OBSTETRICS

General health in a cohort of children conceived after assisted reproductive technology in the United Kingdom: a population-based record-linkage study

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BACKGROUND: Assisted reproductive technology use is increasing annually; however, data on long-term child health outcomes including hospital admissions are limited.

OBJECTIVE: This study aimed to examine the potential effects of assisted reproductive technology on any and cause-specific hospital admissions unrelated to perinatal diagnoses.

STUDY DESIGN: This was a population-based record-linkage study that included a previously established cohort of children born after assisted reproductive technology in the United Kingdom between 1997 and 2009 (n=63,877), their naturally conceived siblings (n=11,343), and matched naturally conceived population controls (n=127,544) linked to their postnatal health outcomes up to March 31, 2016 to provide robust risk estimates of the potential effects of assisted reproductive technology on any and cause-specific hospital admissions unrelated to perinatal diagnoses. In addition, comparison of hospital admissions by type of treatment was made. Cox regression was used to estimate the risk of hospital admission, and negative binomial regression was used to compare the number of hospital admissions per year.

RESULTS: This study had 1.6 million person-years of follow-up (mean, 12.9 years; range, 0–19 years), and the mean age at the time of first hospital admission was 6.5 years (range, 0–19 years). Singletons born after assisted reproductive technology had increased risk of any hospital admission compared with naturally conceived population controls (hazard ratio, 1.08; 95% confidence interval, 1.05–1.10) but not naturally conceived siblings (hazard ratio, 1.01; 95% confidence interval, 0.94–1.09). We observed increased risk of diagnoses related to neoplasms and diseases of the respiratory, musculoskeletal, digestive, and genitourinary systems, and lower risk of injury, poisoning, and consequences of external causes compared with naturally conceived population controls. Children born after intracytoplasmic sperm injection had a lower risk of hospital admission compared with those born after in vitro fertilization, although no such differences were observed between children born after fresh embryo transfers and those born after frozen embryo transfers.

CONCLUSION: Children born after assisted reproductive technology had greater numbers of hospital admissions compared with naturally conceived population controls. Attenuation of these differences in relation to their naturally conceived siblings suggested that this could be partially attributed to the influence of parental subfertility on child health, increased parental concerns, and an actual increase in morbidity in children born after assisted conception.

Key words: assisted conception, assisted reproductive technology, cohort, hospital admissions, naturally conceived controls, naturally conceived siblings, record linkage

Introduction

The number and proportion of children born after assisted reproductive technology (ART) is increasing annually, with >8 million children born after ART globally.[1] Families with ART-conceived children report potential general health risks to their children as their paramount concern,[2] with healthcare providers and stakeholders focusing on the potential adverse short- and long-term effects of ART on the offspring across the life course.[3]

Several studies exploring the association between ART and perinatal outcomes through comparison with the general population and sibling controls have shown that ART is associated with an increased risk of small-for-gestational-age (SGA) neonates and preterm birth (PTB), whereas frozen embryo transfers are associated with increasing risk of large-for-gestational-age (LGA) neonates.[4] Fewer studies have explored longer-term health outcomes in children born after ART, with evidence suggesting increased risk of neurodevelopmental disorders,[5] suboptimal cardiovascular function and high blood pressure that persisted into adolescence,[6] asthma,[7] and deterioration in sperm count in intracytoplasmic sperm injection (ICSI) male offspring.[8] Moreover, more frequent and longer hospital admissions relative to those of naturally conceived (NC) children have also been observed in ART-conceived children, even after the neonatal period. Putative drivers of increased hospitalization rates include higher rates of congenital malformations,[9] infections,[10] respiratory diseases,[11] and disorders of the central nervous system in ART children.[5] Parental factors may also play a role in increased hospital admission rates, with the parents of children who were born after a

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AJOG at a Glance

Why was this study conducted?

Existing evidence on the long-term health outcomes of children born after assisted reproductive technology (ART) is limited by an inability to distinguish the contribution of treatment and parental factors.

Key findings

Children born after ART had greater numbers of hospital admissions compared with naturally conceived population controls. Attenuation of these differences in relation to their naturally conceived siblings suggests that this could be partially attributed to the influence of parental subfertility on child health or increased parental concerns, and an actual increase in morbidity in children born after assisted conception. Children born after intracytoplasmic sperm injection had a lower risk of hospital admission compared with those born after in vitro fertilization.

What does this add to what is known?

The inclusion of 2 control groups allows extrapolation of effect sizes to the general population and the exploration of the effects of family confounders.

prolonged period of involuntary childlessness exhibiting more concern over child morbidity and seeking medical care more frequently.[12]

However, much of the available evidence is often limited by small sample sizes and short follow-up periods leading to contradictory results.[13] Moreover, the inability to distinguish the contribution of ART treatment factors and parental subfertility to adverse health outcomes is a common limitation of many ART follow-up studies.[14] These limitations can be addressed to a certain extent by prospective cohorts consisting of control populations of children born naturally to parents with established subfertility (different from infertility in terms of the time of unwanted nonconception)[15] and by studies that use within-sibling analyses (where comparisons are made between ART children and their NC siblings [NCS]) to better control for factors related to subfertility and other family confounders, under the assumption that these parental factors would be the same (or very similar) within sibling groups.[16]

The objective of the current study was to assess the association of ART conception with future health by using a previously established cohort of children consisting of those born after ART in the United Kingdom between 1997 and 2009, their NCS, and matched NC population (NCP) controls linked to their hospital records up to March 31, 2016 to provide robust risk estimates and rates of hospital admissions in children born after ART, and to compare these findings to appropriately matched NCP controls and NCS.[17] In addition, comparisons of hospital admissions by type of ART treatment (in vitro fertilization [IVF] vs ICSI, embryo cryopreservation) were also performed.

Materials and Methods

Study population

This study used a previously established cohort of children born to women who underwent ART in the United Kingdom between April 1, 1997 and July 31, 2009, their NCS, with 2 NCP controls per ART child matched for age, sex, and multiplicity (Supplemental Table 1).[17] A subgroup of ART children with NCS (sART) was also identified. Record linkage was used to link the Human Fertilisation and Embryology Authority (HFEA) register, the Office for National Statistics (ONS) birth registration dataset, and the Hospital Episode Statistics (HES) database (Supplemental Figures 1 and 2), with details of the linkage methodology previously reported.[17]

All children conceived after ART in the United Kingdom but born outside of England, Wales, and Scotland; those born after ART to women who permanently lived outside the United Kingdom but traveled there for ART treatment; and those born in Northern Ireland were excluded because it would not be possible to link them to ONS birth records. In addition, siblings born outside of the study period (because their conception status could not be verified) and those born outside of England, Wales, and Scotland were also excluded. Cases that had withdrawn consent for their data to be used for research and children born after donor ART (oocytes, sperm, or embryos) were excluded. Finally, triplets and higher-order births were also excluded because they are known to be associated with adverse outcomes such as higher infant mortality, birth defects, premature birth, and low birthweight.[18]

Outcome data

The ART, NCS, and NCP groups were linked to their postnatal health records up to March 31, 2016 using the HES database containing details of all admissions at National Health Service (NHS) hospitals in England[19] in a one-off linkage. Diagnoses were defined using the International Classification of Diseases, Tenth Revision (ICD-10), and conditions that would have originated in the perinatal period. Diagnoses related to pregnancy, childbirth, and the puerperium, and other diagnoses that are vague and cover a range of symptoms, findings, and social circumstances that do not represent specific diagnoses or diseases were excluded from the analysis (the details of included and excluded ICD-10 codes are provided in Supplemental Table 2).

