47.6)
Parous	496,203 (48.7)	241,195 (48.9)	255,008 (48.6)
Missing	41,317 (4.1)	20,955 (4.2)	20,362 (3.9)
Maternal registration status			
Married	581,160 (57.1)	297,381 (60.3)	283,779 (54.0)
Partner	347,366 (34.1)	158,097 (32.1)	189,269 (36.0)
Single	89,610 (8.8)	37,619 (7.6)	51,991 (9.9)
Mother's country of birth			
Non-UK	225,695 (22.2)	121,248 (24.6)	104,447 (19.9)
UK	791,012 (77.7)	371,101 (75.3)	419,911 (80.0)
Missing	1,429 (0.1)	748 (0.2)	681 (0.1)
IMD score (quintiles)			
Q1 (most deprived)	276,838 (27.2)	120,894 (24.5)	155,944 (29.7)
Q2	216,006 (21.2)	103,060 (20.9)	112,946 (21.5)
Q3	180,300 (17.7)	89,733 (18.2)	90,567 (17.2)
Q4	161,793 (15.9)	82,668 (16.8)	79,125 (15.1)
Q5 (least deprived)	157,195 (15.4)	83,869 (17.0)	73,326 (14.0)
Missing	26,004 (2.6)	12,873 (2.6)	13,131 (2.5)
Sex			
Male	521,169 (51.2)	231,013 (46.8)	290,156 (55.3)
Female	496,967 (48.8)	262,084 (53.2)	234,883 (44.7)
Ethnicity (child)			
White British	677,236 (66.5)	299,672 (60.8)	377,564 (71.9)
White Other	59,683 (5.9)	32,799 (6.7)	26,884 (5.1)
Bangladeshi	14,546 (1.4)	6,669 (1.4)	7,877 (1.5)
Indian	27,783 (2.7)	14,517 (2.9)	13,266 (2.5)
Pakistani	41,739 (4.1)	18,583 (3.8)	23,156 (4.4)
Black African	34,571 (3.4)	19,141 (3.9)	15,430 (2.9)
Black Caribbean	12,410 (1.2)	6,507 (1.3)	5,903 (1.1)
Other	91,570 (9.0)	44,370 (9.0)	47,200 (9.0)
Missing	58,598 (5.8)	50,839 (10.3)	7,759 (1.5)

Chi-squared results significant ($p<0.001$) for all variables

Table 2· Birth characteristics of sample population continued (n=1,018,136)

	Total (n=1,018,136) n (%)	**No admission (n=493,097) n (%)**	**Any admission (n=525,039) n (%)**
Gestational age (weeks)			
<28	1,730 (0.2)	103 (0.0)	1,627 (0.3)
28-29	2,089 (0.2)	263 (0.1)	1,826 (0.3)
30-31	3,227 (0.3)	590 (0.1)	2,637 (0.5)
32	2,656 (0.3)	637 (0.1)	2,019 (0.4)
33	4,050 (0.4)	1,035 (0.2)	3,015 (0.6)
34	7,292 (0.7)	2,225 (0.5)	5,067 (1.0)
35	11,663 (1.1)	4,051 (0.8)	7,612 (1.4)
36	23,346 (2.3)	8,822 (1.8)	14,524 (2.8)
37	54,001 (5.3)	22,830 (4.6)	31,171 (5.9)
38	137,926 (13.5)	64,098 (13.0)	73,828 (14.1)
39	231,376 (22.7)	114,208 (23.2)	117,168 (22.3)
40	288,065 (28.3)	145,808 (29.6)	142,257 (27.1)
41	208,757 (20.5)	106,847 (21.7)	101,910 (19.4)
42	41,958 (4.1)	21,580 (4.4)	20,378 (3.9)
Delivery Method			
Vaginal	751,653 (73.8)	368,091 (74.6)	383,562 (73.1)
Caesarean section	222,615 (21.9)	102,853 (20.9)	119,762 (22.8)
Missing	43,868 (4.3)	22,153 (4.5)	21,715 (4.1)
SGA			
No	918,419 (90.2)	448,039 (90.9)	470,380 (89.6)
Yes	99,717 (9.8)	45,058 (9.1)	54,659 (10.4)
Labour induction			
No	626,178 (61.5)	306,105 (62.1)	320,073 (61.0)
Yes	154,851 (15.2)	70,115 (14.2)	84,736 (16.1)
Missing	237,107 (23.3)	116,877 (23.7)	120,230 (22.9)
High-risk*			
No	930,418 (91.4)	476,486 (96.6)	453,932 (86.5)
Yes	87,718 (8.6)	16,611 (3.4)	71,107 (13.5)
Month of birth			
Jan-Mar	236,944 (23.3)	114,296 (23.2)	122,648 (23.4)
Apr-Jun	254,016 (24.9)	122,968 (24.9)	131,048 (25.0)
Jul-Sep	270,282 (26.5)	131,137 (26.6)	139,145 (26.5)
Oct-Dec	256,894 (25.2)	124,696 (25.3)	132,198 (25.2)
Birth admission LOS			
<1 week	970,067 (95.3)	480,360 (97.4)	489,707 (93.3)
1-2 weeks	33,589 (3.3)	10,394 (2.1)	23,195 (4.4)
3-4 weeks	6,782 (0.7)	1,442 (0.3)	5,340 (1.0)
1-2 months	4,600 (0.5)	701 (0.1)	3,899 (0.7)
3+ months	3,098 (0.3)	200 (0.0)	2,898 (0.6)

* High-risk defined as a child with a diagnosis of malignant neoplasm, a blood disorder, chronic kidney disease, cystic fibrosis, immune dysfunction or a congenital anomaly.

