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Running title: ART and neurodevelopmental morbidity

The neurodevelopmental morbidity of children born after assisted reproductive technology: a Nordic register study from the Committee of Nordic Assisted Reproductive Technology and Safety group

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Capsule

Children born after ART have a higher risk of learning and motor functioning disorders, but not of other neurodevelopmental conditions. Type of ART did not associate with neurodevelopmental disorders.

Abstract

Objective: To study the risk of neurodevelopmental disorders in singletons born after the use of assisted reproductive technology (ART) compared with singletons born without the use of ART.

Design: Nordic register-based study

Setting: Cross-linked data from Medical Birth Registers and National ART- and Patient Registers; liveborn singletons in 1995-2014 in Denmark and Finland, 2005-2015 in Norway, and 1995-2015 in Sweden with follow-up to 2014 (Denmark and Finland) or 2015 (Norway and Sweden).

Patients: 5 076 444 singletons: 116 909 (2.3 %) born with and 4 959 535 (97.7 %) without the use of ART (non-ART).

Exposure(s): In vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), fresh and frozen embryo transfer.

Main Outcome Measures: Primary outcomes (ICD-10 codes): learning and motor functioning disorders (F80–F83), autism spectrum disorder (ASD; F84), attention-deficit hyperactivity disorders (ADHD) and conduct disorders (F90–F92), and tic disorders (F95). Crude (HR) and adjusted (aHR) hazard ratios with 95% confidence intervals were calculated.

Results: Singletons in ART cohort had a higher adjusted risk of learning and motor functioning disorders (HR 1.01 [0.96-1.07]; aHR 1.17 [1.11-1.24]), and tendency towards a higher risk of ASD (HR 1.12 [1.04-1.21]; aHR 1.07 [0.98-1.16]) and ADHD and conduct disorders (0.82 [0.77-0.86]; aHR 1.17 [0.99-1.12]), but not of tic disorders (1.21 [1.06-1.38]; aHR 1.17 [0.96-1.27]). No risk difference was found between children born after IVF and ICSI or after fresh and frozen embryo transfer.

Conclusion

Our findings of only small differences in neurodevelopment between ART and non-ART singletons are reassuring and in line with previous studies.

Keywords

assisted reproduction; attention deficit and hyperactivity disorder; autism spectrum disorder; learning and motor functioning disorder; tic disorder

Introduction

The knowledge on the impact of assisted reproductive technology (ART) on offspring neurodevelopmental morbidity is limited, and results from previous studies are inconsistent (1-12). Currently, on average 2-3%, of children in Europe and the United States are born after ART (13, 14). Improved availability and success rates of fertility treatments, as well as the postponement of starting a family and consequently lower natural fertility, partially explain the steadily increasing use of ART (14). As the use of ART is increasing, large populations with long-term follow-up are required to study long-term health after ART, especially for rare disorders. Such studies are needed to provide information for healthcare workers and couples undergoing ART treatment.

The incidence of neurodevelopmental disorders, especially autism spectrum disorders (ASD), increases worldwide (15-17). In the United States, ASD prevalence has increased within less than two decades, from 0.67% to 1.85% among 8-year-olds (18). In the Nordic countries, the overall prevalence of ASD in 7-to 9-year-olds in 2015 was 0.76–2.68% (19). Learning disabilities and attention-deficit hyperactivity disorders (ADHD) are the most common neurodevelopmental disorders, with an estimated prevalence of 7–8% each (20, 21).

Studies indicate either higher (5, 8, 10-12) or comparable risk of neurodevelopmental disorders for children born with or without the use of ART (1-4, 6, 7, 9). Even for the most studied neurodevelopmental disorders, namely ASD, the results are conflicting (1-3, 5, 7, 9, 11, 22, 23). The need for ART and the development of offspring ASD share many risk factors, including advanced parental age (24). Preterm deliveries, a risk factor for ASD, are more common in pregnancies after the use of ART (24-26). The risk of other neurodevelopmental disorders, like ADHD or tic disorder, is also debated, as studies are scarce.