The primary outcome measures were risk of any hospital admission and "relevant" (ie, related to the included diagnostic chapters) diagnosis-specific hospital admissions, whereas the secondary outcomes of interest were the mean overall and diagnostic chapter–specific admission rates (number of admissions per year per child).

Statistical analyses

Primary analysis

A variable was created for the first occurrence of any hospital admission, and Cox proportional regression analyses were used to estimate the hazard ratio (HR) for this outcome, comparing the ART-conceived with the NCS and NCP control groups separately. A series of additional analyses were performed, repeating this primary analysis for each specific diagnosis. Time to event was calculated for each patient from their date of birth until the date of first hospital admission for each outcome, or the last date of follow-up (March 31, 2016) in those without any hospital admission or a diagnosis-specific admission. This was further grouped into <1 day, 1 to 6 days, 7 to 28 days, 29 to 90 days, 91 to 181 days, 182 to 272 days, 273 to 364 days, 1 to 3 years, 4 to 6 years, 7 to 9 years, 10 to 12 years, 12 to 14 years, 15 to 17 years, 18 to 20 years, 21 to 23 years, 24 to 26 years, and 27 to 30 years for ART, NCP, and NCS.

Secondary analysis

Follow-up was defined as the length of time in days from birth to the end of the HES monitoring period (March 31, 2016) and was used to calculate admission rates. An age-stratified negative binomial regression model with an offset for the period at risk (log [months]) was used to compare hospital admissions rates overall and by individual diagnostic chapters between the ART-conceived and NCS and NCP control groups separately. Each child's period at risk was calculated from date of birth until whichever event occurred first: hospital admission, death, or end of the follow-up period (March 31, 2016).

Separate analyses were conducted for singletons and twins.

The ART vs NCP models were adjusted for month and year of birth, maternal age at delivery (grouped into 25−29, 30−34, 35−39, 40−44, and ≥45 years), sex, socioeconomic status (deciles of the UK census-derived Index of Multiple Deprivation [IMD], the official measure of relative deprivation for small areas or neighborhoods in the United Kingdom)[20] at the time of first hospital admission, and ethnicity (grouped into Whitem Asian/Asian British, Black/African/Caribbean/Black British, Chinese;, mixed/multiple ethnic groups, other ethnic group, and not stated/not known). The ART vs NCS family-matched models included a family covariate as strata to allow within-family correlations, and were adjusted for birth year, maternal age at delivery, sex, and order of pregnancy (grouped into first, second, and beyond second). IMD and ethnicity were excluded because the underlying effects they represent would have remained constant within families.

Analysis by assisted reproductive technology treatment type

The effects of ART subgroups (IVF or ICSI and fresh or frozen embryo transfers) were explored using Cox regression to estimate HRs and compare with the NCP cohort. Within-subgroup analyses were also performed. This analysis was not conducted in the sibling cohort because of small numbers.

All statistical analyses were performed using Stata, version 16.0 (StataCorp, College Station, TX).

Role of the funding source

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Ethical approval and patient and public involvement

Because of the very personal nature of the treatments involved, it was not appropriate to contact the patients directly, thus preventing us from involving them in the design, conduct, reporting, and dissemination plans of our research. Before conducting this study, we carried out an a priori investigation (assisted by the The Royal College of Obstetricians and Gynaecologists Women's Voices Involvement Panel and Fertility Network UK) of the health concerns of women who had had ART and women in general to identify their health priorities and primary concerns in relation to the health of their children. The findings showed that the families of ART children had "unmet information needs" regarding the impact of assisted conception on their child's future health.[2]

Ethical approval and waiver of the requirement for individual consent were obtained from the UK Health Research Authority Confidentiality Advisory Group and the London − Hampstead Research Ethics Committee (references ECC 4-03[g]/2012 and 12/LO/1063, respectively).

Results

Characteristics of study population

The original cohort consisted of 63,877 ART children (of which 12,329 ART children had NCS [the sART subgroup]), 127,544 matched NCP controls, and 11,343 NCS.[17] The demographic characteristics of the study cohort have been summarized in Supplemental Table 1.[17]

In total, 124,252 children contributed 1.6 million person-years of follow-up, with the mean follow-up period being 12.9 years (range, 0−19 years). The mean age at the time of first hospital admission was 6.5 years (range, 0−19 years), and >50% of the total cohort had no relevant hospital admissions during the study period.

Primary analyses: risk of any hospital admission and diagnosis-specific admissions

Over the study period, fewer than half of the ART, NCP, and NCS cohorts had relevant hospital admissions, with the most common diagnoses being related to the respiratory system; the digestive system; injury, poisoning, and consequences of external causes; infectious and parasitic diseases; and congenital malformations, deformations, and chromosomal abnormalities (Table 1).

TABLE 1
Hospital admissions by diagnosis, subcohort, and multiplicity

	ART—NCP				sART—NCS	
	Singletons		Twins		Singletons	
Relevant contact	ART (N=37,890)	Control (N=75,642)	ART (N=25,987)	Control (N=51,902)	sART (N=8383)	Siblings (N=10,871)
Absent	20,884 (55.12)	41,168 (54.42)	13,824 (53.20)	26,964 (51.95)	5912 (70.53)	7788 (71.64)
Present	17,006 (44.88)	34,474 (45.58)	12,163 (46.80)	24,938 (48.05)	2470 (29.47)	3083 (28.36)
Infectious and parasitic diseases	3385 (9.25)	6783 (9.94)	2523 (7.61)	5102 (7.56)	686 (8.82)	836 (9.23)
Neoplasm	387 (1.06)	690 (1.01)	310 (0.93)	558 (0.83)	93 (1.20)	99 (1.09)
Blood, blood-forming organs, and immune system	246 (0.67)	515 (0.75)	192 (0.58)	398 (0.59)	66 (0.85)	81 (0.89)
Endocrine, nutritional, and metabolic disorders	331 (0.90)	582 (0.85)	275 (0.83)	504 (0.75)	64 (0.82)	80 (0.88)
Mental health and neurodevelopmental disorders	143 (0.39)	251 (0.37)	86 (0.26)	232 (0.34)	34 (0.44)	36 (0.40)
Nervous system	568 (1.55)	1108 (1.62)	554 (1.67)	1165 (1.73)	114 (1.47)	130 (1.44)
Eye and adnexa	717 (1.96)	1347 (1.97)	696 (2.10)	1364 (2.02)	145 (1.86)	174 (1.92)
Ear and mastoid	1448 (3.96)	2737 (4.01)	1234 (3.72)	2321 (3.44)	335 (4.31)	402 (4.44)
Circulatory system	241 (0.66)	465 (0.68)	183 (0.55)	361 (0.53)	51 (0.66)	85 (0.94)
Respiratory system	6040 (16.50)	12,240 (17.94)	4666 (14.07)	10,274 (15.22)	1293 (16.63)	1610 (17.77)
Digestive system	4128 (11.28)	8815 (12.92)	570 (1.72)	1190 (1.76)	942 (12.11)	1032 (11.39)
Skin and subcutaneous tissue	905 (2.47)	1806 (2.65)	628 (1.89)	1145 (1.70)	188 (2.42)	259 (2.86)
Musculoskeletal system and connective tissue	995 (2.72)	1568 (2.30)	1132 (3.41)	2218 (3.29)	218 (2.80)	206 (2.27)
Genitourinary system	1681 (4.59)	2925 (4.29)	1132 (3.41)	2218 (3.29)	362 (4.65)	368 (4.06)
Congenital malformations, deformations, and chromosomal abnormalities	2568 (7.02)	4386 (6.43)	1878 (5.66)	3653 (5.41)	543 (6.98)	644 (7.11)
Injury, poisoning, and consequences of external causes	3773 (10.31)	8547 (12.53)	2721 (8.20)	6426 (9.52)	822 (10.57)	1157 (12.77)

