Birth prevalence of anorectal malformations in England and five-year survival: a national birth cohort study

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ABSTRACT

Objective: To determine the birth prevalence, maternal risk factors and five-year survival for isolated and complex anorectal malformations.

Design: National birth cohort using hospital admission data and death records.

Setting: All NHS England hospitals.

Patients: Live-born singletons delivered from 2002 through 2018, with evidence in the first year of life of a diagnosis of an anorectal malformation and repair during a hospital admission, or anorectal malformation recorded on the death certificate. Cases were further classified as isolated or complex depending on the presence of additional anomalies.

Main outcome measures: Birth prevalence of anorectal malformations per 10,000 live-births, risk ratios for isolated and complex anorectal malformation by maternal, infant and birth characteristics, and five-year survival.

Results: We identified 3,325 infants with anorectal malformations among 9,474,147 live-born singletons; 61.7% (n=2,050) of cases were complex. Birth prevalence was 3.5 per 10,000 live-births (95% CI, 3.4-3.6). Complex anorectal malformations were associated with maternal age extremes after accounting for other sociodemographic factors. Compared with maternal ages 25-34 years, the risk of complex anorectal malformations was 31% higher for ≥35 years (95% CI, 17-48) and 13% higher for ≤24 years (95%CI, 0-27). Among 2,376 anorectal malformation cases (n=1,450 complex) born from 2002 through 2014, five-year survival was lower for complex (86.9%; 95% CI, 85.1-88.5) than isolated anorectal malformations (98.2%; 95% CI, 97.1-98.9). Preterm infants with complex anorectal malformations had the lowest survival (73.4%; 95% CI, 68.1-78.0).

Conclusions: Differences in maternal risk factors for isolated and complex anorectal malformations may reflect different underlying mechanisms for occurrence. Five-year survival is high but lowest for preterm children with complex anorectal malformations.

INTRODUCTION

Anorectal malformations affect the anus, rectum and genitourinary system and result in lifelong healthcare needs.[1] Infants are typically diagnosed at birth and undergo a single definitive surgery in the first days of life or, more commonly, a series of procedures throughout infancy. Anorectal malformations can occur in isolation but approximately two-thirds of cases are considered complex due to additional anomalies.[2]

Although anorectal malformations are considered the most common congenital digestive tract anomaly, uncertainty remains about the birth prevalence, demographic risk factors, and survival. Reported birth prevalence from population-based studies varies from 2 to 5 cases per 10,000 births, with UK estimates at the lower end of this range (**Appendix Table 1**).[2-10] Most prevalence and survival studies to date have used data from specialist centres or registries that depend on notification of cases from multiple sources.[3,4,6-10] Such studies are susceptible to ascertainment bias as infants may die before transfer to specialist centres and notifications of cases to registries are typically voluntary. Previous studies of potential risk factors for the occurrence of anorectal malformations have been limited by small sample sizes.[11,12] No studies have explored whether risk factors have different associations with isolated and complex anorectal malformations, which would suggest different underlying mechanisms. For example, older maternal age is associated with chromosomal and genetic risk, and younger maternal age is associated with risk factors related to social disadvantage.[13]

We used a national birth cohort of live-born singletons with hospital admission and death registration data to estimate the birth prevalence of anorectal malformations. We described the maternal, infant and birth characteristics of isolated and complex phenotypes and assessed maternal age as a potential risk factor for each phenotype after accounting for demographic factors. We estimated five-year survival, overall, for isolated and complex anorectal malformations, and stratified for preterm or term birth.

METHODS

Data sources

We used Hospital Episode Statistics (HES)[14] linked to Office for National Statistics (ONS) death registrations between 1st April 2002 and 31st March 2019. HES contains details of all admissions to NHS-funded hospitals and captures 97% of births in England.[15] Maternal and infant birth admissions contain information about maternal and infant characteristics while subsequent infant hospital admissions enable longitudinal follow-up.[15,16] Diagnoses and procedures in HES are recorded using the *International Classification of Diseases 10th revision* (ICD-10) and the *Classification of Surgical Operations and Procedures* (OPCS-4), respectively. Death registrations contain all causes of death recorded using ICD-10 codes and the date of death.

Study population

We derived a national cohort of singleton live-births delivered from 1st April 2002 through 31st March 2018 to mothers resident in England using methods described previously.[16, 17] Follow-up started at delivery and ended on 31st March 2019 or the date of death, whichever earliest.

Identifying ARM

Paediatric surgeons (KF, JC) extracted diagnostic and operation codes from previous studies using administrative healthcare data to identify anorectal malformations and categorised them as specific or generic for gastrointestinal disorders[5,18,19] (**Appendix Table 2**). Differential diagnosis codes used to exclude cases unlikely to have anorectal malformations were also defined. The national birth cohort was searched for infants whose hospital or death records contained any of these codes in the first year of life.

KF reviewed all records during infancy for children with different combinations of codes to develop an anorectal malformation case definition. As most cases require repair, our case definition included those infants with an operation and diagnosis code in their hospital or death

record (**Appendix Table 3**). We captured cases that died without repair by including infants with a diagnosis code in their death record; if the diagnosis code in the death record was generic we sought supportive evidence from a specific diagnosis code in the hospital record.

Cases were classified as isolated or complex depending on the presence of additional congenital anomaly diagnoses recorded in hospital or death records during infancy (**Appendix Table 4**).[20] Codes related to anorectal conditions were excluded from this classification.