This Nordic register study aims to assess the risk of neurodevelopmental disorders in singletons born after the use of ART. In comparison to prior studies with partially overlapping data (1, 7, 8, 10, 11, 22, 23, 27), the inclusion of the pooled complete birth cohorts provides the possibility to broaden the scope to other neurodevelopmental diagnoses than the most often studied ASD, and to assess the effect of the type of treatment (in vitro fertilization [IVF], intracytoplasmic sperm injection [ICSI], fresh and frozen embryo transfer). We hypothesized that the use of ART does not associate with neurodevelopmental diagnoses of singleton offspring.

Materials and Methods

The Committee of Nordic Assisted Reproductive Technology and Safety (CoNARTaS) cohort consists of all deliveries in Denmark, Finland, Norway, and Sweden from the year when each country started to collect data on the use of ART until the year 2014 or 2015. The cohort was established by cross-linking data from Medical Birth Registers (MBRs) and National ART- and Patients Registers (NPR) via the unique personal identification number allocated to every citizen and permanent resident in each Nordic country. The registries are described in greater detail previously (28).

Obstetric and perinatal data were obtained from the MBRs, where detailed information on maternal and neonatal health on all births is recorded during pregnancy and childbirth. For this study, data from the MBR included maternal age at delivery, parity, smoking during pregnancy, child's year of birth, sex registered at birth, and gestational age at birth. National ART Registers or Databases in Denmark, Norway, and Sweden provided data about fertilization method (IVF or ICSI), and type of embryo transfer (fresh or frozen). For Finland, data on the use of ART was retrieved from the MBR.

In the Nordic countries, the neurodevelopmental diagnoses are primarily set in specialized health care by a child or adolescent psychiatrists or pediatric neurologists and based on a multidisciplinary assessment. The NPRs provided data on children's neurodevelopmental diagnoses and parental psychiatric diagnoses. The NPRs have a high degree of completeness, and validity studies indicate positive predictive values in the range of 75–99%, depending on the country and diagnosis (28-32). The NPRs include diagnoses from in-hospital care since 1977 in Denmark, 1967 in Finland, 2008 in Norway, and 1987 in Sweden. In Denmark, diagnoses recorded on outpatient visits in specialized health care are included since 1995 in public hospitals and 2003 in private clinics. In Finland, outpatient visits in specialized health care in public hospitals have been included since 1998. Outpatient visits in specialized health care, in both public hospitals and private clinics, have been included since 2008 in Norway and 2001 in Sweden. The National Statistical Bureaus provided socioeconomic data from Denmark, Finland, and Sweden.

The study population included all singleton live births after the use of ART (IVF, ICSI, fresh or frozen embryo transfer) or without the use of ART (non-ART) in Denmark and Finland between 1995 and 2014, in Norway between 2005 and 2015, and in Sweden between 1995 and 2015. The non-ART cohort also includes children born after other medically assisted reproduction (MAR) treatment than ART, e.g., ovulation induction and intrauterine insemination. The flow chart of the children in the study is depicted in Supplemental figure 1. The total study population consisted of 5 076 444 children after excluding those who received a diagnosis of intellectual disability (International Statistical Classification of Diseases and Related Health Problems—Tenth Revision [ICD-10] codes F70–F79), i.e., syndrome or disorder characterized by low intelligence and associated limitations in adaptive behavior (33). Intellectual disabilities were exclusion criteria due to differences in diagnosing other neurodevelopmental diagnoses among children with F70–F79.

The children were followed from birth to the age at the first record of each outcome diagnosis, death, emigration (no data from Finland), 2014 in Denmark and Finland, and 2015 in Norway and Sweden. For Denmark, the follow-up period started in 1995. For Finland (1996) and Sweden (1997), the possibility to detect outcomes began when each country started to use ICD-10 codes. The follow-up was restricted to ICD-10 due to comparability problems with prior codes (ICD-8 in Denmark and ICD-9 in other countries) to ICD-10 codes. For Norway, the cross-linkage between MBR and the NPR was possible only from 2008. Therefore, for the earliest birth year cohorts, the follow-up for the outcomes starts from 0-3 years of age (children born in 1996 in Finland, 1995–1996 in Sweden, and 2005–2007 in Norway). Diagnoses received before (at ICD-8/ICD-9 period) were detected in the data when first was changed to ICD-10 code in the health care.