Data are presented as number (percentage).

ART, assisted reproductive technology; *NCP*, naturally conceived population controls; *NCS*, naturally conceived siblings; *sART*, ART with siblings.

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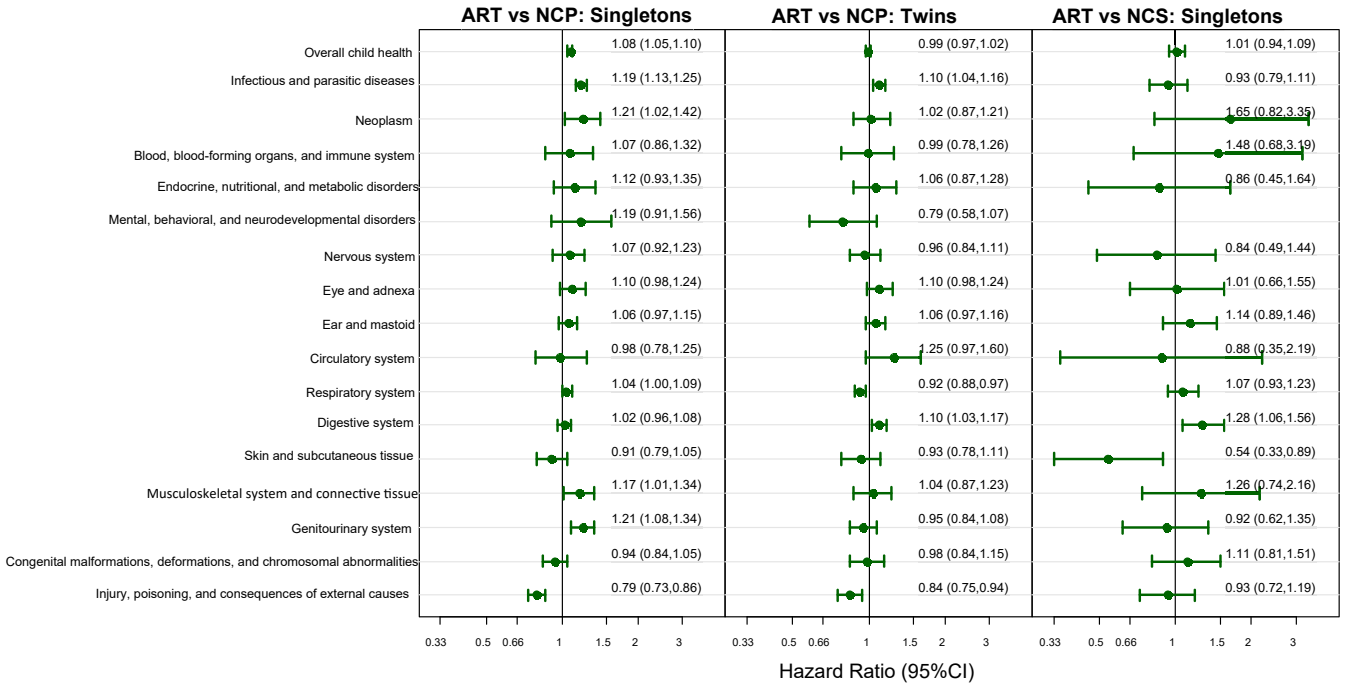
FIGURE 1
Presence or absence of hospital admission (HR and 95% CI) by subcohort and multiplicity



ART, assisted reproductive technology; *CI*, confidence interval; *HR*, hazard ratio; *NCP*, naturally conceived population controls; *NCS*, naturally conceived siblings.

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ART singletons exhibited statistically significantly higher risk of any hospital admission compared with the matched NCP singletons (HR, 1.08; 95% confidence interval [CI], 1.05−1.10). Additional analyses examined hospital admissions owing to specific diagnoses (Figure 1 and Supplemental Table 3). ART singletons had greater risk of admissions for infectious and parasitic diseases (HR, 1.19; 95% CI, 1.13−1.25), neoplasms (HR, 1.21; 95% CI, 1.02−1.42), and diseases of the respiratory (HR, 1.04; 95% CI, 1.00−1.09), musculoskeletal (HR, 1.17; 95% CI, 1.01−1.34), and genitourinary systems (HR, 1.21; 95% CI, 1.08−1.34). These analyses also indicated that ART children may be at lower risk of injury, poisoning, and consequences of external causes (HR, 0.79; 95% CI, 0.73−0.86) when compared with the matched NCP singletons.

There was no difference in risk of any hospital admission between ART-conceived singletons and the singleton NCS of ART-conceived children (HR, 1.01; 95% CI, 0.94−1.09) (Figure 1 and Supplemental Table 3). Additional analyses indicated that ART children had higher risk of admission for diseases of the digestive system (HR, 1.28; 95% CI, 1.06−1.56), and significantly lower risk of diagnoses of the skin and subcutaneous tissue (HR, 0.54; 95% CI, 0.33−0.89) when compared with sibling controls. Again, in the absence of an overall difference in the risk of hospital admission between these groups, these results must be treated with caution unless replicated in independent samples.

There was also no difference in risk of any hospital admission between ART-conceived twins and matched twins in the population control group. Additional analyses indicated that ART twins had greater risk of hospital admissions for diagnoses relating to infectious and parasitic diseases (HR, 1.10; 95% CI, 1.04−1.16) and diseases of the digestive system (HR, 1.10; 95% CI, 1.03−1.17), and lower risk of admissions for diagnoses relating to the respiratory system (HR, 0.92; 95% CI, 0.88−0.97) and injury, poisoning, and consequences of external causes (HR, 0.84; 95% CI, 0.75−0.94) when compared with the matched NCP controls (Figure 1 and Supplemental Table 3). As noted, given the absence of an overall difference in the risk of hospital admission between these groups, these results must be treated with caution unless replicated in independent samples.