Covariates

Maternal characteristics included maternal age at delivery (<20, 20-29, 30-39 and ≥40 years later reclassified as ≤24, 25-34 and ≥35 years due to small numbers), area-based deprivation quintile based on the maternal post-code at delivery and derived using the Index of Multiple Deprivation (IMD)[21], and maternal region of residence at delivery. Infant characteristics included sex and ethnic background. Birth characteristics included gestational age at birth in weeks and birth weight in grams. Calendar birth period was grouped into four-year periods.

Statistical analysis

We described the prevalence of anorectal malformations per 10,000 live-births and the distribution of additional anomalies by system-specific subgroup. Maternal, infant and birth characteristics of infants overall and in the subpopulation of children with complete records on all covariates were described by anorectal malformation status. We estimated the relative birth prevalence, referred to as the crude relative risk, and 95% confidence intervals (95% CIs) for isolated and complex anorectal malformations by each of these characteristics.

To validate the anorectal malformation cohort we compared the birth prevalence, sex, birth characteristics and proportion of deaths in our cohort with a registry of anorectal malformation cases notified to the British Association of Paediatric Surgeons Congenital Anomaly Surveillance System (BAPS-CASS) by UK paediatric surgical units between 2015 and 2016[3].

For comparison, we restricted our cohort to the same period and the registry cohort to those born in England and diagnosed within the first year of life.

We analysed all live-born singletons recorded in NHS hospitals in England to examine maternal age as a potential risk factor for isolated or complex anorectal malformations. We used univariable and multivariable logistic regression sequentially adjusted for birth period, infant ethnicity, maternal deprivation quintile and region of residence. Due to the rarity of anorectal malformations, crude and adjusted risk ratios (RRs) are reported. Infants were included in this analysis if they had complete records for all the covariates examined.

We plotted Kaplan-Meier curves and estimated five-year survival among infants delivered on or before 31st March 2014. Survival was examined for any, isolated and complex anorectal malformations, and for infants born preterm (<37 weeks) or at term (≥37 weeks).

Analyses were performed using Stata V16.

RESULTS

Study population

We identified 3,325 infants with anorectal malformations among 9,474,147 live-born singletons (**Figure 1**). Overall anorectal malformation birth prevalence was 3.5 per 10,000 live-births (95% CI, 3.4-3.6). This was similar among infants with complete records (3.5 per 10,000 live-births; 95% CI, 3.3-3.6). Most anorectal malformation cases were complex (N=2,050, 61.7%) (**Table 1**).

Table 1. Maternal, infant and birth characteristics of infants with and without anorectal malformations

	All anorectal malformations (N=3,325)	Isolated (N=1,275)	Complex (N=2,050)	No anorectal malformation (N=9,470,822)
	n (%)	n (%)	n (%)	n (%)
Birth period				
2002/03-2005/06	670 (20.2)	283 (22.2)	387 (18.9)	2,152,829 (22.7)
2006/07-2009/10	761 (22.9)	285 (22.4)	476 (23.2)	2,417,274 (25.5)
2010/11-2013/14	945 (28.4)	358 (28.1)	587 (28.6)	2,503,466 (26.4)
2014/15-2017/18	949 (28.5)	349 (27.4)	600 (29.3)	2,397,253 (25.3)
Maternal age (years)[a]				
<20	208 (6.3)	74 (5.8)	134 (6.5)	502,148 (5.3)
20-29	1,412 (42.5)	564 (45.0)	838 (40.9)	4,201,160 (44.4)
30-39	1,351 (40.6)	518 (40.6)	833 (40.6)	4,225,073 (44.6)
≥40	144 (4.3)	39 (3.1)	105 (5.1)	339,330 (3.6)
Unknown	210 (6.3)	70 (5.5)	140 (6.8)	203,11 (2.1)
Maternal deprivation quintile				
Most deprived quintile	1,149 (34.3)	416 (32.6)	724 (35.3)	2,625,033 (27.7)
2	716 (21.5)	267 (20.9)	449 (21.9)	2,083,943 (22.0)
3	596 (17.9)	225 (17.7)	371 (18.1)	1,731,658 (18.3)
4	456 (13.7)	191 (15.0)	265 (12.9)	1,531,662 (16.2)
Least deprived quintile	416 (12.5)	176 (13.8)	240 (11.7)	1,467,794 (15.5)
Unknown	1 (0.03)	-	1 (0.1)	30,732 (0.3)
Maternal region of residence				
London	509 (15.3)	189 (14.8)	320 (15.6)	1,787,990 (18.9)
North East	188 (5.7)	87 (6.8)	101 (4.9)	436,844 (5.7)
North West	497 (15.0)	172 (13.5)	325 (15.9)	1,251,238 (13.2)
Yorkshire & Humber	420 (12.6)	160 (12.6)	260 (12.7)	939,051 (9.9)
East Midlands	293 (8.8)	124 (9.7)	169 (8.2)	758,389 (8.0)
West Midlands	420 (12.6)	169 (13.3)	251 (12.2)	1,019,487 (10.8)
East of England	305 (9.2)	108 (8.5)	197 (9.6)	1,000,179 (10.6)
South East	483 (13.2)	177 (13.9)	261 (12.7)	1458392 (15.4)
South West	255 (7.7)	89 (7.0)	166 (8.1)	819,252 (8.7)
Infant sex				
Male	1,864 (56.1)	669 (52.5)	1,195 (58.3)	4,853,246 (51.2)
Infant ethnicity				
White	2,229 (67.0)	851 (66.8)	1,378 (67.2)	5,994,151 (63.3)
South Asian	402 (12.1)	144 (11.3)	258 (12.6)	839, 134 (8.9)
Black	113 (3.4)	41 (3.2)	72 (3.5)	427,566 (4.5)
Other	120 (3.6)	44 (3.5)	76 (3.7)	255,811 (2.7)
Mixed	104 (3.1)	46 (3.6)	58 (2.8)	354,184 (3.7)
Unknown	357 (10.7)	149 (11.7)	208 (10.2)	1,599,976 (16.9)
Gestational age (weeks)				
≤32	200 (6.0)	41 (3.2)	159 (7.8)	91,406 (1.0)
33-36	388 (11.7)	91 (7.1)	297 (14.5)	356,118 (3.8)
37-38	646 (19.4)	214 (16.8)	432 (21.1)	1,463,812 (15.5)
≥39	1,313 (39.5)	638 (50.0)	675 (32.9)	5,743,860 (60.7)
Unknown	778 (23.4)	291 (22.8)	487 (23.8)	1,825,626 (9.2)
Birth weight (g)				
≤2,499	617 (18.6)	140 (11.0)	477 (23.3)	452,506 (4.8)
2,500-3,499	1,395 (42.0)	558 (43.8)	837 (40.8)	4,283,524 (45.2)
≥3,500	670 (20.2)	349 (27.4)	321 (15.7)	3,356,177 (35.4)
Unknown	643 (19.3)	228 (17.9)	415 (20.2)	1,378,675 (14.6)