Exposures

Exposures were any ART, IVF, ICSI, fresh embryo transfer (either after IVF or ICSI), and frozen embryo transfer (either after IVF or ICSI).

Outcomes

The primary outcomes (ICD-10 codes) were defined as the first recorded contact with each of the following diagnoses: learning and motor functioning disorders (i.e., specific developmental disorders of speech and language, scholastic skills, or motor function; F80–F83), ASD (F84), ADHD and conduct disorders (F90–F92), and tic disorders (F95). All diagnoses were studied separately, as one child can have more than one diagnosis.

Statistical analyses

Descriptive statistics are presented as means with standard deviations (SD) and numbers with percentages. We also present Kaplan-Meier curves for diagnose-free follow-up time until 15 years

of age. After testing the proportional hazards assumptions, Cox regression analyses were used to estimate crude hazard ratios (HR) with 95 % confidence intervals (CI) of neurodevelopmental diagnoses in children in ART and non-ART cohorts. The main adjusted Cox regression analyses included all children with no missing information on background variables, and were adjusted for country, year of birth, offspring sex, maternal age at delivery (continuous), parity (number of prior deliveries, continuous), smoking during pregnancy (yes/no/missing), and maternal ever history of any psychiatric morbidity (ICD-8/9: 290–319, ICD-10: F00–99, yes/no).

The rate of preterm deliveries is higher among pregnancies after the use of ART compared with pregnancies without the use of ART (25). Further, preterm birth is associated with a higher risk of ASD (34) and ADHD (35). Gestational age was therefore considered as a mediator and not as a confounder.

Subgroup analyses stratified by offspring sex were made similarly, except without offspring sex as a confounder. Further subgroup analyses, including additional confounders compared to the main model, were performed according to the availability of the data. Information on maternal education was not available from Norway. Consequently, we adjusted for the highest obtained maternal education level (primary education, secondary or post-secondary non-tertiary education, bachelor's or equivalent or higher level, and unknown) in a subgroup including deliveries from Denmark, Finland, and Sweden. Subgroup analyses of deliveries from Denmark and Sweden were made to adjust for ever history of paternal psychiatric morbidity (ICD-8/9: 290–319, ICD-10: F00–99, yes/no), and from Norway and Sweden to adjust for paternal age (continuous).

To assess the effect of the type of ART, subgroup analyses were made to estimate crude and adjusted HR of neurodevelopmental diagnoses between children born after specific types of ART

(ICSI vs. IVF and frozen vs. fresh embryo transfer). The adjusted Cox regressions for these analyses included the same confounders as the main analyses. As the information on the type of ART was not available in Finland, these analyses included only data from Denmark, Norway, and Sweden.

The associations of maternal background characteristics with the offspring's outcomes were assessed within the main adjusted Cox regression model. Lastly, to assess possible time trends, adjusted Cox regression for children born with and without the use of ART was made stratified by five-year intervals of the year of birth (1995–1999, 2000–2004, 2005–2009, and 2010–2014/2015).

The analyses were performed using SAS software (version 9.4), SAS Institute Inc., North Carolina, USA.

Ethical approval

In Denmark and Finland, ethical approval is not required for scientific projects based solely on registry data and with no personal involvement of the participants. For Norway and Sweden, the Institutional Review Boards approved the study: the Regional Committee for Medical and Health Research Ethics in Norway and the scientific Ethics Committee in Gothenburg in Sweden (28). The registry-keeping authorities approved data retrieval in each country (28). No informed consent is required for register-based studies in Nordic countries.