Secondary analyses: rates per child of any hospital admission and diagnosis-specific hospital admissions

Multiple hospital admissions were observed in most children with relevant hospital contacts in the ART, NCS, and NCP cohorts. The 3 cohorts exhibited similar mean hospital admission rates overall, and the highest rates were observed for infectious and parasitic diseases; congenital malformations,

TABLE 2
Mean admission rate (number of admissions per year per child) in children with multiple admissions

	ART—NCP				sART—NCS	
	Singletons		Twins		Singletons	
Diagnosis	ART (N=37,890)	Control (N=75,642)	ART (N=25,987)	Control (N=51,902)	sART (N=8383)	Siblings (N=10,871)
Overall	0.0997	0.1046	0.1136	0.1317	0.0879	0.0994
Infectious and parasitic diseases	0.0101	0.0119	0.0121	0.0127	0.0081	0.00904
Neoplasm	0.0058	0.0052	0.0057	0.0072	0.0064	0.0049
Blood, blood-forming organs, and immune system	0.0016	0.0027	0.0017	0.0033	0.0018	0.0052
Endocrine, nutritional, and metabolic disorders	0.0019	0.0024	0.0015	0.0021	0.0016	0.0022
Mental, behavioral, and neurodevelopmental disorders	0.00036	0.00033	0.00038	0.00051	0.0003	0.0004
Nervous system	0.0031	0.0027	0.0053	0.0051	0.0022	0.0038
Eye and adnexa	0.0021	0.0024	0.00305	0.0031	0.0017	0.0018
Ear and mastoid	0.0047	0.0047	0.0066	0.0059	0.0047	0.0051
Circulatory system	0.0301	0.0043	0.0034	0.006	0.0006	0.0008
Respiratory system	0.0223	0.0256	0.0276	0.0342	0.0198	0.0218
Digestive system	0.0127	0.0151	0.0160	0.0166	0.0121	0.0128
Skin and subcutaneous tissue	0.0024	0.0025	0.0021	0.0025	0.0023	0.0027
Musculoskeletal system and connective tissue	0.0034	0.0028	0.0033	0.0029	0.0024	0.0029
Genitourinary system	0.0075	0.0046	0.0052	0.0059	0.0044	0.0038
Congenital malformations, deformations, and chromosomal abnormalities	0.0108	0.0092	0.0121	0.0157	0.0088	0.0123
Injury, poisoning, and consequences of external causes	0.0099	0.0118	0.0107	0.0139	0.0094	0.0111

ART, assisted reproductive technology; *NCP*, naturally conceived population controls; *NCS*, naturally conceived siblings; *sART*, ART with siblings.
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deformations, and chromosomal abnormalities; and diseases of the circulatory, respiratory, and genitourinary systems (Table 2).

ART singletons had a higher rate of hospital admissions overall (for all diagnostic chapters excluding perinatal events; incidence rate ratio [IRR], 1.08; 95% CI, 1.07—1.09) and of admissions for a range of diagnoses when compared with the matched NCP singletons (Figure 2 and Supplemental Table 4). However, this difference in overall rates did not persist on comparison of sART and NCS singletons (IRR, 0.96; 95% CI, 0.90—1.02) (Figure 2 and Supplemental Table 4). ART twins had a lower number of admissions overall (IRR, 0.91; 95% CI, 0.90—0.92) and a higher number of admissions for a range of diagnoses when compared with matched NCP twins (Figure 2 and Supplemental Table 4).

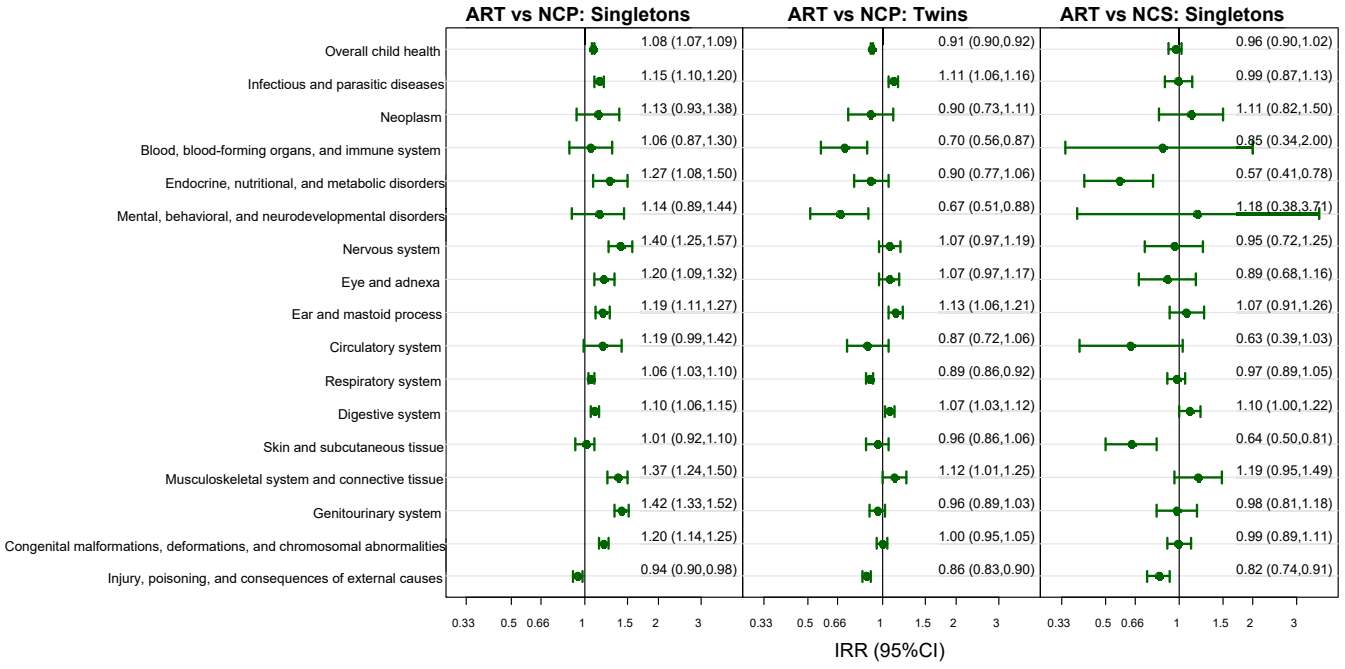
Analysis by assisted reproductive technology treatment type

Analysis by treatment parameters showed that, compared with the matched NCP, IVF with and without ICSI and fresh and frozen transfers all involved similar higher risk of hospital admissions (Table 3). Compared with the matched NCP, children born after ICSI had a somewhat lower risk than that observed for IVF without ICSI.

Children born after ICSI were at a lower risk of hospital admission compared with those born after IVF (HR, 0.95; 95% CI, 0.92—0.97). No differences in risk of hospital admissions were observed between children born after fresh embryo transfers and those born after frozen embryo transfers (HR, 1.01; 95% CI, 0.97—1.04).

Analyses by treatment type with comparisons with NCS were not possible because of small numbers with discordant siblings.

FIGURE 2
Number of hospital admissions per year by diagnosis, subcohort, and multiplicity



ART, assisted reproductive technology; *CI*, confidence interval; *IRR*, incidence rate ratio; *NCP*, naturally conceived population controls; *NCS*, naturally conceived siblings.

