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General Health in a cohort of children conceived after assisted reproductive technology in the UK: a population-based record-linkage study

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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.

What are the key findings? Children born after assisted reproductive technology showed greater numbers of hospital admissions compared to 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 as well as 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 to those born after in-vitro fertilization.

What does this study add to what is already known? The inclusion of two control groups allows extrapolation of effect sizes to the general population along with exploration of the effects of family confounders.
ABSTRACT

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

Objectives: To examine the potential effects of assisted reproductive technology on any and cause-specific hospital admissions not related to perinatal diagnoses.

Study design: Population-based record-linkage study utilizing a previously established cohort of children born after assisted reproductive technology in the United Kingdom between 1997 and 2009 (n=63877), their naturally conceived siblings (n=11343), and matched naturally conceived population (n=127544) controls linked to their postnatal health outcomes up to 31st March 2016 to provide robust risk estimates of the potential effects of assisted reproductive technology on any and cause-specific hospital admissions not related to perinatal diagnoses. Additionally, comparison of hospital admissions by type of treatment was performed. Cox regression was used to estimate the risk of hospital admissions 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 to 19 years], and the mean age at the time of first hospital admission was 6.5 years [range 0 to 19 years]. Singletons born after assisted reproductive technology had increased risk of any hospital admission compared to naturally conceived population controls [Hazard ratio: 1.08; 95% CI: 1.05 to 1.10] but not naturally conceived siblings [Hazard ratio: 1.01; 95% CI: 0.94 to 1.09]. We observed increased risk for 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 to naturally conceived population controls. Children born after intracytoplasmic sperm injection had a lower risk of hospital admission compared to those born after in-vitro fertilization,
although no such differences were observed between children born after fresh and frozen embryo transfers.

Conclusions: Children born after assisted reproductive technology showed greater numbers of hospital admissions compared to 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 as well as an actual increase in morbidity in children born after assisted conception.

Keywords: assisted reproductive technology; assisted conception; hospital admissions; naturally conceived siblings; naturally conceived controls; record linkage; cohort
INTRODUCTION

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

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) and preterm birth (PTB) while frozen embryo transfers are associated with increasing risk of large for gestational age (LGA). Fewer studies have explored longer-term health outcomes in children born after ART, with evidence suggesting increased risk of neurodevelopmental disorders, suboptimal cardiovascular function and high blood pressure which persisted into adolescence, asthma, and deterioration in sperm count in ICSI male offspring. Moreover, ART-conceived children have also been seen to exhibit more frequent and longer hospital admissions than naturally conceived (NC) children, even after the neonatal period. Putative drivers of increased hospitalization rates include higher rates of congenital malformations, infections, respiratory diseases, and disorders of the central nervous system in ART children. Parental factors may also play a role in increased hospital admission rates, with the parents of children who were born after a prolonged period of involuntary childlessness exhibiting more concern over child morbidity and seeking medical care more frequently.

However, much of the available evidence is often limited by small sample sizes and short follow-up periods leading to contradictory results. Moreover, the inability to distinguish the contribution of
ART treatment factors and parental sub-fertility to adverse health outcomes is a common limitation of many ART follow-up studies. 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 non-conception] as well as studies that utilize within sibling analyses [where comparisons are made between ART and their naturally conceived (NC) siblings] to better control for factors related to sub-fertility and other family confounders, under the assumption that these parental factors would be the same (or very similar) within sibling groups.

The objective of the current study is to assess the association of ART conception with future health by utilizing a previously established cohort of children consisting of those born after ART in the UK between 1997 and 2009, their naturally conceived siblings (NCS), and matched naturally conceived population (NCP) controls linked to their hospital records up to 31st March 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 as well as NCS. Additionally, comparisons of hospital admissions by type of ART treatment (IVF vs ICSI, embryo cryopreservation) were also performed.