Chi-squared results significant ($p<0.001$) for all variables, except for month of birth ($p=0.13$)

Experiencing ≥1 admission was associated with having a younger, unmarried, UK-born mother, living in a more deprived area, being male, white, preterm, born via caesarean section, SGA, 'high-risk' and having a long birth admission LOS (Tables 1 and 2). Crude admission rates were highest in infancy and for those born preterm. Children born at <28 weeks' gestation experienced the highest admission rate (253/100PY), compared to those born at 40 weeks' gestation (28/100PY). However, admission rates decreased with increasing chronological age and by 7-10 years, those born at <28 weeks' gestation had a crude admission rate of 26/100PY, compared to a rate of 7/100PY for those born at 40 weeks' gestation (Table 3). Even children born a few weeks early had higher admission rates. Compared to those born at 40 weeks, being born at 37, 38 and 39 weeks gestation was associated with a rate difference of 19, 9 and 3 admissions per 100 person years during infancy, respectively.

Table 3. Descriptive characteristics of hospital admissions by gestational age and age at admission

	<1 year				1-2 years				3-4 years				5-6 years				7-10 years		
	% ≥1	R	PY	Rate	% ≥1	R	PY	Rate	% ≥1	R	PY	Rate	% ≥1	R	PY	Rate	% ≥1	R	PY
Gestational age																			
<28	68·7	3,146	1,244	253	61·5	3,223	3,413	94	41·0	1,754	3,395	52	30·2	1,174	3,391	35	24·6	974	3,784
28-29	58·8	2,723	1,712	159	47·9	2,398	4,138	58	32·8	1,470	4,130	36	26·1	1,109	4,130	27	21·0	966	4,649
30-31	50·5	3,372	2,856	118	40·3	2,722	6,427	42	28·2	2,074	6,415	32	22·8	1,587	6,416	25	17·5	1,232	7,144
32	43·5	2,298	2,446	94	36·6	2,324	5,289	44	26·2	1,665	5,279	32	20·9	1,157	5,280	22	18·3	875	5,859
33	41·3	3,020	3,803	79	34·0	2,710	8,035	34	23·3	1,732	8,022	22	19·4	1,382	8,025	17	17·7	1,196	9,003
34	37·7	4,987	6,994	71	30·6	4,313	14,486	30	20·7	2,726	14,466	19	17·9	2,430	14,471	17	14·6	1,866	16,173
35	33·5	6,777	11,362	60	27·7	5,883	23,186	25	19·6	3,916	23,147	17	16·3	3,030	23,156	13	13·9	2,795	25,842
36	32·3	12,924	22,946	56	25·8	11,818	46,543	25	18·6	7,925	46,543	17	15·7	6,237	46,543	13	12·7	5,338	52,019
37	27·6	24,897	53,388	47	23·6	22,954	107,598	21	17·0	16,197	107,598	15	14·4	12,938	107,598	12	12·3	11,727	120,192
38	23·3	50,096	136,619	37	21·6	51,351	273,785	19	15·6	36,194	273,785	13	13·2	29,287	273,785	11	11·1	26,035	306,639
39	20·4	70,567	229,432	31	20·1	75,329	462,697	16	14·7	55,379	459,959	12	12·3	44,628	462,697	10	10·4	39,538	514,716
40	18·9	79,680	284,736	28	19·4	89,689	574,949	16	14·2	63,762	574,949	11	12·1	52,498	574,949	9	10·2	46,033	640,657
41	17·9	53,818	206,982	26	19·3	63,940	416,153	15	14·3	47,575	416,153	11	12·1	38,250	416,153	9	10·2	34,461	465,435
42	17·6	10,717	41,615	26	19·4	12,757	83,778	15	14·3	9,601	83,778	12	12·0	7,477	83,778	9	10·2	6,715	93,361
Overall	35·1	329,022	100,6135	33	30·6	351,411	203,0477	17	21·5	251,970	2,027,619	12	17·5	203,184	2,030,372	10	14·6	179,751	2,265,473

% ≥1 = % of children with one or more readmissions during age period

R = Number of hospital readmissions

PY = Total person years of follow up (note: child not at risk of subsequent hospital admission until discharged from hospital after birth admission)

Rate = Rate per 100 person years

In the unadjusted model, admission rates during childhood were inversely associated with gestational age (Table 4). Children born <28 weeks' of gestational age had an admission rate that was five times higher than that for children born at 40 weeks (RR=5·24 [4·91 to5·60]; p<0.001). The RRs steadily decreased by week of gestational age at birth. However, even those born at 38 weeks (RR=1·22 [1·19 to1·24]) and those born at 39 weeks (RR=1·07 [1·05 to1·09]; p<0.001) had a significantly higher admission rate during childhood. Once the model was adjusted for other covariates (N=893,662), the RRs were slightly attenuated but remained statistically significant. Those born at <28 weeks had a RR of 4·92 (4.58 to 5.30) compared to those born at 40 weeks. Those born at 38 weeks still had a rate almost 20% higher than those born at 40 weeks (RR=1·19 [1·16 to1·22]; p<0·001).

There were 86,418 children defined as 'high-risk'. When these were excluded from the model, the adjusted RRs (N=814,852) decreased from 4·92 (4.58 to 5.30) to 3·24 (2.98 to 3.53) for those born at <28 weeks. The decline in rates was greater in those born very preterm, with only small differences observed in those born at early term (Table 4).

Table 4. Unadjusted and adjusted rate ratios (RR) and 95% confidence intervals (CI for hospital admissions during childhood by gestational age

	Unadjusted (n=1,018,136)	Adjusted* (n=893,662)	Adjusted: excluding high-risk children^ (n=814,852)
Gestational age (weeks)	RR (95% CI)	RR (95% CI)	RR (95% CI)
<28	5.24 (4·91 to 5.60)	4.92 (4·58 to 5.30)	3.24 (2·98 to 3.53)
28-29	3.63 (3·33 to 3.97)	3.27 (2·99 to 3.57)	2.83 (2·66 to 3.01)
30-31	2.97 (2·53 to 3.49)	2.65 (2·22 to 3.17)	2.19 (2·09 to 2.31)
32	2.74 (2·42 to 3.10)	2.46 (2·17 to 2.78)	2.00 (1·89 to 2.11)
33	2.18 (2·05 to 2.31)	1.95 (1·83 to 2.07)	1.81 (1·72 to 1.90)
34	1.95 (1·84 to 2.06)	1.81 (1·71 to 1.92)	1.57 (1·52 to 1.63)
35	1.68 (1·61 to 1.75)	1.57 (1·50 to 1.64)	1.48 (1·43 to 1.53)
36	1.65 (1·58 to 1.73)	1.58 (1·51 to 1.65)	1.38 (1·35 to 1.42)
37	1.43 (1·39 to 1.47)	1.39 (1·35 to 1.43)	1.30 (1·28 to 1.33)
38	1.22 (1·19 to 1.24)	1.19 (1·16 to 1.22)	1.13 (1·12 to 1.15)
39	1.07 (1·05 to 1.09)	1.06 (1·04 to 1.08)	1.05 (1·04 to 1.06)
40	1.00	1.00	1.00
41	0.99 (0·97 to 1.01)	0.98 (0·96 to 1.01)	0.98 (0·97 to 0.99)
42	0.98 (0·95 to 1.01)	0.97 (0·94 to 1.00)	0.96 (0·94 to 0.98)