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Discussion

Principal findings

This longitudinal study of hospital admissions excluding perinatal events showed that ART singletons had a higher risk of hospital admission over the follow-up period, overall and for a large number of the diagnostic chapters included in this study, when compared with the matched NCP controls. The most common diagnoses observed were related to the respiratory system; the digestive system; injury, poisoning, and consequences of external causes; infectious and parasitic diseases; and congenital malformations, deformations, and chromosomal abnormalities. However, this difference disappeared on comparison of sART and NCS singletons, suggesting that it could have been the result of a selection effect rather than because of the ART procedure itself.

Meaning of the study: possible explanations and implications

Although the role of biological mechanisms is still unclear, potential explanations could include perturbed fetal growth (PTB and low birthweight) and subsequent child growth,[17] and social explanations such as increased parental concern, with parents of ART children viewing their offspring as more vulnerable (higher risks to child) and subsequently being more likely to seek medical help for less severe conditions compared with parents of NC children.[21] The differences in hospital admission were generally attenuated (and virtually eliminated for the primary all-admissions outcome) in the sibling comparisons, suggesting a role of parental factors, such as subfertility and greater parental health concerns in parents who accessed ART. This interpretation holds true for the various disease categories recorded, and the relative contribution of the different causes is complex. However, we note that one category—admissions for injury and poisoning—cannot reasonably be linked to ART causes (parental subfertility or ART treatment) and can therefore be considered responsive to parental concern alone. In this context, we note that such admissions are in fact reduced in ART children, suggesting that parental concern does not necessarily drive increased hospital admission.

The increased risk of congenital defects observed was consistent with a recent meta-analysis that reported similar outcomes in ART children,[22] with the underlying mechanism potentially including factors related to the ART procedure itself (such as medications used for the induction of ovulation or maintenance of pregnancy in the early stages, the composition of culture media and freezing and thawing culture duration, of embryos, delayed fertilization of the oocyte, altered hormonal environment during implantation, etc.). The underlying cause of infertility[23] may also play a role, with the current study also observing an increased risk of congenital malformations in ART children when compared with that of their NCS.

When comparing ART type with the NCP, an increased risk of hospital admission was observed for both IVF and ICSI and also for fresh and frozen embryo transfers. The associations were

TABLE 3
Hazard ratios in subsets receiving different assisted reproductive technology treatments

Subset	HR (95% CI)	
ICSI vs NCP	1.03	(1.01–1.05)
IVF vs NCP	1.08	(1.06–1.10)
ICSI vs IVF	0.95	(0.92–0.97)
Fresh embryo transfer vs NCP	1.06	(1.04–1.08)
Frozen embryo transfer vs NCP	1.06	(1.02–1.10)
Fresh embryo transfer vs frozen embryo transfer	1.01	(0.97–1.04)

CI, confidence interval; *HR*, hazard ratio; *ICSI*, intracytoplasmic sperm injection; *IVF*, in vitro fertilization; *NCP*, naturally conceived population controls.

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relatively weak, suggesting relative increases of 5% to 8%. ICSI children were at a lower risk of hospital admission compared with those born after IVF. There is no clear explanation for this finding because ICSI is an invasive technique associated with male subfertility, frequently with a genetic background, and children born subsequently have been found to have higher rates of congenital anomalies.[24] Therefore, these findings could potentially indicate an association with the nature of the underlying cause of subfertility (ie, nonmale-factor subfertility), unmeasured clinical or socioeconomic factors, or could be the result of a statistical artifact. Further studies are necessary to clarify this. No differences in risk of admission were observed between children born after fresh embryo transfers and those born after frozen embryo transfers. In contrast, our previous analyses of fetal growth (PTB, birthweight) and child growth have shown a clear difference between fresh and frozen transfer infants, with fresh transfer infants being lighter and exhibiting catch-up growth.[17,25] It is notable, therefore, that this increased risk profile for fresh vs frozen transfer infants does not equate to a difference in early-life hospital admissions.

Strengths and weaknesses

The main strength of this study lies in the meticulous linkage of robust, routinely collected administrative health data to provide long-term mortality and morbidity outcome data on offspring.[17] The mandatory nature of reporting all ART cycles carried out in the United Kingdom to the HFEA[26] minimizes the risk of selection bias, whereas linkage to longitudinal health outcome data allows effective monitoring of outcome patterns in relation to advancements in treatment methods, thus representing a high-quality cross-sectoral evidence base that can be used for research, policy planning, and strategic development. Most studies to date investigating health outcomes and hospital utilization of children born after ART have been limited by sample size and short follow-up,[13] with previous population-based data-linkage studies carried out in Sweden and Denmark including 2.5 million infants (of whom approximately 31,000 [1.2%] were conceived after ART) and 589,000 children (of whom 33,000 [5.6%] were conceived after ART), respectively.[27,28] In contrast, the current study included 202,764 children (ART: 63,877 [31.5%]; NCP: 127,544 [62.9%]; NCS: 11,343 [5.59%]), thus increasing the generalizability and precision of results. Another key strength is the inclusion of 2 control groups (NCP and NCS), thus allowing extrapolation of effect sizes and risk estimates to the general ART population along with exploration of the effects of family confounders such as genetic and behavioral factors related to infertility and socioeconomic background. The 2 comparator groups have different sources of bias, including residual family-level confounding in the population analyses and possible bias owing to carry-over effects in the sibling comparisons. The latter refers to situations where the exposure in one sibling influences outcomes in the other.[29] When this is combined with selective fertility, it can result in strong bias, as has been observed in 3 studies reporting within-sibling analyses suggesting that ART protects against perinatal mortality, despite within-sibling and conventional general-population analyses in the same studies showing that ART increases rates of PTB and SGA neonates.[14,30,31] Thus, where results from the 2 comparator groups are similar, there is increased confidence in the findings despite differences in bias. However, where there are differences, caution is needed in assuming that one of the comparisons is likely to be the least biased.

The main limitations of this study are related to the identification of the study cohort itself and subsequent linkage to the HES database.[19,32] These include the method of definition of NC siblings used given that this would be very sensitive to any errors in linkage, with missed second ART infants appearing as conventional siblings. To minimize the chances of such errors, extensive quality assurance procedures were carried out in the linkage process.[17] Approximately 23% of children were also lost during the linkage process because of the weak or inaccurate identifier data on the HFEA register and the high threshold used for matching. However, although this was unavailable for the study period explored here, future studies may be able to avoid such loss to follow-up given that the HFEA now records both the mother's and child's NHS number in their register. Gestational age and prematurity data could not be included as outcomes or used to explore whether results for other outcomes were mediated through gestational age because these data are not available for the NC children. They are not recorded in the birth registration

dataset and are incomplete in maternal HES data (>50% missing). Finally, children born to women who underwent ART before 1997 could not be linked to any hospital records because of unavailability of HES data, thus limiting our ability to examine health outcomes in these children and to explore the effects of changes in ART techniques over that period. Moreover, some cohort participants would not have HES records because they may have sought privately commissioned health treatment, or their records were unavailable because of record-keeping error, coding error, or linkage error, or have been removed as a result of ethico-legal filtering (eg, removal of selected patient records from extracts because of patients registering an objection to their records being used for this purpose).[32] However, it has been estimated that approximately 98% to 99% of hospital activity in England is funded by the NHS, and the HES Admitted Patient Care database covers all births in NHS hospitals, representing approximately 97.3% of births in England, thus making creation of nationally representative cohorts possible.[19] On the basis of these facts, we believe that the cohort will capture the vast majority of outcomes in couples who became pregnant.