[a]Maternal age was grouped as ≤24, 25-34 and ≥35 years in analyses to address low event rates.

The most common additional anomalies among all infants with anorectal malformations involved the cardiac (1,212; 36.5%), urinary (n=838; 25.5%) and musculoskeletal (n=600; 18.1%) systems (**Appendix Table 4**). Our anorectal malformation cohort was comparable to the BAPS-CASS cohort although our prevalence estimate was higher (**Appendix Table 5**).

Most infants with anorectal malformations were male (n=1,864, 56.1%), white (n=2,229; 67.0%) and born at ≥37 weeks gestation (n=1,959, 58.9%) and with weight of ≥2,500g (n=2,065; 62.1%) (**Table 1**). A high proportion of infants had incompletely recorded ethnicity and birth characteristics but after restricting to infants with complete records the distribution of most characteristics remained similar (**Table 1**). Although infants with complete records were more likely to be born at ≥37 weeks or with weight ≥2,500g, this was the same for infants without anorectal malformations (**Appendix Table 6**).

Characteristics of isolated and complex anorectal malformation **cases**

There were two similarities in the crude relative risk of isolated and complex anorectal malformations by infant and birth characteristics (**Figure 2**). First, compared with white infants, the relative risk of both anorectal malformation subgroups was higher among South Asian infants and lower among those of Black ethnicity (**Figure 2**). Second, the relative risk of both anorectal malformation subgroups was greater among those born preterm (≤37 weeks) or underweight (<2,500g) compared with those born at 37-38 weeks or weighing 2,500g-3,499g, respectively (**Figure 2**). The anorectal malformation subgroups differed in that the crude risk of isolated anorectal malformations did not differ by sex or across the study period whereas the crude risk of complex anorectal malformations was higher in males compared with females and higher after 2010 compared with 2002-2005 (**Appendix Figure 1; Figure 2**).

The crude risk of isolated and complex anorectal malformations was also associated with maternal characteristics (**Figure 2**). Infants born to mothers aged ≤24 and ≥35 years were at higher risk of complex anorectal malformations compared with ages 25-34 years (**Figure 2A**).

The risk of isolated anorectal malformations also appeared greater for maternal age ≤24 years but evidence for this was weak as the confidence interval crossed the null (**Figure 2B**). The risk of both anorectal malformation subgroups was greater among infants born to mothers who lived in the most deprived areas compared with most affluent, or who lived in the north of England or Midlands compared with London (**Figure 2**).

Maternal age as a potential risk factor

There were 6,384,923 infants with complete records for maternal and infant characteristics; 2,785 had anorectal malformations and 1,720 were complex cases. There was evidence of an association between maternal age and complex anorectal malformations in univariable and multivariable models whereas there was no evidence of an association with isolated anorectal malformations (**Table 2A-2B**).

Table 2A. Crude and adjusted risk ratios for complex anorectal malformations **compared to none, by maternal age at delivery.**