Results

Table 1 presents the characteristics of the included 5 076 444 singleton live births: 116 909 (2.3 %) after the use of ART and 4 959 535 (97.7 %) without the use of ART. In ART pregnancies, both mothers and fathers were older at delivery and less likely to have a psychiatric diagnosis during

follow-up than parents of the singletons born without the use of ART. Mothers with ART pregnancies had higher education levels at the end of follow-up, were more often nulliparous, and were less likely to smoke during pregnancy than mothers with non-ART pregnancies (Table 1).

The proportion of children born after the use of ART increased during the study period from 1.3% during the first quartile to 3.2% during the last (Table 1). The average follow-up time was 7.8 years (SD 5.4) and 9.6 years (SD 5.8) for children born with and without the use of ART.

Overall, the most common neurodevelopmental disorders were ADHD and conduct disorders with an incidence proportion of 1.74% (n = 88 471), followed by learning and motor functioning disorders (1.40%, n=70 914), ASD (0.66%, n=33 394), and tic disorders (0.22%, n=11 236) (Table 2). Figure 1 shows the Kaplan-Meier curves of diagnosis-free follow-up time until 15 years of age for children born with and without the use of ART.

Learning and motor functioning disorders (F80–F83)

In the crude Cox regression, there was no difference in the risk for learning and motor functioning disorders between children born with and without the use of ART (Table 2). However, after adjusting for confounding factors, the risk was higher among children born after the use of ART. When analyzed separately, the higher risk after adjustments was seen among both boys and girls. Further adjustments for maternal education (Supplemental table 1), paternal psychiatric morbidity (Supplemental table 2), or paternal age (Supplemental table 3) did not change the results.

Autism spectrum disorders (F84)

Children born after the use of ART had in the crude Cox regression a higher risk of ASD diagnosis than children born without ART (Table 2). After adjustment, the point estimate was lower, with a

tendency for higher risk among children born after the use of ART. In subgroup analyses stratified by child sex, the higher crude risk, and the tendency for higher adjusted risk was seen only among boys. Additional adjustments did not change the results in further subgroup analyses, except when adjusting for paternal psychiatric morbidity (Supplemental tables 1-3).

Attention-deficit hyperactivity disorders and conduct disorders (F90- F92)

The risk of ADHD and conduct disorders in crude Cox regression was lower among children born with than without the use of ART, also in boys. However, after adjustments, a tendency towards higher risk of ADHD and conduct disorders was observed among children born after the use of ART. After additional adjustment for paternal psychiatric morbidity (Supplemental table 2) and paternal age (Supplemental table 3), children born after the use of ART had a higher risk of ADHD and conduct disorders.

Tic disorders (F95)

Children born after the use of ART, compared to no use of ART had higher risk of tic disorder in the crude analysis, but after adjustment, no difference was seen (Table 2 and Supplemental tables 1-3).

Type of assisted reproductive technology

In adjusted models, there was no association between the type of ART (IVF vs. ICSI and fresh vs. frozen ET) and the risk of neurodevelopmental disorders (Table 3).

Associations with maternal factors and time trends

ART was only associated with learning and motor functioning disorders in the main adjusted model. Maternal psychiatric morbidity was the strongest maternal predictor in the main model for

all the assessed outcomes (Supplemental table 4). Another predictor for all offspring neurodevelopmental diagnoses was smoking during pregnancy. Further, higher parity was associated with a higher risk of learning and motor functioning disorders, ADHD and conduct disorders, and a lower risk for ASD and tic disorders. No time trend in the HRs for the four assessed outcomes was seen when stratifying the analysis by five-year periods.

Discussion

In this cohort, children born after the use of ART had a higher risk of learning and motor functioning disorders and a tendency towards higher risk for ASD and ADHD and conduct disorders compared with children born without the use of ART. No difference was found in the risk of neurodevelopmental disorders between children born after IVF versus ICSI or after fresh versus frozen embryo transfer.