* Adjusted for maternal age at delivery, mother's country of birth, marital status, sex, SGA, parity, delivery method, IMD score, child's ethnicity and season of birth

^ High-risk children defined as a child with diagnosis of malignant neoplasm, blood disorder, cystic fibrosis, immune dysfunction or congenital anomaly

The population attributable fractions (PAF) were highest during infancy and then declined over time. Approximately 9.2%, 8.8% and 4.2% of admissions during infancy were attributable to being born at 37, 38 and 39 weeks gestation, respectively (Table 5); which equates to roughly 7,373 excess admissions in infants each year.

There was evidence of a strong interaction between gestational age at birth and age at admission ($p<0{\cdot}001$), with RRs for gestational age inversely associated with chronological age, particularly after the age of two years (Figure 2). During infancy, the admission rate was six times higher in babies born at <28 weeks compared with those born at 40 weeks (RR=6·34 [5·80 to 6·85]) and it was 10% higher for those born at 39 weeks compared to 40 weeks (RR=1·10 [1·08 to1·11]). However, by 7-10 years of age, the RRs had decreased to 3·28 (2.82 to 3.82) for those born at <28 weeks and 1·06 (1.03 to 1.08) for those born at 39 weeks. Before the age of three, being born at 41 or 42 weeks gestation was associated with lower admission rates compared to those born at 40 weeks. However, by 5-6 years of age the RRs were close to one and no longer statistically significant (Table 6).

The results remained relatively stable in the other five sensitivity analyses (see Table S5 in supplementary information) and when restricted to emergency hospital admissions (results not presented).

Table 5. Population attributable fractions (PAF) with 95% confidence intervals for each gestational age category and age at admission* (%)

Gestational age	Overall	<1 year	1-2 years	3-4 years	5-6 years	7-10 years
<28	2.39 (2.35 to 2.44)	3.20 (3.14 to 3.24)	2.87 (2.81 to 2.92)	2.06 (1.98 to 2.13)	1.56 (1.47 to 1.64)	1.44 (1.34 to 1.53)
28-29	1.77 (1.69 to 1.83)	2.53 (2.47 to 2.59)	1.82 (1.75 to 1.89)	1.48 (1.39 to 1.56)	1.30 (1.20 to 1.39)	1.30 (1.18 to 1.39)
30-31	2.00 (1.76 to 2.20)	2.86 (2.77 to 2.93)	1.72 (1.62 to 1.81)	1.95 (1.83 to 2.05)	1.77 (1.65 to 1.88)	1.43 (1.29 to 1.56)
32	1.45 (1.32 to 1.57)	1.82 (1.74 to 1.89)	1.51 (1.42 to 1.59)	1.51 (1.40 to 1.61)	1.20 (1.09 to 1.30)	0.87 (0.73 to 0.99)
33	1.43 (1.33 to 1.52)	2.13 (2.03 to 2.22)	1.41 (1.29 to 1.51)	1.14 (1.01 to 1.27)	1.08 (0.93 to 1.21)	1.03 (0.86 to 1.18)
34	2.10 (1.95 to 2.25)	3.33 (3.20 to 3.44)	1.97 (1.83 to 2.11)	1.50 (1.32 to 1.67)	1.89 (1.71 to 2.06)	1.28 (1.05 to 1.48)
35	2.29 (2.12 to 2.46)	3.88 (3.72 to 4.03)	2.09 (1.91 to 2.27)	1.67 (1.44 to 1.89)	1.42 (1.17 to 1.65)	1.71 (1.44 to1.97)
36	4.30 (3.95 to 4.63)	6.71 (6.49 to 6.91)	4.12 (3.87 to 4.36)	3.42 (3.12 to 3.72)	3.03 (2.70 to 3.35)	2.79 (2.41 to 3.14)
37	5.93 (5.48 to 6.38)	9.19 (8.88 to 9.49)	4.98 (4.62 to 5.33)	4.69 (4.25 to 5.11)	4.37 (3.90 to 4.83)	5.03 (4.51 to 5.53)
38	5.87 (5.19 to 6.54)	8.76 (8.29 to 9.23)	5.13 (4.60 to 5.65)	4.68 (4.03 to 5.31)	4.18 (3.48 to 4.86)	4.99 (4.22 to 5.74)
39	2.69 (1.87 to 3.50)	4.19 (3.59 to 4.77)	1.51 (0.87 to 2.15)	2.96 (2.19 to 3.71)	2.37 (1.54 to 3.18)	2.46 (1.53 to 3.37)

*PAFs not calculated for 41 and 42 weeks as rate ratios <1

Table 6. Adjusted rate ratios (RR) and 95% confidence intervals (CI) for hospital admissions during childhood, stratified by age at admission