	Crude risk ratio (95% CI)	Partially-adjusted risk ratio (95% CI)			Fully-adjusted risk ratio (95% CI); p-value	
		Birth period	Birth period & ethnicity	Birth period, ethnicity & deprivation	Birth period, ethnicity, deprivation & region	
Maternal age						
≤24	1.21 (1.08-1.36)	1.22 (1.09-1.37)	1.24 (1.11-1.40)	1.14 (1.02-1.29)	1.13 (1.00-1.27)	0.0001
25-34	1.00	1.00	1.00	1.00	1.00	
≥35	1.22 (1.08-1.37)	1.22 (1.08-1.37)	1.24 (1.10-1.40)	1.29 (1.15-1.46)	1.31 (1.17-1.48)	
Birth period						
2002/03-2005/06		1.00	1.00	1.00	1.00	0.06
2006/07-2009/10		0.98 (0.84-1.15)	0.98 (0.84-1.14)	0.98 (0.84-1.14)	0.99 (0.85-1.15)	
2010/11-2013/14		1.10 (0.95-1.27)	1.09 (0.94-1.26)	1.09 (0.94-1.26)	1.10 (0.95-1.27)	
2014/15-2017/18		1.16 (1.00-1.34)	1.16 (1.00-1.34)	1.16 (1.00-1.34)	1.16 (1.00-1.34)	
Infant ethnicity						
White			1.00	1.00	1.00	<0.0001
South Asian			1.38 (1.20-1.58)	1.23 (1.07-1.42)	1.28 (1.11-1.48)	
Black			0.77 (0.61-0.98)	0.67 (0.52-0.85)	0.76 (0.59-0.98)	
Other			1.31 (1.03-1.66)	1.20 (0.94-1.52)	1.28 (1.01-1.64)	
Mixed			0.69 (0.52-0.90)	0.66 (0.50-0.86)	0.69 (0.53-0.91)	
Maternal deprivation quintile						
Most deprived				1.70 (1.44-2.00)	1.60 (1.34-1.90)	<0.0001
2				1.29 (1.08-1.54)	1.28 (1.07-1.53)	
3				1.32 (1.10-1.57)	1.31 (1.09-1.56)	
4				1.03 (0.85-1.24)	1.01 (0.83-1.23)	
Least deprived				1.00	1.00	
Maternal region of residence						
London					1.00	<0.0001
North East					1.26 (0.99-1.61)	
North West					1.46 (1.22-1.73)	
Yorkshire & Humber					1.50 (1.25-1.80)	
East Midlands					1.45 (1.18-1.78)	
West Midlands					1.35 (1.13-1.62)	
East of England					1.25 (1.02-1.52)	
South East					1.07 (0.88-1.30)	
South West					1.22 (0.99-1.51)	

Abbreviations: 95% CI, 95% confidence interval.

Table 2B. Crude and adjusted risk ratios for isolated anorectal malformations **compared to none, by maternal age at delivery.**

	Crude risk ratio (95% CI)	Partially-adjusted risk ratio (95% CI)			Fully-adjusted risk ratio (95% CI); p-value	
		Birth period	Birth period & ethnicity	Birth period, ethnicity & deprivation	Birth period, ethnicity, deprivation & region	
Maternal age						
≤24	1.13 (0.98-1.30)	1.14 (0.98-1.31)	1.14 (0.99-1.32)	1.10 (0.95-1.27)	1.07 (0.93-1.25)	0.59
25-34	1.00	1.00	1.00	1.00	1.00	
≥35	1.00 (0.85-1.17)	1.00 (0.85-1.17)	1.01 (0.86-1.19)	1.03 (0.88-1.21)	1.05 (0.90-1.23)	
Birth period						
2002/03-2005/06		1.00	1.00	1.00	1.00	0.11
2006/07-2009/10		0.85 (0.70-1.03)	0.85 (0.70-1.03)	0.85 (0.70-1.03)	0.86 (0.71-1.04)	
2010/11-2013/14		1.01 (0.84-1.21)	1.00 (0.84-1.20)	1.01 (0.84-1.20)	1.01 (0.85-1.21)	
2014/15-2017/18		1.04 (0.87-1.25)	1.04 (0.86-1.24)	1.04 (0.87-1.24)	1.04 (0.87-1.25)	
Infant ethnicity						
White			1.00	1.00	1.00	0.05
South Asian			1.20 (1.00-1.44)	1.13 (0.94-1.37)	1.20 (0.99-1.45)	
Black			0.69 (0.50-0.95)	0.64 (0.46-0.89)	0.75 (0.54-1.05)	
Other			1.24 (0.91-1.69)	1.18 (0.87-1.62)	1.25 (0.91-1.72)	
Mixed			0.90 (0.66-1.22)	0.88 (0.65-1.19)	0.93 (0.69-1.27)	
Maternal deprivation quintile						
Most deprived				1.28 (1.05-1.56)	1.21 (0.98-1.49)	0.20
2				1.01 (0.82-1.25)	1.01 (0.82-1.26)	
3				1.04 (0.84-1.29)	1.05 (0.84-1.31)	
4				1.00 (0.80-1.25)	1.00 (0.80-1.26)	
Least deprived				1.00	1.00	
Maternal region of residence						
London					1.00	<0.0001
North East					1.90 (1.44-2.50)	
North West					1.27 (1.00-1.61)	
Yorkshire & Humber					1.56 (1.23-1.97)	
East Midlands					1.70 (1.32-2.20)	
West Midlands					1.53 (1.21-1.93)	
East of England					1.09 (0.83-1.42)	
South East					1.28 (1.01-1.63)	
South West					1.06 (0.79-1.41)	

Abbreviations: 95% CI, 95% confidence interval.

In the fully-adjusted model, the risk of complex anorectal malformations was 31% higher for children of mothers aged ≥35 years (95% CI, 17-48) and 13% higher for children of mothers aged ≤24 years (95% CI, 0-27) compared with ages 25-34 years. The effect estimate for complex anorectal malformations among children of mothers aged ≤24 years was markedly reduced after accounting for deprivation whereas accounting for birth period, ethnicity and region did not considerably alter estimates. The associations between complex anorectal malformations and ethnicity, deprivation and region observed in crude analyses persisted even after adjusting for maternal age. Similar, but weaker associations with deprivation were found for isolated anorectal malformations.