A systematic review from 2013 by Hart and Norman, based on studies including either singletons only or all children, concluded that children born with and without the use of ART have similar cognitive scores, school performance, and neuromotor development (6). In two more recent large Swedish studies, the overall school performance of children born after the use of ART was, in the crude analysis, slightly better compared with other children, both when including multiples (36) and in singletons only (37) while in the adjusted analyses slightly lower school performances were noticed. Similar findings have been published from a Danish cohort of singletons (38). In a Danish study of 4 294 singletons and twins up to 18 years old, children born with and without the use of ART had a similar cumulative prevalence of various psychiatric and neurodevelopmental disorders, including specific disorders of development (defined as ICD-10 F80–F83) (27). In contrast, after adjustments for confounding factors, the risk of learning and motor functioning disorders in our

cohort was higher in singletons born after the use of ART. The smaller sample size and unadjusted analyses in the Danish study may explain the difference in the findings.

Most previous studies suggesting a higher risk of ASD among children born after the use of ART include a notable proportion of multiple pregnancies (5, 22). In the largest cohort study to date, including 5 926 251 children (of whom 48 865 were born after ART [>50% multiples]), in California, the incidence of ASD was twice as high for children born with than without the use of ART (5). Our results of no association of ASD with ART are in line with previous analyses restricted to singletons (11, 22, 23, 26, 39).

In a small cross-sectional survey among young adults born after IVF, the combined incidence of attention deficit disorder and ADHD was relatively high, 27.1%, compared with estimations of prevalence among the general population (40). A weak association between ADHD and ART conception was found in a Swedish study of 2.4 million children born 1982–2005, including both singletons and multiples (8). Like in our study, however, no difference in risk of ADHD and conduct disorders was present among singletons only (adjusted Odds Ratio 1.05 [95% CI 0.89-1.23]) (8). Further, in a more recent Swedish study of children born in 1996–2012, the adjusted risk of ADHD was similar in children born with and without the use of ART (aHR 1.05 [95% CI 1.00-1.09] (36).

Tic disorders were not associated with the use of ART in our cohort, in line with smaller studies from Japan and Denmark (12, 27). In a larger Danish cohort, including 588 967 children (including singletons and multiples) aged 8–17 years, the risk of tic disorders was higher among children born with than without the use of ART (aHR 1.40 [95% CI 1.01-1.95]) (1). In analyses restricted to singletons, the association attenuated (1).

In our cohort, the use of ART was associated with a higher risk of learning and motor functioning disorders. Other background factors were, however, stronger predictors for offspring neurodevelopmental morbidity. Maternal psychiatric morbidity was the strongest predictor of offspring neurodevelopmental diagnoses, consistent with previous observations that parental depression or other psychiatric morbidity is associated with a higher risk of ASD and ADHD (41, 42).

Advanced parental age is associated with ASD and pervasive developmental disorders (43, 44). However, in our cohort, the association with maternal age was minimal, and associations with risk of learning and motor functioning disorders, ADHD and conduct disorders persisted after additional adjustment for paternal age.

It has been suggested that the association of ART with offspring morbidity may be secondary to the underlying reason for subfertility or infertility (6, 45-47). In a case-control study including 1 538 2–5-year-old children in the United States, maternal infertility diagnosis was associated with a higher risk for ASD (47), but not with ART or non-ART infertility treatments and ASD (47). Polycystic ovary syndrome and anovulatory infertility were associated with a higher risk of offspring's specific developmental disorders (F80–83), ASD (F84), ADHD and conduct disorders (F90–91), and tic disorders (F95) in a large Finnish cohort (45). However, the use of any fertility treatment had a small additive effect on the risk of all the above-mentioned neurodevelopmental disorders (45).

Male-factor infertility has been suggested to be associated with a risk of mental retardation and autism (46). In a Swedish study, offspring ASD was associated with ICSI using surgically extracted sperm compared with IVF (11). Similarly, in a study from the United States, a higher risk of autism

was found when ICSI was used over IVF (48). However, in analyses within the male-factor infertility subgroup, the association attenuated (48). Similar findings come from other studies (11, 47). Compared to some countries, where ICSI is used in most cycles (14), ICSI in the Nordic countries is mainly used in cases of male-factor infertility or fertilization failure after IVF. Since we lack sufficient information on male-factor infertility, it is not possible to draw any conclusions on the potential association between male factor infertility and offspring neurodevelopment. Our results of similar risk of neurodevelopmental disorders between children born with and without the use of ART are nonetheless reassuring. Moreover, in line with our results, ICSI compared to IVF or frozen compared to fresh embryo transfers were not associated with the risk of ADHD in a Swedish cohort (49).