**METHODS**

**Study population**

This study utilized a previously established cohort of children born to women who underwent ART in the UK between 1st April 1997 and 31st July 2009, their NCS, with 2 NCP controls per ART child matched for age, sex, and multiplicity. A sub-group of ART children with NCS (sART) was also identified. Record linkage was used to link the Human Fertilization & Embryology Authority (HFEA)
register, the Office for National Statistics (ONS) birth registration dataset, and the Hospital Episode Statistics (HES) database (Supplementary figures S1 & S2), with details of the linkage methodology previously reported. \(^{17}\)

All children conceived in the UK after ART but born outside of England, Wales, and Scotland; those born after ART to women who permanently lived outside the UK but travelled to the UK for ART treatment and those born in Northern Ireland were excluded as it would not be possible to link them to ONS birth records. Additionally, siblings born outside of the study period (as their conception status could not be verified) as well as 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 as 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 post-natal health records up to 31\textsuperscript{st} March 2016 using the HES database containing details of all admissions at NHS hospitals in England\(^ {19}\) in a one-off linkage. Diagnoses were defined using ICD-10 (International classification of diseases 10\textsuperscript{th} revision), and conditions that would have originated in the perinatal period; those 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 (details of ICD10 codes included and excluded are provided in Supplementary Table S4).
The primary outcome measures were risk of any hospital admission and ‘relevant’ (i.e., related to the included diagnostic chapters) diagnostic specific hospital admissions, while 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 for this outcome comparing the ART-conceived to the NCP and NCS control groups separately. A series of additional analyses were carried out, 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 (31st March 2016) in those not experiencing any or a diagnostic specific admission. This was further grouped into <1 day, 1-6 days, 7-28 days, 29-90 days, 91-181 days, 182-272 days, 273-364 days, 1-3 years, 4-6 years, 7-9 years, 10-12 years, 12-14 years, 15-17 years, 18-20 years, 21-23 years, 24-26 years, and 27-30 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 (31st March 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 NCP and NCS control groups separately. Each child’s period at risk was calculated from date of birth until which ever event occurred first: hospital admission, death, or end of the follow-up period (31st March 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, & ≥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 UK] at the time of first hospital admission; and ethnicity (grouped into White; 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 for within family correlations and were adjusted for birth year; maternal age at delivery; sex; and order of pregnancy (grouped into 1st, 2nd, and >2nd). IMD and ethnicity were excluded as the underlying effects they represent would have remained constant within families.

Analysis by ART treatment type: The effects of ART subgroups (IVF/ICSI and fresh/frozen embryo transfers) were explored using Cox regression to estimate hazard ratios and compare with the NCP cohort. Within sub-group analyses were also performed. This analysis was not conducted in the sibling cohort due to small numbers.

All statistical analyses were performed using STATA v16.0.

Role of the funding source

This work was supported by the UK Medical Research Council [Grant number MR/L020335/1]. DAL’s contribution to the paper was additionally supported by the University of Bristol and UK Medical Research Council via the MRC Integrative Epidemiology Unit (MC_UU_00011/1-6) and European Research Council (grant agreement: 101021566). The funders had no role in the study design, data collection, analyses, or interpretation of findings. Views expressed in this paper are those of the authors and not necessarily any funder.
Due to 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, or dissemination plans of our research. Prior to conducting this study, we carried out an a priori investigation (assisted by the Royal College of Obstetrics and Gynecology Women’s Health panel and Infertility UK) of the health concerns of women who had had ART and women as a whole 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’ about the impact of assisted conception on their child’s future health. Ethical approval and waiver of the requirement for individual consent were obtained from the UK Health Research Authority Confidentiality Advisory Group and London Research Ethics Committee - Hampstead (references ECC 4-03(g)/2012 and 12/LO/1063, respectively).

RESULTS

Characteristics of study population

The original cohort consisted of 63877 ART children [of which 12329 ART children had naturally conceived siblings (sART)], 127544 matched NCP controls, and 11343 NCS. The demographic characteristics of the study cohort have been summarized in Supplementary table S3. In total, 124252 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 diagnostic specific admissions

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

ART singletons exhibited statistically significantly higher risk of any hospital admission compared to the matched NCP singletons (HR: 1·08; 95% CI: 1·05, 1·10). Additional analyses examined hospital admissions due to specific diagnoses (Figure 1 & Supplemental table S5). 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 to the matched NCP singletons.