Survival

Of the 2,376 infants with anorectal malformations included in survival analyses, 207 (8.7%) died within five years. Most deaths occurred in the first year of life (n=169). Estimated five-year survival from delivery among infants with anorectal malformations overall was 91.3% (95% CI, 90.1-92.4) (**Figure 3A**). Estimated five-year survival from delivery among the 1,450 complex cases was 86.9% (95% CI, 85.1-88.5) (contributary cause of death detailed in **Appendix Table 7)** and for the remainder with isolated anorectal malformations was 98.2% (95% CI, 97.1-98.9) (**Figure 3A**). Infants born preterm (<37 weeks) had lower estimated five-year survival (78.6%; 95% CI, 74.3-82.3) than term (≥37 weeks) infants (95.2%; 95% CI, 93.9-96.2) (**Figure 3B**). Infants with complex anorectal malformations who were born preterm had the lowest estimated survival (73.4%; 95% CI, 68.1-78.0) (**Figure 3D**).

DISCUSSION

Main findings

We used a national birth cohort of infants in England and estimated the birth prevalence of anorectal malformations to be 3.5 per 10,000 live-births. Advanced and young maternal age were associated with an increased risk of complex anorectal malformations after accounting for factors including ethnicity and deprivation, though evidence was weaker for young maternal age. There was no evidence of an association between maternal age and isolated anorectal malformations. Estimated five-year survival for infants with anorectal malformations was 91.3% (95% CI, 90.1-92.4), with most deaths occurring in infancy. Survival was lowest in infants with complex anorectal malformations and in those born preterm. Among the complex cases that died, cardiac defects were the most frequently recorded additional anomaly on the death certificate.

Strengths & Limitations

We used a nationally representative and validated birth cohort known to include 97% of all births in England[19] to conduct the largest study to date quantifying anorectal malformation birth prevalence. Despite the rarity of anorectal malformations, the size of our study allowed us to investigate heterogeneity in the characteristics, potential risk factors and five-year survival of isolated and complex phenotypes. Linkage of the maternal and infant birth records to subsequent hospital admissions for the infant allowed us to report detailed maternal, infant and birth characteristics while linkage to death registrations allowed for the ascertainment of infants that died outside of a hospital setting or prior to transfer to a paediatric surgical centre. Finally, we maximised ascertainment of anorectal malformations by searching for evidence of the condition in the first year of life after a previous study reported that 18% of cases were undetected at birth but underwent surgical repair in early infancy.[22]

A limitation of this work was the high proportion of infants with incomplete birth characteristics which has been reported in previous studies.[15,17] However, we found the distribution of

characteristics was comparable among the full birth cohort and among infants with complete records and did not vary by anorectal malformation status. A further limitation was that existing diagnostic and procedure codes lacked the granularity needed to identify the anorectal malformation site or surgical approach. We were also unable to examine VACTERL, a syndrome commonly associated with ARM, as there was no corresponding and specific ICD-10 code. As BAPS-CASS studies collect more detailed information, including free-text, from paediatric surgeons on procedure type, anatomical site and associated abnormalities, they may usefully complement work carried out in administrative data. A third limitation was that we may have missed a small number of early, undiagnosed postnatal deaths which could result in an underestimate of the birth prevalence of anorectal malformations. Finally, our results only relate to singleton live-births; we did not include stillbirths due to poor quality recording of malformations and analyses were restricted to singleton live-births as longitudinal follow up is more accurate than for multiple births.[15]

Results in context

Few studies have examined the UK prevalence of anorectal malformations. Registry data from the North of England (NorCAS) reported a prevalence of 1.9 (95% CI, 1.6-2.2) per 10,000 live-births between 1985 and 2010.[23] Unpublished BAPS-CASS data from 2015-2016 suggested a prevalence of 2.1 (95% CI, 1.8-2.5) per 10,000 live-births. Both were lower than our estimate of 3.5 (95% CI, 3.4-3.6) per 10,000 live-births between 2002 and 2018. Lower prevalence in NorCAS could be explained by the exclusion of cases with chromosomal anomalies (which we estimated were present in 6% of infants with anorectal malformations) and under-ascertainment of post-natal diagnoses.[24] While all cases seen in paediatric surgical units across the UK are reported to BAPS-CASS, lower prevalence in this data-source could result from not capturing those who died before transfer from a birth unit to a specialist centre.

Our findings suggested ethnicity, deprivation at the small-area level and region were associated with the crude risk of both isolated and complex anorectal malformations. These

measures are broad and reflect both health inequalities and sociocultural influences. Regional differences, which have been previously described, may also be indicative of ascertainment differences (for example due to variation in recording practices or the distribution of specialist centres for diagnosis)[25, 26]. We also found an increase in the birth prevalence of complex cases over time. While this could be a true increase, it could also reflect external influences which increased the recording of additional anomalies. A 2014 HES audit, for example, called for improved recording of co-morbidities.[27]

Previous studies have reported a wide prevalence (30-72%) of associated anomalies which may be due, in part, to differences in case definitions and insufficient follow-up time after delivery.[11,28–31] These estimates were in line with findings from our study indicating that 67.9% of infants with anorectal malformations had additional anomalies. Our finding of the three most prevalent additional anomalies being cardiac, urinary, and musculoskeletal is also synonymous with other studies.[28, 32]