	<1 year (n=893,662) RR (95% CI)	**1-2 years (n=892,611)** RR (95% CI)	**3-4 years (n=892,112)** RR (95% CI)	**5-6 years (n=891,885)** RR (95% CI)	**7-10 years (n=891,745)** RR (95% CI)
Gestational age (weeks)					
<28	6.34 (5·80 to 6.85)	5.78 (5·25 to 6.37)	4.35 (3·86 to 4.91)	3.49 (3·06 to 3.98)	3.28 (2·82 to 3.82)
28-29	4.26 (3·94 to 4.61)	3.32 (3·03 to 3.64)	2.91 (2·6 to 3.25)	2.69 (2·39 to 3.04)	2.70 (2·36 to 3.11)
30-31	3.37 (3·14 to 3.60)	2.41 (2·23 to 2.60)	2.61 (2·38 to 2.87)	2.52 (2·28 to 2.78)	2.21 (1·97 to 2.48)
32	2.84 (2·64 to 3.06)	2.48 (2·29 to 2.70)	2.47 (2·23 to 2.73)	2.25 (2·02 to 2.52)	1.87 (1·64 to 2.13)
33	2.40 (2·25 to 2.56)	1.92 (1·79 to 2.06)	1.76 (1·62 to 1.92)	1.72 (1·57 to 1.89)	1.69 (1·52 to 1.88)
34	2.30 (2·19 to 2.41)	1.75 (1·66 to 1.85)	1.58 (1·48 to 1.69)	1.75 (1·63 to 1.88)	1.49 (1·37 to 1.61)
35	1.98 (1·90 to 2.06)	1.51 (1·45 to 1.58)	1.41 (1·33 to 1.49)	1.35 (1·27 to 1.43)	1.43 (1·33 to 1.52)
36	1.92 (1·87 to 1.98)	1.55 (1·50 to 1.60)	1.45 (1·39 to 1.51)	1.40 (1·34 to 1.46)	1.37 (1·30 to 1.43)
37	1.63 (1·60 to 1.66)	1.32 (1·29 to 1.35)	1.30 (1·27 to 1.34)	1.28 (1·25 to 1.32)	1.33 (1·29 to 1.37)
38	1.29 (1·27 to 1.31)	1.16 (1·14 to 1.18)	1.15 (1·13 to 1.17)	1.13 (1·11 to 1.16)	1.16 (1·13 to 1.19)
39	1.10 (1·08 to 1.11)	1.03 (1·02 to 1.05)	1.07 (1·05 to 1.09)	1.05 (1·03 to 1.07)	1.06 (1·03 to 1.08)
40	1.00	1.00	1.00	1.00	1.00
41	0.92 (0·91 to 0.93)	0.97 (0·96 to 0.99)	1.03 (1·01 to 1.05)	1.01 (0·99 to 1.03)	1.03 (1·01 to 1.05)
42	0.92 (0·89 to 0.94)	0.96 (0·93 to 0.99)	1.02 (0·98 to 1.05)	0.97 (0·94 to 1.00)	1.00 (0·96 to 1.04)

* Adjusted for mother's age at delivery, mother's country of birth, marital status, sex, SGA, parity, delivery method, IMD score, child's ethnicity and month of birth

Figure 3 and supplementary Table S7 present crude hospital admission rates per 100 person years for key causes of morbidity by gestational age (<28, 28-31, 32-33, 34-36, 37-38, and 39-42 weeks) and age at admission (<1, 1-2, 3-4, 5-6, and 7-10). The highest hospital admission rates were seen in infancy and these continued to decline with increasing age.

At all ages, infection was the most common cause of admission and the rate increased markedly as gestational age decreased, suggesting that the excess admissions in children born before 39-42 weeks were largely due to infection, in particular respiratory infections (Figure 3). In infancy, there were also excess admissions in children born before 39-42 weeks due to non-infection GI-tract in children born <37 weeks gestation and non-infection respiratory causes in children born <34 weeks. At 1-2 and 3-4 years, there were also excess admissions due to non-infection respiratory causes in children born <34 weeks gestation. At 5-6 and 7-10 years, injuries were the second most common cause of admission (after infection) and accounted for a large proportion of excess admissions in children born before 39-42 weeks, particularly in children born <32 weeks. However, in children born <34 weeks, CNS causes also accounted for many excess admissions and the most common ICD10 codes were related to epilepsy and cerebral palsy. Crude rates are presented in Table S7 in the supplementary information.

Almost all (97%) of infection-related admissions during infancy were emergency admissions, however, this declined over time and at 7-10 years 19,555 (63%) of infection-related admissions were emergency admissions. Similar patterns were observed for non-infection respiratory admissions and non-infection GI tract admissions.

Discussion

Principal findings

The results from our study show that gestational age at birth is a strong predictor of severe morbidity throughout childhood in England. Children had a consistently lower admission rate with each additional week of gestational age at birth. Adjusting for other prognostic characteristics altered the strength of this relationship very little, as

did the various sensitivity analyses conducted. Importantly, the relationship between gestational age and severe morbidity ameliorated over time, with the sharpest decline in rates observed after two years of age, particularly in those born extremely preterm. However, in the age-stratified analysis, the effect of gestational age persisted in later stages of childhood, even for those born at 38 and 39 weeks.

The results were attenuated when 'high-risk' children were excluded, with the most marked decrease observed in those born at ≤32 weeks' of gestation, suggesting there is heterogeneity within gestational age groups. Infection accounted for the majority of hospital admissions at all ages and there was a strong relationship between infection-related admissions and age at admission. Other common causes of admission were respiratory (non-infection) and GI tract-related, especially in younger children, and injuries and CNS-related in older children. Many of these cause-specific rates showed a marked increase as gestational age at birth decreased. Amongst those born extremely preterm, the most common cause of admission by 7-10 years of age was CNS-related issues, primarily cerebral palsy and epilepsy.