Conclusion

The current study showed modestly increased hospital admissions among ART-conceived children compared with NCP controls (Video 1). An attenuated trend was also observed in the sibling's analysis, suggesting that this finding could be attributed to parental factors such as the influence of parental subfertility on child health or increased parental concerns. ■

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Data sharing statement: Deidentified linked cohort data can be accessed from the Human Fertilisation and Embryology Authority and National Health Service Digital where it will be held with restricted access. Specific ethical approval from the Research Ethics Committee and the Confidentiality Advisory Group of the Health Research Authority will be required for access.

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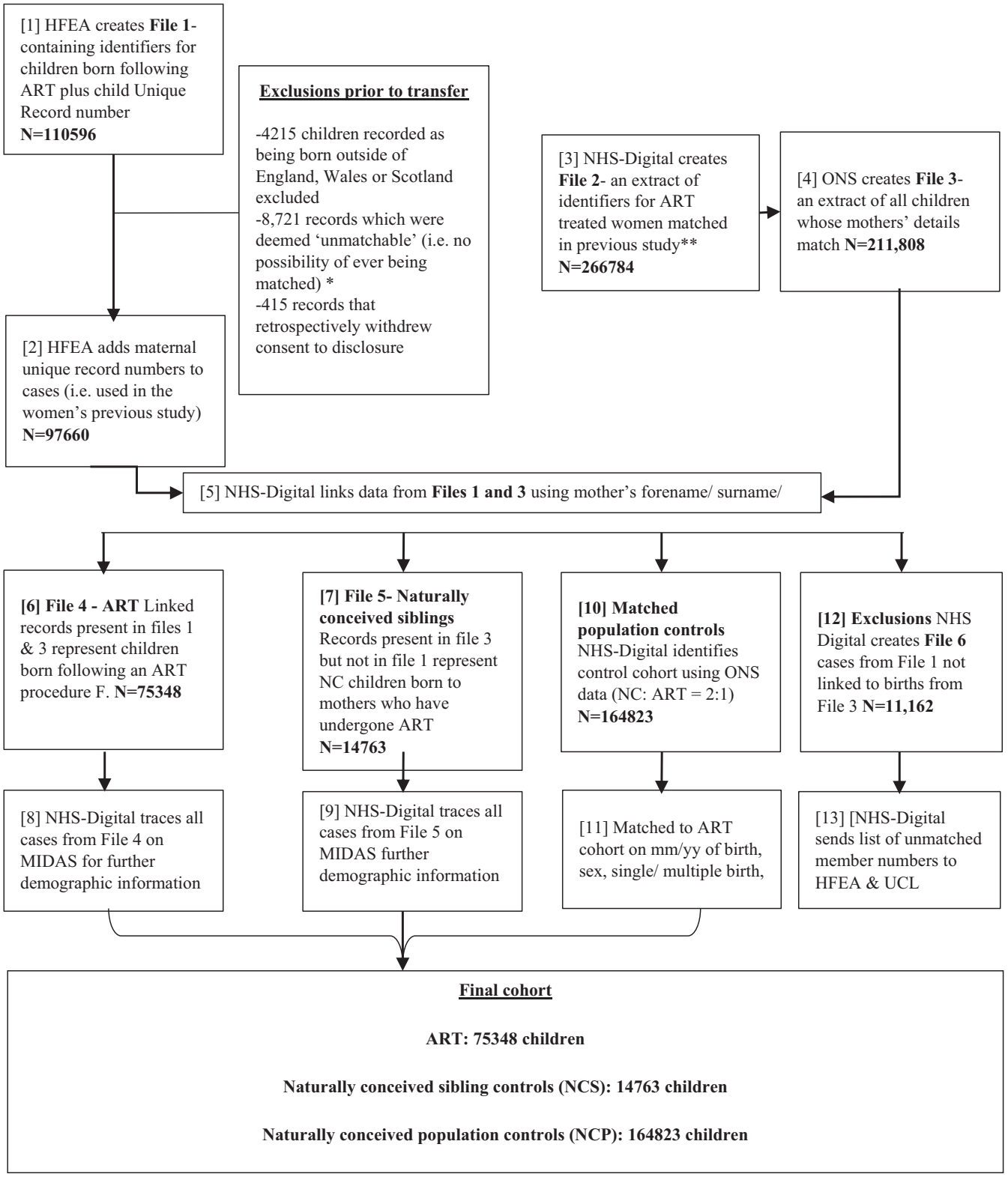
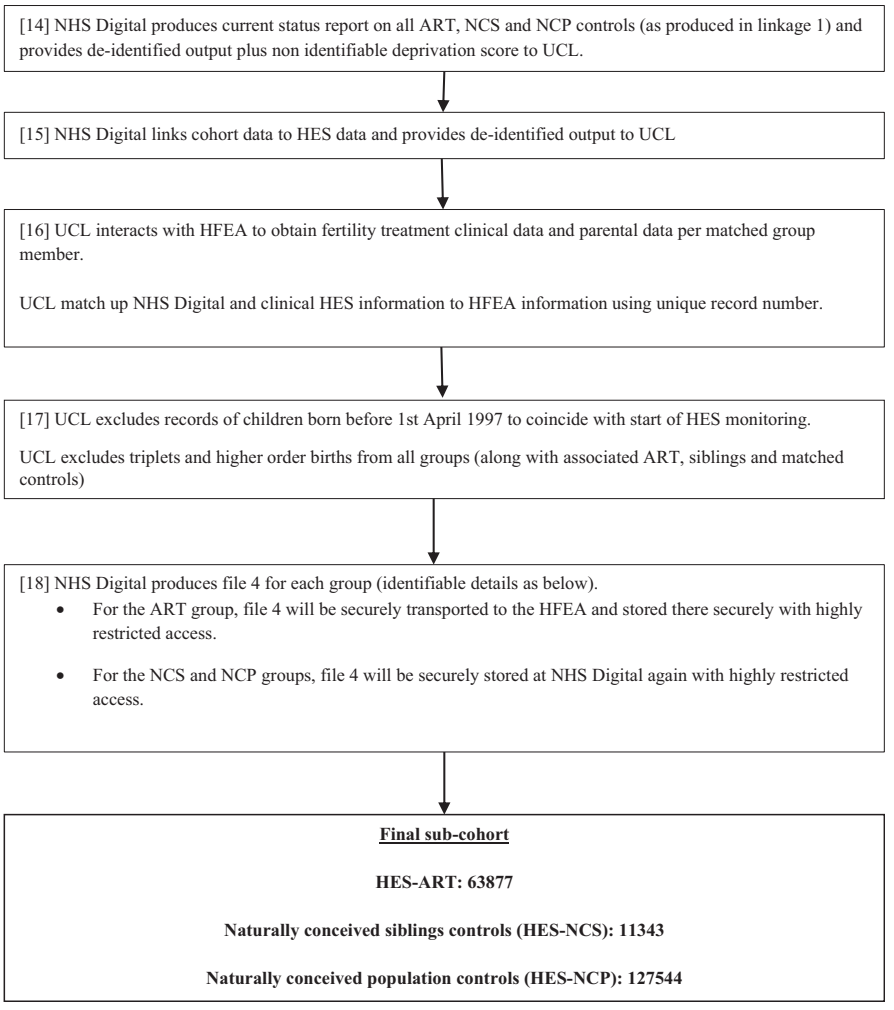
SUPPLEMENTAL FIGURE 1