There was no difference in risk of any hospital admission between ART conceived singletons and the naturally conceived singleton siblings of ART conceived children (HR: 1·01; 95% CI: 0·94, 1·09) (Figure 1 & Supplemental table S5). 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 for diagnoses of the skin & 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 to the matched NCP controls (Figure 1 & Supplemental table S5). 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.

Secondary analyses: Rates per child of any hospital admission and diagnostic specific hospital admissions

Multiple hospital admissions were observed in the majority of children with relevant hospital contacts in the ART, NCS and NCP cohorts. The three cohorts exhibited similar mean hospital admission rates overall, and the highest rates were seen for infectious and parasitic diseases; congenital malformations, 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; IRR: 1.08; 95% CI: 1.07, 1.09) as well as for a range of diagnoses when compared to the matched NCP singletons (Figure 2 & Supplemental table S6). However, this difference in overall rates did not persist upon comparison of sART and NCS singletons (IRR: 0.96; 95% CI: 0.90, 1.02; Figure 2 & Supplemental table S6). 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 to matched NCP twins (Figure 2 & Supplemental table S6).
Analysis by ART treatment type

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

Children born after ICSI were at a lower risk of hospital admission compared to those born after IVF [HR: 0·95, 95% CI: 0·92, 0·97]. No differences in risk of hospital admissions were seen between children born after fresh and frozen embryo transfers [HR: 1·01, 95% CI 0·97, 1·04].

Analyses by treatment type with comparison to NCS were not possible due to small numbers with discordant siblings.

DISCUSSION

Principal findings

This longitudinal study of hospital admissions excluding perinatal events showed that ART singletons exhibited 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 to the matched NCP controls. The most common diagnoses observed were those related to the respiratory system; the digestive system; injury, poisoning, and consequences of external causes; infectious & parasitic diseases; and congenital malformations, deformations, and chromosomal abnormalities. However, this difference disappeared upon comparison of sART and NCS singletons suggesting that this could be the result of a selection effect rather than due to 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 (pre-term birth and low birthweight) and subsequent child growth as well as 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 to parents of naturally conceived children. The differences in hospital admission were generally attenuated (and virtually eliminated for the primary all admissions outcome) in the sibling comparisons, suggesting a role for 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 admission to hospital.