Strengths and limitations

To our knowledge, this is the largest study to date to investigate the association between gestational age at birth and longer-term health outcomes in England. A key strength of this study is its large size, providing sufficient power to investigate the effects across the full spectrum of gestational age, thereby detecting even small differences in hospital admission rates between gestational age categories. In addition, we were able to analyse up to 10 years of follow up data, enabling us to estimate hospital admission trajectories through early and mid-childhood. Finally, the use of routinely collected data means that the results are largely unaffected by recall and social desirability bias.[33]

There is also a number of study limitations. HES data are collected primarily for financial reimbursement rather than research purposes, leading to large variations in the quality and completeness for particular data fields[16]. Whilst linkage to birth registration data made it possible to overcome some of these quality issues, there were

some fields, such as parity and labour induction, where it was not possible to recover or validate some of this missing or poor quality data. However, we were able to conduct two sensitivity analyses where we adjusted for labour induction and excluded hospitals that were defined as 'poor reporters' of parity, but neither of these approaches had much impact on the results. The HES dataset also does not provide information on migration from the NHS, therefore, it is possible that children may have moved outside of England or transferred care to private or military hospitals, which would not be reflected in the admission rates. However, this would be a very small proportion of the sample population and is unlikely to change the estimates generated. In addition, it was not possible to adjust for particular confounders demonstrated in other research studies as predictive of adverse long-term sequelae in children, such as maternal smoking, breastfeeding, individual level markers of social deprivation or maternal conditions associated with preterm birth, as these variables are not recorded reliably or at all in birth registration records or in HES. Moreover, the cause of admission was defined using the primary diagnosis code; whilst this is often the main reason for admission, in some cases this will reflect the most expensive diagnosis rather than key reason for admission. Finally, a complete case analysis was conducted rather than using multiple imputation to deal with the missing data. Whilst the estimates remained fairly stable in all models, we cannot rule out the potential for bias in the results from the fully adjusted model due to excluding participants with missing data.

Comparison with other studies

Whilst there have been many studies investigating the effect of preterm birth on offspring outcomes, few studies have been conducted looking at all-cause, long-term hospital admissions across the whole spectrum of gestational age, particularly in UK populations. Whilst UK studies all report a decline in hospitalisation rates with increasing gestational age, they either group gestational age in broad categories[4,13,34] or focus on specific causes of hospitalisation.[9,14,34]

Our study found 52% of children to have had at least one hospital admission by 10 years of age. Two Australian studies reported that 62%[5] and 56%[15] of study participants had experienced at least one hospital admission by 18

years of age, with the vast majority of admissions occurring before age 12 years. In our study, very and extremely preterm babies had much higher admission rates during infancy compared to those born full term, which is consistent with published data. Similar studies in Australia[15] and France[35] have reported admission rates in extremely and very preterm babies to be seven and three times higher than those born full term, respectively. Other studies conducted in Australia[36,37] and the US[6] found very preterm babies were 2-3 times more likely than those born at full term to be admitted to hospital during infancy. Whilst these results are important contributors to this area, differences in health and social care systems mean results may not be generalisable to UK populations.

Few UK based studies have explored how risk of admission changes during childhood. One UK study[13] found that compared to full term babies, very preterm infants were more than 13 times more likely by 9 months of age, and six time more likely at age five to have ≥3 hospital admissions.[13] A study conducted in Australia[15] reported lower admission rates among older children; compared to full term infants, admission rates declined from 7·77 in infancy to 2·94 at 5-12 years of age. Similar findings have been reported in other studes;[5] however, due to the narrower age groups in our study, our findings suggest that the sharpest decline in hospital admissions is seen after the age of two, particularly in those born extremely preterm.

The increased risk of admission in children born at 38 and 39 gestational weeks is consistent with other research. Globally, the rates of births before 40 weeks' gestation have been increasing over the last 20 years and the average gestational age at delivery has consequently decreased from 40 to 39 weeks.[38,39] This is attributed to an increase in caesarean sections and induction rates, and a clinical perception that there is little risk from being born a week or two before 40 weeks' gestation.[40] Whilst the rates of admission are only slightly higher for those born at 38 and 39 weeks compared to those born at 40 weeks, they account for 37% of births within our cohort. Approximately 13% of admissions (PAFs 8.76 + 4.19) during infancy could be avoided if these babies were born at 40 weeks gestation. However, this must also be balanced with the risk of stillbirth, and short-term risks and safety of the mother and baby. Medically indicated birth before 40 weeks' gestation will be due to clinical concern

for the health of either the mother or baby. Therefore, it is possible that poorer outcomes in these children are as much or more related to the effects of maternal illness or complications of pregnancy as early term birth itself.[41]

Admission rates in children born post-term (≥42 weeks' gestation) were slightly lower compared to full term infants, but in stratified analyses, this pattern disappeared after age two. Similar findings were also observed in a number of other studies,[10,36,37] though it was not possible to see how this effect changed over time. In contrast, a study conducted in Australia[15] reported an increased rate of hospitalisation in children born at ≥42 weeks when stratified by age, with the highest rates of admission seen within the first year of life. However, our results suggest that not all post-term children will have poorer outcomes compared to those born at full term, and that future research should explore the effect of post-term birth by each week of gestational age.

Our study has revealed that infections, particularly respiratory infections, account for the majority of hospital admissions during childhood. Infection-related admissions were strongly associated with gestational age, and whilst rates declined with age, they were still the most common cause of admission at 7-10 years. Preterm infants are at increased risk of infection due to their immature immune systems, which continue to develop at a slower rate throughout childhood compared to their full term peers.[42] They are also at increased risk of impaired lung function, leaving them particularly vulnerable to respiratory problems.[43] Our results suggest that even children born early term are at increased risk of infections throughout early childhood, particularly during infancy when compared with those born at full term.

Our findings suggest that children born at <34 weeks' gestation are particularly at risk of CNS related admissions, specifically epilepsy and cerebral palsy, and in extremely preterm children, these were the most common causes of hospital admission at age 7-10 years. A study conducted in Australia reported similar findings[5] and an increased risk of brain injury such as intraventricular haemorrhage and periventricular leucomalacia, or severe illness in the early neonatal period may be responsible for this relationship.[44]

It is also striking that other causes of admission showed a strong association with gestational age. For example, rates of injury related admissions, which were relatively common from age 3-10 years, increased as gestational age decreased. This has been observed in a similar study[5] and it is possible that neurobehavioral disorders and impaired cognitive function associated with preterm birth may account for this.[45]

Whilst there are often physiological characteristics which cause morbidity in preterm children, it is also possible that the knowledge of a child being born preterm played a role in their admission to hospital. Vulnerable child syndrome (VCS) describes children who are perceived, usually by parents, to be at greater risk of developmental delays and adverse health outcomes, and preterm birth is a known risk factor.[46] Children with increased perceived vulnerability are likely to experience high numbers of emergency department visits during childhood[48] and a study conducted in Australia found that clinicians often overestimated the adverse outcomes of extremely preterm infants.[49] Therefore it is plausible that the perception of vulnerability may be driving some of the excess admissions in children who are preterm.