Stage 1 of linkage (HFEA-ONS)



SUPPLEMENTAL FIGURE 2
Stage 2 of linkage (HFEA-ONS-HES)



ART, assisted reproductive technology; *HES*, Hospital Episode Statistics database; *HFEA*, Human Fertilization and Embryology Authority; *NCS*, naturally conceived siblings; *NHS*, National Health Service; *ONS*, Office for National Statistics; *UCL*, University College London.

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Single asterisk denotes as they were (1) births outside of England/Wales; (2) births before 1993 (when ONS systems were automated and thus the date from which linkage is possible to ONS records); and (3) to mothers which were not included in file 2 (as it was not possible to identify them on NHS-Digital systems previously- 'women's study'). *Double asterisks* denote that Supplemental Figure 2 provides cohort flow.

ART, assisted reproductive technology; *HES*, Hospital Episode Statistics database; *HFEA*, Human Fertilization and Embryology Authority; *MIDAS*, Medical Integrated Database and Administration System; *NCS*, naturally conceived siblings; *NHS*, National Health Service; *ONS*, Office for National Statistics; *UCL*, University College London.

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SUPPLEMENTAL TABLE 1
Demographic characteristics of study cohort

	ART	NCP	sART	NCS
Infants	63,877	127,544	12,329	11,343
Follow-up period in days				
Median (IQR)	4429 (2181)	4409 (2141)	4635 (1846)	4307 (2029)
Mean birthweight (SD)				
Singleton	3166.95 (742.25)	3271.67 (648.46)	3222.25 (699.31)	3346.54 (712.02)
Multiple	2172.27 (715.42)	2155.77 (683.93)	2201.58 (724.87)	2301.17 (677.82)
Sex				
Female	31,435 (49.21)	62,785 (49.22)	5907 (47.91)	5573 (49.12)
Male	32,442 (50.79)	64,759 (50.78)	6422 (52.09)	5770 (50.88)
Multiplicity				
Singleton children	37,890 (59.36)	75,642 (59.30)	8383 (68.04)	10,815 (95.83)
Multiple children	25,987 (40.64)	51,902 (40.70)	3946 (31.96)	528 (4.17)
IMD decile at earliest appointmentappointment				
1 (most deprived)	2045 (3.20)	12,696 (9.94)	349 (2.82)	299 (2.63)
2	2650 (4.15)	11,104 (8.71)	458 (3.72)	396 (3.51)
3	3311 (5.19)	10,057 (7.87)	539 (4.40)	463 (4.07)
4	3926 (6.14)	9550 (7.49)	678 (5.44)	588 (5.19)
5	4666 (7.28)	9161 (7.49)	862 (6.98)	746 (6.57)
6	5350 (8.39)	8872 (6.95)	1084 (8.82)	921 (8.09)
7	6142 (9.61)	8842 (6.94)	1205 (9.77)	1044 (9.20)
8	6675 (10.46)	8925 (7.01)	1299 (10.54)	1161 (10.25)
9	7729 (12.10)	9083 (7.11)	1557 (12.58)	1386 (12.21)
10 (least deprived)	7710 (12.07)	8299 (6.53)	1720 (14.00)	1499 (13.25)
Missing	13673 (21.41)	30,955 (24.26)	2580 (20.94)	2840 (25.02)
Birth year				
1997	2597 (4.06)	5160 (4.07)	518 (4.21)	242 (2.14)
1998	3708 (5.81)	7389 (5.85)	743 (6.03)	419 (3.68)
1999	4083 (6.40)	8126 (6.49)	852 (6.92)	560 (4.94)
2000	4310 (6.75)	8633 (6.91)	925 (7.51)	781 (6.85)
2001	4559 (7.14)	9160 (7.33)	972 (7.89)	879 (7.76)
2002	4980 (7.79)	9933 (7.87)	1171 (9.50)	937 (8.27)
2003	5379 (8.42)	10,788 (8.49)	1253 (10.17)	1012 (8.92)
2004	5561 (8.71)	11,082 (8.66)	1271 (10.31)	1067 (9.41)
2005	5662 (8.87)	11,326 (8.83)	1271 (10.30)	1078 (9.51)
2006	6275 (9.82)	12,513 (9.68)	1217 (9.86)	1100 (9.70)
2007	6342 (9.93)	12,701 (9.84)	1058 (8.56)	1199 (10.56)
2008	6347 (9.93)	12,718 (9.81)	670 (5.44)	1260 (11.11)
2009	4074 (6.37)	8015 (6.17)	408 (3.30)	809 (7.14)
Ethnicity				

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SUPPLEMENTAL TABLE 1
Demographic characteristics of study cohort *(continued)*

	ART	NCP	sART	NCS
White	61,921 (96.94)	122,050 (95.69)	11,983 (97.19)	11,084 (97.72)
Asian/Asian British	959 (1.50)	2496 (1.96)	197 (1.60)	153 (1.35)
Chinese	35 (0.05)	89 (0.07)	8 (0.06)	1 (0.01)
Black/African/Caribbean /Black British	433 (0.68)	5268 (4.04)	61 (0.49)	39 (0.34)
Mixed/Multiple ethnic groups	318 (0.50)	721 (0.57)	38 (0.31)	27 (0.24)
Other ethnic group	211 (0.33)	498 (0.39)	42 (0.34)	39 (0.34)
Maternal age at delivery				
≤25	710 (1.11)	27,783 (21.88)	241 (1.95)	317 (2.86)
25–29	5085 (7.96)	25,115 (19.70)	1209 (9.81)	887 (7.80)
30–34	21,994 (34.44)	38,896 (30.50)	4797 (38.92)	3309 (29.12)
35–39	27,682 (43.35)	25,907 (20.29)	4998 (40.57)	4954 (43.67)
40–44	8164 (12.99)	6419 (5.21)	1057 (8.57)	1830 (16.15)
≥45	217 (0.34)	772 (0.61)	20 (0.16)	45 (0.40)
Missing	25 (0.04)	2652 (2.02)	7 (0.01)	1 (0.00)

ART, assisted reproductive technology; *IMD*, Index of Multiple Deprivation; *IQR*, interquartile range; *NCP*, naturally conceived population controls; *NCS*, naturally conceived siblings; *sART*, ART with siblings.