The association between advanced maternal age (≥35 years) and complex anorectal malformations persisted after accounting for birth period, deprivation, ethnicity and region. In contrast, the association between complex anorectal malformations and young maternal age (≤24 years) was reduced after accounting for deprivation. The mechanism of occurrence of complex anorectal malformations among older mothers may relate in part to increased biological risk and chromosomal anomalies. Conversely, the mechanism among younger mothers may occur through social disadvantage. Prior research suggests young maternal age is associated with higher levels of deprivation which may affect health-related behaviours, health-seeking or access to antenatal and other care.[13, 33] Other studies have reported associations between syndromic anorectal malformations and pre-gestational diabetes, maternal obesity and paternal smoking, which could not be examined in this study.[34, 35] Different mechanisms may influence the occurrence of isolated anorectal malformations which was not associated with maternal age. Future studies involving linkage

to genomic and additional health data may help identify genetic and environmental risk factors. Our findings suggested that increased deprivation, deprived regions and ethnic group are associated with the crude risk of both isolated and complex anorectal malformations. These broad measures reflect multiple factors including health inequalities and sociocultural influences. The increased birth prevalence of complex anorectal malformations over time may be due to improved coding depth.

Ours is the first study to report five-year survival of anorectal malformation cases in England. Other population-based studies reporting survival are in line with ours, with one-year estimates ranging from 87-99% and ten-year estimates ranging from 86-99%.[10, 36, 37] Identified risk factors for mortality include coexisting congenital anomalies[10, 28, 38, 39] and low birth weight.[10]

Implications

This study has three important implications. First, we have described an algorithm for identifying patients with anorectal malformations using hospital and death records which can be applied in future studies. Second, we have shown that maternal age may be a potential risk factor for complex but not isolated anorectal malformations which highlights that anorectal malformation subtypes may have different mechanisms of occurrence. Third we found high rates of five-year survival and showed prematurity and complex anorectal malformations are important determinants of survival. Our findings underscore the need for further research to understand maternal risk factors and the extent to which they relate to other contributory factors of anorectal malformations.

“What is already known on this topic”

1. The reported birth prevalence of anorectal malformations varies and although survival has been examined in other countries there are no data on survival from England.

2. Prevalence and survival studies have been small in size and typically have relied on disease registries which are susceptible to ascertainment bias.

3. To date no studies have explored whether risk factors have different associations with isolated and complex anorectal malformations.

“What this study adds”

1. A reproducible, clinically driven process to identify anorectal malformations for birth prevalence and follow up through administrative hospital data.

2. Advanced maternal age was associated with complex but not isolated anorectal malformations.

3. Estimated five-year survival was high, but lowest in children with complex anorectal malformations born preterm.

“**How this study might affect research, practice or policy”**

1. The methodology of identifying complex congenital anomalies within national data is applicable to other conditions for research purposes or for provider or practitioner outcome reporting.

2. We have demonstrated the value of administrative data and recommend it’s use in collaboration with other population-based registries in the future.

3. We have identified two distinct mechanisms behind anorectal malformation subtypes which require further study.

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Contributorship statement

All authors contributed to the design of the study. KF and MP carried out analyses. KF wrote the first draft of the manuscript. All authors were involved in the interpretation of the data and made critical revisions to subsequent drafts. All authors have seen and approved the final version. KF and MP had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the analyses.

Ethics approval

We have a data sharing agreement with National Health Service (NHS) Digital to use a de-identified extract of Hospital Episode Statistics linked to Office for National Statistics death registration data; therefore, we did not require ethics approval to use English data sets.