Implications

Overall, the findings from this study have illustrated the need for strategies aimed at the prevention and management of infections in infancy and childhood in children born preterm and close to term. In addition, it is particularly important for children born at <34 weeks, who continue to have increased admissions due to CNS causes up to age 10 years, to be monitored closely. The National Institute for Clinical Excellence (NICE) currently recommend that children born before 30 weeks', and those born between 30 and 36 weeks' gestation who have additional risk factors, should be monitored and assessed up to two years of age for developmental deficits, and up to four years of age for those at highest risk (born <28 weeks' gestation). However, risk factors in more mature preterm and early term births have not been clearly elucidated, and a report found that there was wide variation in the provision of clinical surveillance across the UK.[48] Many medically indicated births before 40 weeks cannot be avoided as risks of delaying delivery often outweigh potential benefits. However, where the clinical decision for early delivery is not as clear cut, for example whether low-risk women aged 35 and over should be induced

before 40 weeks' gestation,[49,50] the long term risks should be discussed with parents. Neonatal, paediatric and primary care clinicians should be aware of the increased likelihood of infections, respiratory and GI tract problems that children born even a small number of weeks early may experience, in order to advise parents appropriately.

The findings indicate a need for future research to move towards looking at the full spectrum of gestational age, week-by-week, with a focus on understanding the long-term health outcomes of early-term, late-term and post-term births. A small group of children born very and extremely preterm did not experience any hospital admissions up to 10 years of age, which suggests there are children with different risk profiles within gestational age categories. By exploring this heterogeneity, it might be possible to identify factors associated with better long-term outcomes within these groups. In addition, the small, but increased rates of hospital admission in children born a week or two early suggest there should be a move away from the assumption that birth at 39 weeks carries no additional risk to the child. Finally, there is a need for future research to understand more fully the clinical decision making around hospital admissions among children born before 40 weeks' gestation, as these may be amendable to intervention and therefore be important in reducing admission rates.

Conclusions

The findings from this study show that gestational age at birth is a strong predictor of childhood morbidity, with those born extremely preterm being at the greatest risk of hospital admission throughout childhood. The risk of hospital admission associated with gestational age decreased over time, particularly after two years of age; however, an excess risk remained up to 10 years of age, even for children born at 38 and 39 weeks of gestation. Whilst the excess risk at 38 and 39 weeks was relatively small, the large numbers of babies born globally at these gestational ages suggests that they are likely to contribute a significant clinical and economic burden. Strategies aimed at the prevention and management of childhood infections should target preterm children and also those born close to full term. Future research should consider gestational age as a continuum and explore it in relation to outcomes week-by-week.

Acknowledgements

We are grateful to the following organisations and individuals who were involved in this study: Medical Research Council (MRC) for funding this project (MR/M01228X/1); The Office for National Statistics (ONS) for providing access to data and hosting it within the Safe Research Setting (SRS); NHS Digital for linking and providing access to the data; Nirupa Dattani for providing her expertise on record linkage and data management; Rod Gibson, for his help cleaning the data; the TIGAR Patient and Public Involvement (PPI) group and National Childbirth Trust (NCT) representatives for their input in the study objectives and design; and the TIGAR Advisory Group for their input on the study design and dissemination.

Contributors

MAQ (guarantor) designed the study with input from EB, CC, SJ, JJK, AJM, SP and ORA. MAQ and AJM were responsible for the acquisition of the data. VC (guarantor), MAQ and AJM were involved in data cleaning with input from Rod Gibson (Data management consultant) and Nirupa Dattani (Data analyst at City University). Statistical analysis was performed by VC and MAQ. VC, EB, CC, SJ, JJK, AJM, SP, ORA, MAQ were all involved in the interpretation of the data. VC was responsible for the initial draft of the manuscript. EB, CC, SJ, JJK, AJM, SP, ORA and MAQ reviewed and contributed to drafts of the manuscript, and all authors have reviewed the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted

Funding

The TIGAR study was funded by a research grant from the Medical Research Council (MR/M01228X/1), who mandate open access publication, therefore, A CC BY licence is required. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication

Competing Interests

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work..

Approvals

Ethics approval for this study was granted by the Health Research Authority Research Ethics Committee (South West – Frenchay; REC reference 15/SW/0294) and was provided by the Health Research Authority following Advice from the Confidential Advisory Group (CAG reference 15/CAG/0196).

The TIGAR study used data linked as part of a previous study led by City, University of London. For that study Permission to use patient-identifiable data without consent under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 ('section 251 support') was initially granted by the Patient Information Advisory Group PIAG 2-10(g)/2005. Renewals and amendments and a second permission, CAG 9-08(b)2014, under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 (or 'same legislation') were granted by the Secretary of State for Health and the Health Research Authority following advice from the CAG. A second permission CAG 9-08(b)2014 to use patient-identifiable data without consent under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 and create a research database held at the ONS for analyses relating to inequalities in the outcome of pregnancy and to inform maternity service users about the outcome of midwifery, obstetric and neonatal care was granted by the Health Research Authority. For

the TIGAR study, permission to use patient-identifiable data without consent under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 was granted by the Secretary of State for Health and the Health Research Authority following advice from the CAG (CAG reference 15/CAG/0196). Permission from the Health and Social Care Information Centre for preliminary quality assurance work was included in Data Sharing Agreement NIC-273840-N0N0 N. Permission for the subsequent analyses in the TIGAR study were included in Data Sharing Agreement NIC-09637-Y8T1N-v1.3.

Data Sharing

The authors do not have permission to supply data or identifiable information to third parties, including other researchers, but the team at City, University of London has permission under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to analyse patient-identifiable data for England and Wales without consent and create a research database that could be accessed by other researchers using the SRS at the ONS. The TIGAR team has permission under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to analyse these Anyone wishing to access the linked datasets for research purposes should apply via the CAG to the Health Research Authority to access patient-identifiable data without consent and then to the ONS and NHS Digital. In the first instance, enquiries about access to the data should be addressed to Alison Macfarlane.