The increased risk of congenital defects observed was consistent with a recent meta-analysis that reported similar outcomes in ART children, 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 culture duration, freezing and thawing of embryos, delayed fertilization of the oocyte, altered hormonal environment during implantation etc.). The underlying cause of infertility may also play a role, with the current study also observing an increased risk of congenital malformations in ART children when compared to their NCS.
When comparing ART type to NCP, an increased risk of hospital admission was seen for both IVF and ICSI and also for fresh and frozen embryo transfers. The associations were relatively small, suggesting relative increases of 5 to 8%. ICSI children were at a lower risk of hospital admission compared to those born after IVF. There is no clear explanation for this finding as 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. Therefore, these findings could potentially indicate an association with the nature of the underlying cause of subfertility (i.e. non-male 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 seen between children born after fresh and frozen embryo transfers. In contrast, our previous analysis of fetal growth (pre-term birth, birthweight) and child growth have shown a clear difference between fresh and frozen transfer babies, with fresh transfer babies being lighter and exhibiting catch-up growth. It is notable therefore that this increased risk profile for fresh versus frozen transfer babies 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. The mandatory nature of reporting all ART cycles carried out in the UK to the HFEA minimizes the risk of selection bias, while linkage to longitudinal health outcome data allows for effective monitoring of outcome patterns in relation to advancements in treatments 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, with previous population-based data-linkage studies carried out in Sweden and Denmark including 2.5 million infants [of which around 31,000 (1.2%) were conceived after ART] and 589,000 children [of which 33,000 (5.6%) were conceived after ART], respectively. In contrast, the current study included 202,764 children [ART: 63,877 (31.5%); NCP: 127,544 (62.9%); NCS: 11,343], thus increasing the generalizability and precision of results. Another key strength is the inclusion of two 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 two comparator groups have different sources of bias, including residual family level confounding in the population analyses and possible bias due to carry-over effects in the sibling comparisons. The latter refers to situations where the exposure in one sibling influences outcomes in the other. When this is combined with selective fertility, it can result in strong bias as has been observed in three 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 ART increases preterm birth and SGA. Thus, where results from the two 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 include those related to identification of the study cohort itself and subsequent linkage to the HES database. These include the method of definition of NC siblings used as this would be very sensitive to any errors in linkage, with missed second ART babies appearing as conventional siblings. For this reason, extensive quality assurance procedures were carried out on the linkage process to minimize this. Approximately 23% of children were also lost
during the linkage process due to the weak/inaccurate identifier data on the HFEA register and the high threshold used for matching; however, although unavailable for the study period explored here, future studies may be able to avoid this loss to follow-up as the HFEA now record both the mother and child’s NHS number on their register. Gestational age/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 prior to 1997 could not be linked to any hospital records due to 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 as they may have sought privately commissioned health treatment or their records were unavailable due to record keeping error, coding error, linkage error or has been removed as a result of ethico-legal filtering (e.g. where selected patients records are removed from extracts as they have registered an objection to their records being used for this purpose). However, it has been estimated that approximately 98–99% 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. Based on these facts we believe that the cohort will capture the vast majority of outcomes in couples who became pregnant.

CONCLUSION

The current study showed modest increased hospital admissions among ART-conceived children compared to NCP controls. An attenuated trend was also observed in the sibling’s analysis.
suggesting that this usage could be attributed to parental factors such as the influence of parental subfertility on child health or increased parental concerns.
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**Ethical considerations:** Ethical approval and Section 251 support were obtained from the NHS Research Ethics Committee and Confidentiality Advisory Group, respectively. Additional data access permissions were sought from the HFEA Register Research Panel, ONS Micro-Data Release board, and the NHS Digital Medical Register. All researchers with data access underwent NHS Digital Data Security Awareness and ONS Safe Researcher accreditation.

**Data sharing statement:** De-identified linked cohort data can be accessed from the Human Fertilization and Embryology Authority and NHS Digital where it will be held with restricted access. Specific ethical approval from the Research Ethics Committee (REC) and the Confidentiality Advisory Group (CAG) of the Health Research Authority (HRA) will be required for access.
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Table 1: Hospital admissions by diagnosis, sub-cohort, and multiplicity

| Relevant contact | ART –NCP | | | | sART - NCS | | | |
|---|---|---|---|---|---|---|---|---|
| | ART (N=37890) | Control (N=75642) | Twins | Control (N=25987) | Control (N=51902) | sART (N=8383) | Singletons (N=10871) | |
| Absent | 20884 (55·12%) | 41168 (54·42%) | 13824 (53·20%) | 26964 (51·95%) | 5912 (70·53%) | 7788 (71·64%) | |
| Present | 17006 (44·88%) | 34474 (45·58%) | 12163 (46·80%) | 24938 (48·05%) | 2470 (29·47%) | 3083 (28·36%) | |
| Infectious & 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 & immune system | 246 (0·67%) | 515 (0·75%) | 192 (0·58%) | 398 (0·59%) | 66 (0·85%) | 81 (0·89%) | |
| Endocrine, nutritional & metabolic disorders | 331 (0·90%) | 582 (0·85%) | 275 (0·83%) | 504 (0·75%) | 64 (0·82%) | 80 (0·88%) | |
| Mental health & 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 & adnexa | 717 (1·96%) | 1347 (1·97%) | 696 (2·10%) | 1364 (2·02%) | 145 (1·86%) | 174 (1·92%) | |
| Ear & 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%) | |
| System                                                                 | ART: 6040 (16·50%) | NCP: 12240 (17·94%) | sART: 4666 (14·07%) | NCS: 10274 (15·22%) | ART: 1293 (16·63%) | NCP: 1610 (17·77%) |
|------------------------------------------------------------------------|---------------------|----------------------|----------------------|----------------------|---------------------|---------------------|
| Respiratory system                                                     | 570 (1·72%)         | 1190 (1·76%)         | 1145 (1·70%)         | 2218 (3·29%)         | 188 (2·42%)         | 259 (2·86%)         |
| Digestive system                                                       | 628 (1·89%)         | 1145 (1·70%)         | 1145 (1·70%)         | 2218 (3·29%)         | 188 (2·42%)         | 259 (2·86%)         |
| Skin & subcutaneous tissue                                             | 905 (2·47%)         | 1806 (2·65%)         | 628 (1·89%)          | 1145 (1·70%)         | 188 (2·42%)         | 259 (2·86%)         |
| Musculoskeletal system & 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, déformations, & 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%)       |