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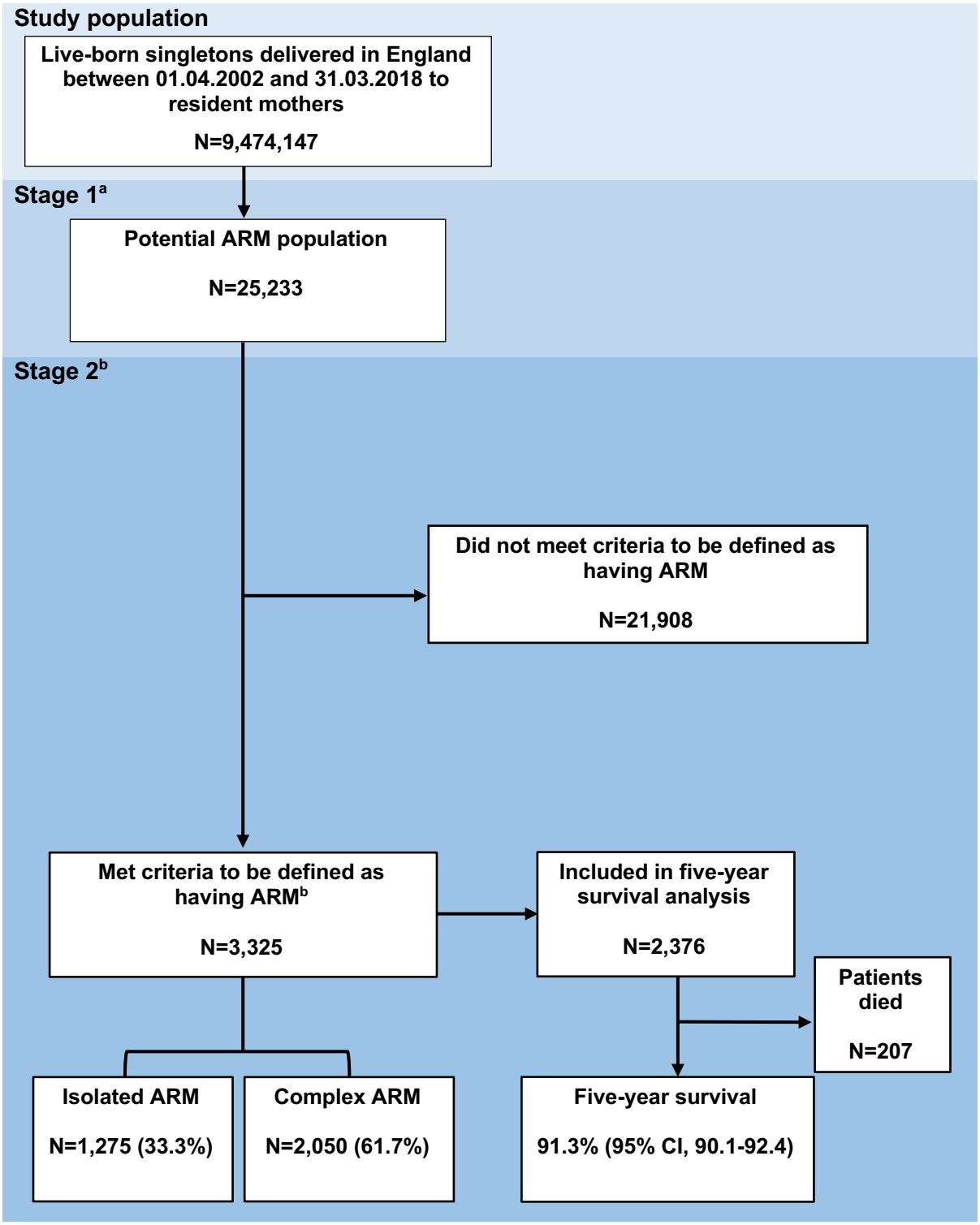
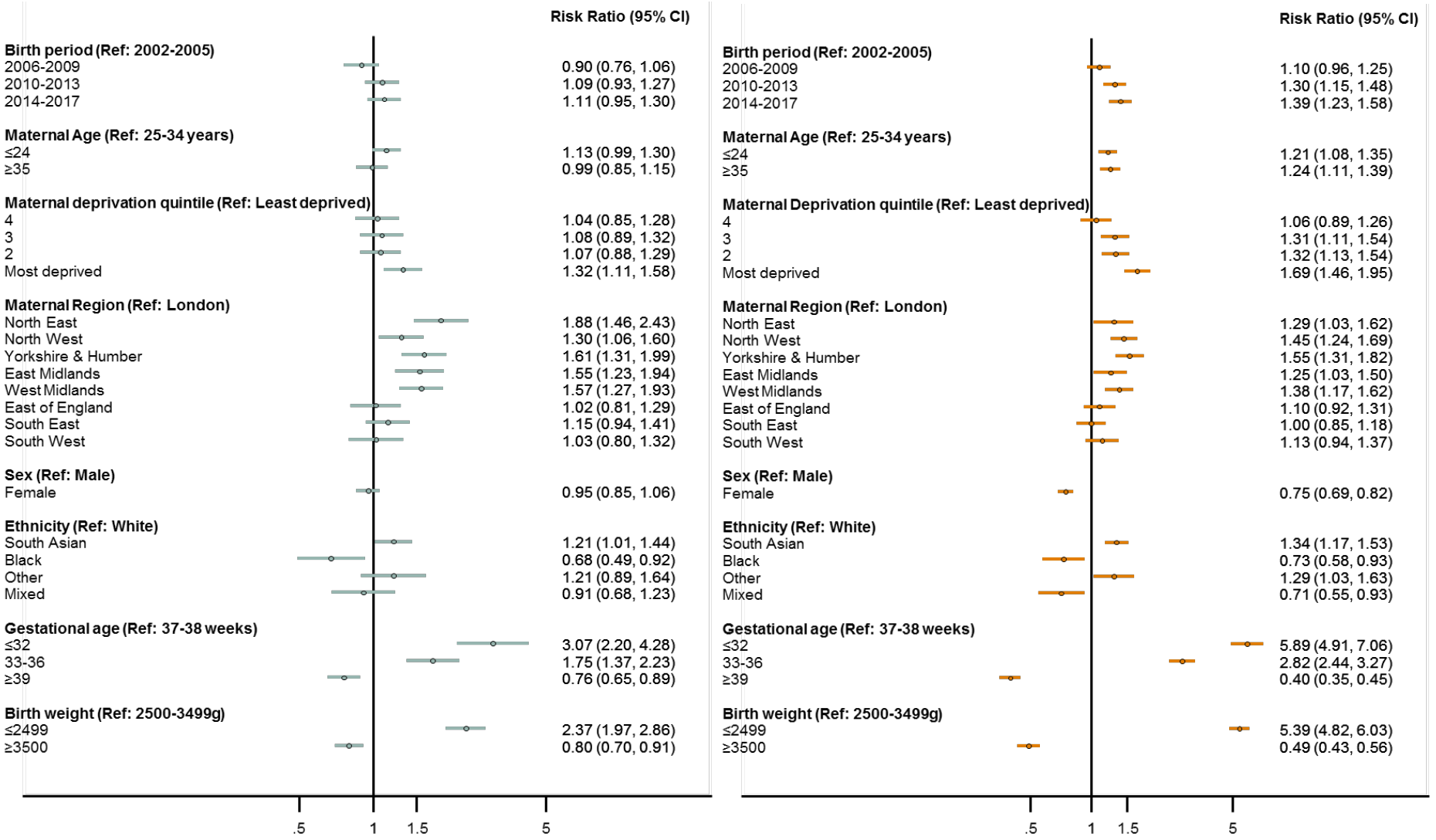
Figure 1. Derivation of the anorectal malformation cohort from the study population.