Transparency

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities

As study data were pseudonymised, it is not possible to send findings directly to the study participants. The findings from the TIGAR study (including those from this paper) will be disseminated via our PPI parent group

and the charities which have supported the study. The results will also be made available on the TIGAR webpage https://www.npeu.ox.ac.uk/tigar

Provenance and peer review

Provenance and peer review: Not commissioned; externally peer reviewed.

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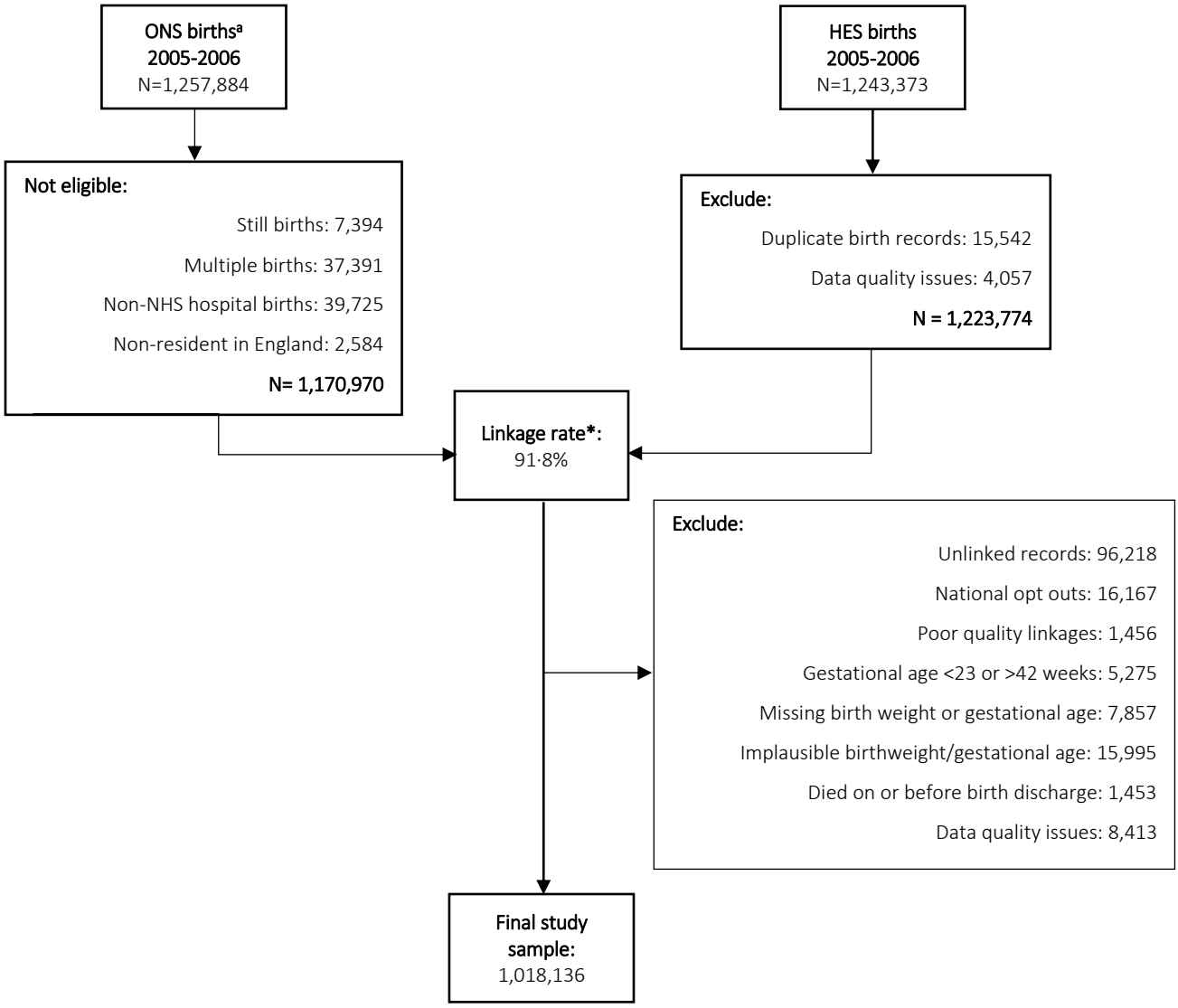
Figure legends

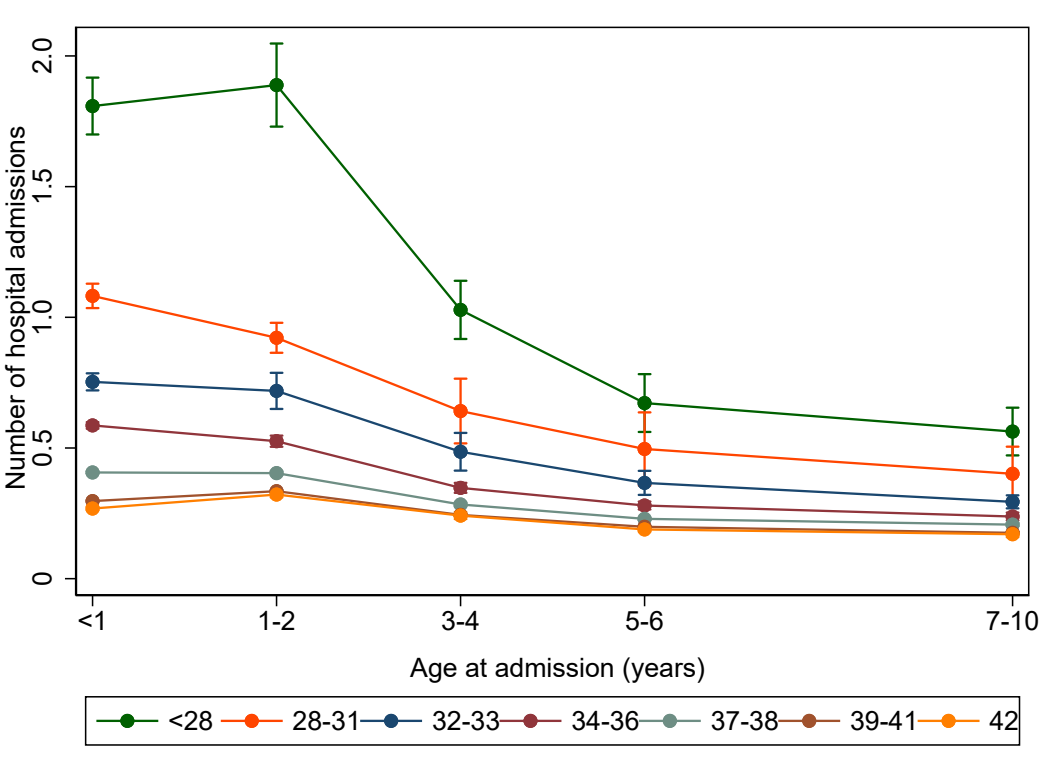
Figure 1. Flow chart of study population