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SUPPLEMENTAL TABLE 2

List of International Classification of Diseases Tenth Revision codes included in this study

ICD codes	Description	Inclusion /exclusion status
A00—B99	Certain infectious and parasitic diseases	✓
C00—D48	Neoplasms	✓
D50—D89	Diseases of the blood and blood-forming organs & certain disorders involving the immune mechanism	✓
E00—E90	Endocrine, nutritional and metabolic diseases	✓
F00—F99	Mental and behavioral disorders	✓
G00—G99	Diseases of the nervous system	✓
H00—H59	Diseases of the eye and adnexa	✓
H60—H95	Diseases of the ear and mastoid process	✓
I00—I99	Diseases of the circulatory system	✓
J00—J99	Diseases of the respiratory system	✓
K00—K93	Diseases of the digestive system	✓
L00—L99	Diseases of the skin and subcutaneous tissue	✓
M00—M99	Diseases of the musculoskeletal system and connective tissue	✓
N00—N99	Diseases of the genitourinary system	✓
O00—O99	Pregnancy, childbirth and the puerperium	X
P00-P96	Certain conditions originating in the perinatal period	X
Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities	✓
R00—R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	X
S00—T98	Injury, poisoning and certain other consequences of external causes	✓
U00—U99	Codes for special purposes	X
Z00—Z99	Factors influencing health status and contact with health services	X

ICD-10, International Classification of Diseases Tenth Revision.

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SUPPLEMENTAL TABLE 3
Cox proportional hazard model

	ART-NCP adjusted for month and year of birth, sex, IMD decile, ethnicity, maternal age group at delivery				sART–NCS adjusted for sex, birth year, maternal age group at delivery, birth order (+ family as matching variable)	
	Singletons		Twins		Singletons	
Diagnosis	HR	95% CI	HR	95% CI	HR	95% CI
Overall child health	1.08[a]	1.05–1.10[a]	0.99[a]	0.97–1.02[a]	1.01[a]	0.94–1.09[a]
Infectious & parasitic diseases	1.19[a]	1.13–1.25	1.10[a]	1.04–1.16	0.93	0.79–1.11
Neoplasm	1.21[a]	1.02–1.42	1.02	0.87–1.21	1.65	0.82–3.35
Blood, blood-forming organs & immune system	1.07	0.86–1.32	0.99	0.78–1.26	1.48	0.68–3.19
Endocrine, nutritional & metabolic disorders	1.12	0.93–1.35	1.06	0.87–1.28	0.86	0.45–1.64
Mental, behavioral & neurodevelopmental disorders	1.19	0.91–1.56	0.79	0.58–1.07	—	—
Nervous system	1.07	0.92–1.23	0.96	0.84–1.11	0.84	0.49–1.44
Eye & adnexa	1.10	0.98–1.24	1.10	0.98–1.24	1.01	0.66–1.55
Ear & mastoid	1.06	0.97–1.15	1.06	0.97–1.16	1.14	0.89–1.46
Circulatory system	0.98	0.78–1.25	1.25	0.97–1.60	0.88	0.35–2.19
Respiratory system	1.04[a]	1.00–1.09	0.92[a]	0.88–0.97	1.07	0.93–1.23
Digestive system	1.02	0.96–1.08	1.10[a]	1.03–1.17	1.28[a]	1.06–1.56
Skin & subcutaneous tissue	0.91	0.79–1.05	0.93	0.78–1.11	0.54[a]	0.33–0.89
Musculoskeletal system & connective tissue	1.17[a]	1.01–1.34	1.04	0.87–1.23	1.26	0.74–2.16
Genitourinary system	1.21[a]	1.08–1.34	0.95	0.84–1.08	0.92	0.62–1.35
Congenital malformations, deformations and chromosomal abnormalities	0.94	0.84–1.05	0.98	0.84–1.15	1.11	0.81–1.51
Injury, poisoning, and consequences of external causes	0.79[a]	0.73–0.86	0.84[a]	0.75–0.94	0.93	0.72–1.19

ART, assisted reproductive technology; *CI*, confidence interval; *HR*, hazard ratio; *IMD*, Index of Multiple Deprivation; *NCP*, naturally conceived population controls; *NCS*, naturally conceived siblings; *sART*, ART with siblings.

[a] Indicates statistical significance.

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SUPPLEMENTAL TABLE 4

Negative binomial regression analysis-number of admissions by diagnosis chapter

	ART-NCP adjusted for month and year of birth, sex, IMD, ethnicity, maternal age group at delivery				sART−NCS adjusted for sex, birth year, maternal age group at delivery, birth order (+family as matching variable)	
	Singletons		Twins		Singletons	
	IRR (95% CI)		IRR (95% CI)		IRR (95% CI)	
Overall child health	1.08[a]	1.07−1.09[a]	0.91[a]	0.90−0.92[a]	0.96[a]	0.90−1.02[a]
Infectious and parasitic diseases	1.15[a]	1.10−1.20	1.11[a]	1.06−1.16	0.99	0.87−1.13
Neoplasm	1.13	0.93−1.38	0.90	0.73−1.11	1.11	0.82−1.50
Blood, blood-forming organs & immune system	1.06	0.87−1.30	0.70[a]	0.56−0.87	0.85	0.34−2.00
Endocrine, nutritional and metabolic disorders	1.27[a]	1.08−1.50	0.90	0.77−1.06	0.57[a]	0.41−0.78
Mental, behavioral & neurodevelopmental disorders	1.14	0.89−1.44	0.67[a]	0.51−0.88	1.18	0.38−3.71
Nervous system	1.40[a]	1.25−1.57	1.07	0.97−1.19	0.95	0.72−1.25
Eye and adnexa	1.20[a]	1.09−1.32	1.07	0.97−1.17	0.89	0.68−1.16
Ear and mastoid process	1.19[a]	1.11−1.27	1.13[a]	1.06−1.21	1.07	0.91−1.26
Circulatory system	1.19	0.99−1.42	0.87	0.72−1.06	0.63	0.39−1.03
Respiratory system	1.06[a]	1.03−1.10	0.89[a]	0.86−0.92	0.97	0.89−1.05
Digestive system	1.10[a]	1.06−1.15	1.07[a]	1.03−1.12	1.10[a]	1.00−1.22
Skin and subcutaneous tissue	1.01	0.92−1.10	0.96	0.86−1.06	0.64[a]	0.50−0.81
Musculoskeletal system and connective tissue	1.37[a]	1.24−1.50	1.12[a]	1.01−1.25	1.19	0.95−1.49
Genitourinary system	1.42[a]	1.33−1.52	0.96	0.89−1.03	0.98	0.81−1.18
Congenital malformations, deformations and chromosomal abnormalities	1.20[a]	1.14−1.25	1.00	0.95−1.05	0.99	0.89−1.11
Injury, poisoning, and consequences of external causes	0.94[a]	0.90−0.98	0.86[a]	0.83−0.90	0.82[a]	0.74−0.91

ART, assisted reproductive technology; *CI*, confidence interval; *HR*, hazard ratio; *IMD*, Index of Multiple Deprivation; *NCP*, naturally conceived population controls; *NCS*, naturally conceived siblings; *sART*, ART with siblings.

[a] Indicates statistical significance

Sutcliffe. General health of children conceived after assisted reproductive technology. Am J Obstet Gynecol 2022.