[a]The potential population included infants with evidence in the first year of life of an anorectal malformation diagnosis, procedure or differential diagnosis recorded during a hospital admission or recorded on the death certificate; [b]Infants met criteria if there was: (i) evidence

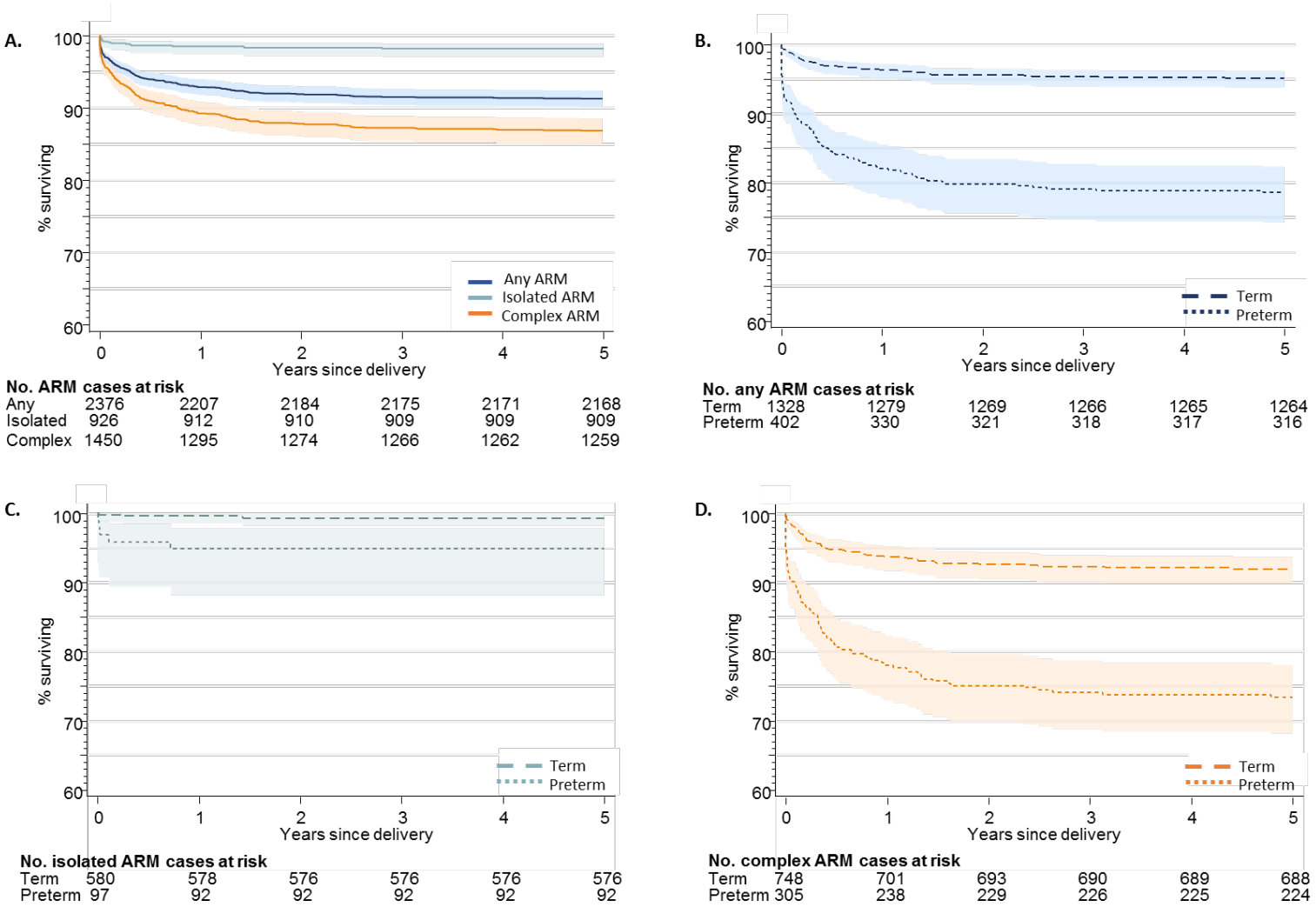
of an anorectal malformation-related procedure as well as a diagnosis recorded in hospital or anywhere on the death certificate, or (ii) a specific diagnosis code for anorectal malformations on the death certificate. Infants with a procedure for stoma creation, a generic diagnosis code for gastrointestinal disorders and a differential diagnosis code were not considered cases despite meeting (i).

Figure 2. Crude risk ratios for (a) complex and (b) isolated anorectal malformations by birth period, maternal, infant and birth characteristics.



Abbreviations: 95% CI, 95% confidence interval.

Figure 3. Five-year survival for (A) all infants with ARM, (B) infants with ARM stratified by gestational age at delivery, (C) infants with isolated ARM stratified by gestational age at delivery and (D) infants with complex ARM **stratified by gestational age at delivery.**



Abbreviations: ARM, anorectal malformation