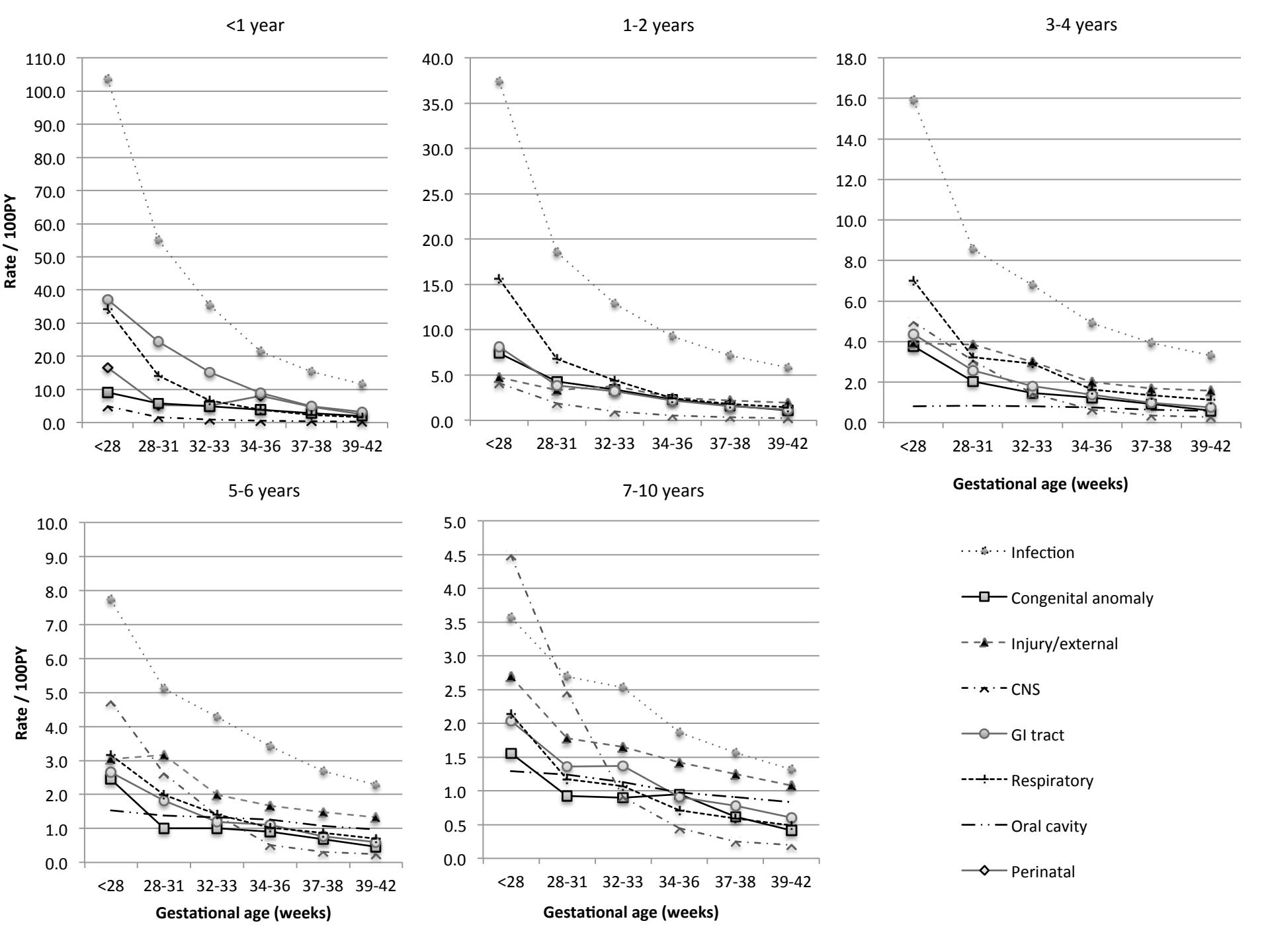
Figure 2. Mean hospital admissions by gestational age over time, adjusted for maternal age at delivery, mother's country of birth, marital status, sex, SGA, parity, delivery method, IMD score, child's ethnicity and season of birth

Figure 3. Crude hospital admission rates per 100 person years (PY) by cause of morbidity, gestational age and age at admission



ONS = Office for National Statistics
HES = Hospital Episode Statistics
[a] ONS births comprises routinely linked data from birth registration and birth notification records (NN4B)
* Linkage methods described elsewhere[1]


Number of hospital admissions
0
0.5
1.0
1.5
2.0
<1
1-2
3-4
5-6
7-10
Age at admission (years)
<28
28-31
32-33
34-36
37-38
39-41
42


<1 year
1-2 years
3-4 years
5-6 years
7-10 years
Rate / 100PY
Gestational age (weeks)
<28
28-31
32-33
34-36
37-38
39-42
Infection
Congenital anomaly
Injury/external
CNS
GI tract
Respiratory
Oral cavity
Perinatal