Strengths and weaknesses

A major strength of this study is the large sample, with a complete birth cohort of singletons and their mothers from the four Nordic countries. Health data pooling is justified, as the Nordic countries are comparable in demography, health care, and social security systems. Meanwhile, this relatively homogeneous population limits the generalizability of the findings. Registries with prospectively collected data, a low proportion of missing data, and high validity limit selection bias (28-32).

Another strength is that the diagnoses used in this study are mainly set by a child or adolescent psychiatrists or pediatric neurologists. To increase the comparability, only ICD-10 codes were included. In the Nordic countries, all children are entitled to equal, free of charge and comprehensive public health care, including child health clinics and school health care that refer patients to specialist health care if needed. As the Nordic countries publicly subsidize ART

treatment, medical indication rather than the couple's financial situation mainly determines the use of ART, limiting selection bias (28, 50).

An additional strength is the opportunity to explore the association separately for IVF and ICSI, and fresh and frozen embryo transfers, and the risk of neurodevelopmental disorders. Further, we were able to adjust for several known confounders.

Limitations relate mainly to differences in registration practice and data availability in each country. Parental factors, especially paternal factors like age and psychiatric morbidity, were not available in all countries, limiting the possibility to use them as confounders in the main analyses. Additionally, we acknowledge that our control group includes children born after the use of ovulation induction and intrauterine insemination. Other MAR treatments than ART are only registered in Denmark (since 2007) and Finland (since 2004). However, the numbers are low compared to the large size of the whole cohort and would have no or only minor effect on our results. Similarly, as we lack data on duration and cause of infertility (28), also the control group includes children born without the use of any MAR treatments to couples with underlying infertility issues. With our data we cannot therefore separate the effect of infertility problems and MAR treatments. Further, we cannot exclude residual confounding due to unknown or suspected confounders, such as substance use other than self-reported smoking status during pregnancy, information on perinatal vitamin supplementation, and maternal somatic morbidity.

Some limitations are related to the length of the study period. Changes in the ART treatments might impact on the offspring outcomes, but we lack details of stimulation protocols, embryology laboratory methods, and data from the most recent years. No time trend was detected, however. Changes in diagnostic practice and increasing awareness of neurodevelopmental disorders may

influence the registration of outcomes (16). As the proportion of children born after the use of ART increased during the study period, such changes may have influenced the two cohorts of children differently. The increase in the proportion of children born after the use of ART explains the shorter follow-up of the ART cohort. Lastly, as most neurodevelopmental diagnoses are set after 3-4 years of age, follow-up may not be sufficient for the youngest children.

Conclusions

While the risk of learning and motor functioning disorders in this study was higher among singletons born after the use of ART, the risks were small. Our results are reassuring and support prior literature of mostly comparable neurodevelopment between singletons born with and without the use of ART. This information is essential for both healthcare workers and couples undergoing ART treatment. Future directions include studies with longer follow-up of the most recent birth cohorts with the possibility to study the effect of new techniques in assisted reproduction.

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Author contributions

M.G. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in the study design. M.G., S.R., A.L.S., A.A.H., and S.O. harmonized and merged data. M.G. analyzed the data, and K.R. drafted the first version of the manuscript. All authors contributed to interpreting the data and writing, approved the final manuscript, and agreed upon the authors' listing.

Conflict of interest disclosures

The authors have no conflicts of interest related to this study.