ART: Assisted reproductive technology; NCP: Naturally conceived population controls; sART: ART with siblings; NCS: Naturally conceived siblings.
Table 2: Mean admission rate (number of admissions per year per child) in children with multiple admissions

| Category                                                                 | ART – NCP | sART - NCP |
|--------------------------------------------------------------------------|-----------|------------|
|                                                                          | Singletons| Singletons |
|                                                                          | Twins     | Siblings   |
|                                                                          | ART       | Control    | ART       | Control    | sART       | Siblings   |
| Overall                                                                  | 0.0997    | 0.1046     | 0.1136    | 0.1317     | 0.0879     | 0.0994     |
| Infectious & 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 & immune system                             | 0.0016    | 0.0027     | 0.0017    | 0.0033     | 0.0018     | 0.0052     |
| Endocrine, nutritional & metabolic disorders                             | 0.0019    | 0.0024     | 0.0015    | 0.0021     | 0.0016     | 0.0022     |
| Mental, behavioral & neurodevelopmental disorders                        | 0.0036    | 0.0033     | 0.0038    | 0.0051     | 0.0003     | 0.0004     |
| Nervous system                                                           | 0.0031    | 0.0027     | 0.0053    | 0.0051     | 0.0022     | 0.0038     |
| Eye & adnexa                                                             | 0.0021    | 0.0024     | 0.00305   | 0.0031     | 0.0017     | 0.0018     |
| Ear & 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 & subcutaneous tissue                                               | 0.0024    | 0.0025     | 0.0021    | 0.0025     | 0.0023     | 0.0027     |
| Musculoskeletal system & 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; sART: ART with siblings; NCS: Naturally conceived siblings
Table 3: Hazard ratios in subsets receiving different ART treatments.

| Comparison                                | 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) |

HR: Hazards Ratio; NCP: Naturally conceived population controls; CI: Confidence interval; ICSI: Intracytoplasmic sperm injection; IVF: In-vitro fertilization
## Table 1: Hospital admissions by diagnosis, sub-cohort and multiplicity

| Relevant contact                                      | ART –NCP | Control (N=75642) | Twins | Control (N=51902) | sART - NCS | Siblings (N=10871) |
|-------------------------------------------------------|----------|-------------------|-------|-------------------|------------|--------------------|
| Absent                                                | 20884 (55.12%) | 41168 (54.42%) | 13824 (53.20%) | 26964 (51.95%) | 5912 (70.53%) | 7788 (71.64%) |
| Present                                               | 17006 (44.88%) | 34474 (45.58%) | 12163 (46.80%) | 24938 (48.05%) | 2470 (29.47%) | 3083 (28.36%) |
| Infectious & 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 & immune system           | 246 (0.67%) | 515 (0.75%) | 192 (0.58%) | 398 (0.59%) | 66 (0.85%) | 81 (0.89%) |
| Endocrine, nutritional & metabolic disorders           | 331 (0.90%) | 582 (0.85%) | 275 (0.83%) | 504 (0.75%) | 64 (0.82%) | 80 (0.88%) |
| Mental health & 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 & adnexa                                          | 717 (1.96%) | 1347 (1.97%) | 696 (2.10%) | 1364 (2.02%) | 145 (1.86%) | 174 (1.92%) |
| Ear & 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%) | 12240 (17.94%) | 4666 (14.07%) | 10274 (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 & subcutaneous tissue                            | 905 (2.47%) | 1806 (2.65%) | 628 (1.89%) | 1145 (1.70%) | 188 (2.42%) | 259 (2.86%) |
| Musculoskeletal system & 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, déformations, & 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\%) |