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Figure legends

Figure 1 Kaplan-Meier curves of diagnose free follow-up time for neurodevelopmental disorders as percentages of the cohorts of Nordic singletons born after the use of assisted reproductive technology (ART) and without the use of ART (non-ART).
(A) learning and motor functioning disorders (F80–83) (B) autism spectrum disorders (F84) (C) attention-deficit hyperactivity disorders and conduct disorders (F90-92) and (D) tic disorders (F95)

Supplemental figure 1 Flow chart of Nordic children in the study. The cohort includes deliveries from Denmark and Finland between 1995 and 2014, Norway between 2005 and 2015, and Sweden between 1995 and 2015.

Table 1 Characteristics of Nordic singleton live births after the use of assisted reproductive technology (ART) and without the use of ART (non-ART)[a]

	ART (n = 116 909)	**non-ART (n = 4 959 535)**	**p-value**
Country, n (%)			
Sweden	47 433 (40.6)	1 989 122 (40.1)	
Denmark	30 928 (26.5)	1 201 939 (24.2)	<0.001
Finland	20 735 (17.7)	1 107 990 (22.3)	
Norway	17 813 (15.2)	660 484 (13.3)	
Offspring characteristics			
Year of birth, n (%)			
1995–1999	13 574 (11.6)	1 030 065 (20.8)	
2000–2004	19 489 (16.7)	1 013 226 (20.4)	<0.001
2005–2009	33 669 (28.8)	1 366 757 (27.6)	
2010–2015	50 177 (42.9)	1 549 487 (31.2)	
Boys, n (%)	59 703 (51.1)	2 544 412 (51.3)	0.111
Sex unknown	2 (0.00)	62 (0.00)	
Gestational age at birth (weeks), mean ± SD	39.5 ± 2.2	39.8 ±1.8	<0.001
Gestational age at birth unknown	1 301 (1.1)	76 968 (1.6)	
Preterm birth (< 37 weeks)	8 928 (7.6)	229 483 (4.6)	<0.001
Maternal characteristics			
Age at delivery, mean ± SD	34.0 ± 4.3	30.2 ± 5.2	<0.001
Age at delivery unknown	0 (0.0)	4 (0.0)	
Age at delivery, n (%)			
<25	1 602 (1.4)	699 967 (14.1)	
25–29	16 735 (14.3)	1 538 505 (31.0)	
30–34	45 079 (38.6)	1 708 688 (34.5)	<0.001
35–39	41 208 (35.2)	827 619 (16.7)	
≥40	12 285 (10.5)	184 752 (3.7)	
Psychiatric disorder (ever), n (%)	15 872 (13.6)	781 268 (15.8)	<0.001
Highest education at the end of follow-up, n (%)[b]			
Primary education	6 663 (6.7)	523 595 (12.2)	
Secondary or post-secondary non tertiary education	42 671 (43.1)	2 019 422 (47.0)	<0.001
Bachelor's or equivalent or higher level	46 723 (47.1)	1 535 685 (35.7)	
Unknown	3 039 (0.3)	220 349 (5.1)	
Nulliparous, n (%)	78 966 (67.5)	2 107 348 (42.5)	<0.001
Parity unknown	650 (0.6)	33 356 (0.7)	
Smoking during pregnancy, n(%)	5 979 (5.1)	582 078 (11.7)	<0.001
Smoking status unknown	4 879 (4.2)	257 689 (5.2)	
Paternal characteristics			
Age at offspring birth, mean ± SD [c,d]	36.7 ± 5.7	33.1 ± 6.2	<0.001
Age at offspring birth, n (%)[c,d]			
<25	260 (6.5)	171 373 (0.4)	<0.001
25–29	4912 (21.9)	58 0314 (7.5)	

30–34	18 967 (33.6)	890 832 (29.1)	
35–39	22 763 (23.0)	610 019 (34.9)	
40–	17 631 (13.9)	367 457 (27.0)	
Unknown (excluding countries with no information)	713 (1.1)	29 611 (1.1)	
Psychiatric disorder (ever), n (%)[b,c]	3 704 (4.7)	188 687 (5.9)	<0.001
ART procedure, n (%)[c]			
Method of fertilization			
IVF	52 160 (54.1)		
ICSI	37 504 (38.9)		
IVF + ICSI	1 374 (1.4)		
Non-ejaculated sperm[e]	2 129 (2.2)		
Unknown	3 173 (3.3)		
Embryo transfer			
Fresh	76 194 (79.1)		
Frozen	18 563 (19.3)		
Unknown	1 583 (1.6)		