ART: Assisted reproductive technology; NCP: Naturally conceived population controls; sART: ART with siblings; NCS: Naturally conceived siblings
Table 2: Mean admission rate (number of admissions per year per child) in children with multiple admissions

| Category                                                | ART – NCP | sART - NCS |
|---------------------------------------------------------|-----------|-----------|
|                                                         |ART (N=37890) | Control (N=75642) |ART (N=25987) | Control (N=51902) |sART (N=8383) | Siblings (N=10871) |
| Overall                                                 | 0·0997    | 0·1046    | 0·1136    | 0·1317    | 0·0879    | 0·0994    |
| Infectious & 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 & immune system             | 0·0016    | 0·0027    | 0·0017    | 0·0033    | 0·0018    | 0·0052    |
| Endocrine, nutritional & metabolic disorders             | 0·0019    | 0·0024    | 0·0015    | 0·0021    | 0·0016    | 0·0022    |
| Mental, behavioural & 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 & adnexa                                             | 0·0021    | 0·0024    | 0·00305   | 0·0031    | 0·0017    | 0·0018    |
| Ear & 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 & subcutaneous tissue                               | 0·0024    | 0·0025    | 0·0021    | 0·0025    | 0·0023    | 0·0027    |
| Musculoskeletal system & 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; sART: ART with siblings; NCS: Naturally conceived siblings
| Comparison                                      | 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) |

HR: Hazards Ratio; NCP: Naturally conceived population controls; CI: Confidence interval; ICSI: Intracytoplasmic sperm injection; IVF: In-vitro fertilization
Figure 1 Presence/absence of hospital admission (HR & 95%CI) by sub-cohort and multiplicity

ART vs NCP: Singletons

| Condition                                                                 | ART vs NCP | ART vs NCP: Twins | ART vs NCS: Singletons |
|--------------------------------------------------------------------------|------------|------------------|------------------------|
| Overall child health                                                     | 1.08 (1.05,1.10) | 0.99 (0.97,1.02) | 1.01 (0.94,1.09) |
| Infectious & parasitic diseases                                          | 1.19 (1.13,1.25) | 1.10 (1.04,1.16) | 0.93 (0.79,1.11) |
| Neoplasm                                                                 | 1.21 (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, behavioural & 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 (1.00,1.09) | 0.92 (0.88,0.97) | 1.07 (0.93,1.23) |
| Digestive system                                                         | 1.02 (0.96,1.08) | 1.10 (1.03,1.17) | 1.28 (1.06,1.56) |
| Skin & subcutaneous tissue                                              | 0.91 (0.79,1.05) | 0.93 (0.78,1.11) | 0.54 (0.33,0.89) |
| Musculoskeletal system & connective tissue                              | 1.17 (1.01,1.34) | 1.04 (0.87,1.23) | 1.28 (0.74,2.16) |
| Genitourinary system                                                     | 1.21 (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 (0.73,0.86) | 0.84 (0.75,0.94) | 0.93 (0.72,1.19) |

Hazard Ratio (95%CI)

*HR: Hazard Ratio; CI: Confidence interval; NCP: naturally conceived population controls; NCS: naturally conceived siblings
Figure 2 Number of hospital admissions per year by diagnosis, sub-cohort, and multiplicity

*IRR: Incidence Rate Ratio; CI: Confidence interval; NCP: naturally conceived population controls; NCS: naturally conceived siblings