[a]Data available for 1995–2014 in Denmark and Finland, 1995–2015 in Sweden; and 2005–2015 in Norway
[b]No data available from Norway
[c]No data available from Finland
[d]No data available from Denmark
[e]Testicular Sperm Aspiration (TESA), Testicular Sperm Extraction (TESE), Microsurgical Epididymal Sperm Aspiration (MESA), Percutaneous Epididymal Sperm Aspiration (51)
IVF = *in vitro* fertilization, ICSI = intracytoplasmic sperm injection

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Table 2 Neurodevelopmental diagnoses for Nordic singleton live births after the use of assisted reproductive technology (ART) and without the use of ART (non-ART)[a]

	ART n (%)	non-ART n (%)	ART n/1000 person years	non-ART n/1000 person years	Crude HR[b] (95% CI)	aHR[b] (95% CI)
All	**n = 116 909**	**n = 4 959 535**	**876 144 person years**	**46 181 452 person years**		
Learning and motor functioning disorders (F80–83)	1334 (1.1)	69580 (1.4)	1.5	1.5	1.01 (0.96-1.07)	1.17 (1.11-1.24)
Autism spectrum disorders (F84)	628 (0.5)	32766 (0.7)	0.7	0.7	1.12 (1.04-1.21)	1.07 (0.98-1.16)
Attention-deficit hyperactivity disorders and conduct disorders (F90–92)	1162 (1.0)	87309 (1.8)	1.3	1.9	0.82 (0.77-0.86)	1.05 (0.99-1.12)
Tic disorders (F95)	222 (0.2)	11 014 (0.2)	0.3	0.2	1.21 (1.06-1.38)	1.10 (0.96-1.27)
Boys	**n = 59 703**	**n = 2 544 412**	**442 755 person years**	**23 425 588 person years**		
Learning and motor functioning disorders (F80–83)	933 (1.6)	48 706 (1.9)	2.1	2.1	1.01 (0.95–1.08)	1.16 (1.09–1.24)
Autism spectrum disorders (F84)	471 (0.8)	23 683 (0.9)	1.1	1.0	1.14 (1.04–1.24)	1.08 (0.98–1.19)
Attention-deficit hyperactivity disorders and conduct disorders (F90–92)	848 (1.4)	61 349 (2.4)	1.9	2.6	0.83 (0.77–0.89)	1.07 (0.996–1.15)
Tic disorders (F95)	158 (0.3)	8 325 (0.3)	0.4	0.4	1.13 (0.97–1.30)	1.06 (0.90–1.25)
Girls	**n = 57 204**	**n = 2 415 061**	**433 389 person years**	**22 755 864 person years**		
Learning and motor functioning disorders (F80–83)	401 (0.7)	20 874 (0.9)	0.9	0.9	1.02 (0.92–1.13)	1.20 (1.09–1.33)
Autism spectrum disorders (F84)	157 (0.3)	9083 (0.4)	0.4	0.4	1.08 (0.92–1.27)	1.04 (0.88–1.22)
Attention-deficit hyperactivity disorders and conduct disorders (F90–92)	314 (0.5)	25960 (1.1)	0.7	1.1	0.78 (0.70–0.88)	1.02 (0.91–1.14)
Tic disorders (F95)	64 (0.1)	2689 (0.1)	0.1	0.1	1.42 (1.11–1.82)	1.23 (0.96–1.58)

[a]Data available for 1995–2014 in Denmark and Finland, 1995–2015 in Sweden; and 2005–2015 in Norway

[b]Cox regressions; aHR adjusted for country, year of birth, offspring sex (for analyses of all children), mother's age at delivery, parity, smoking during pregnancy, and maternal psychiatric morbidity

HR= Hazard Ratio, CI = Confidence Interval

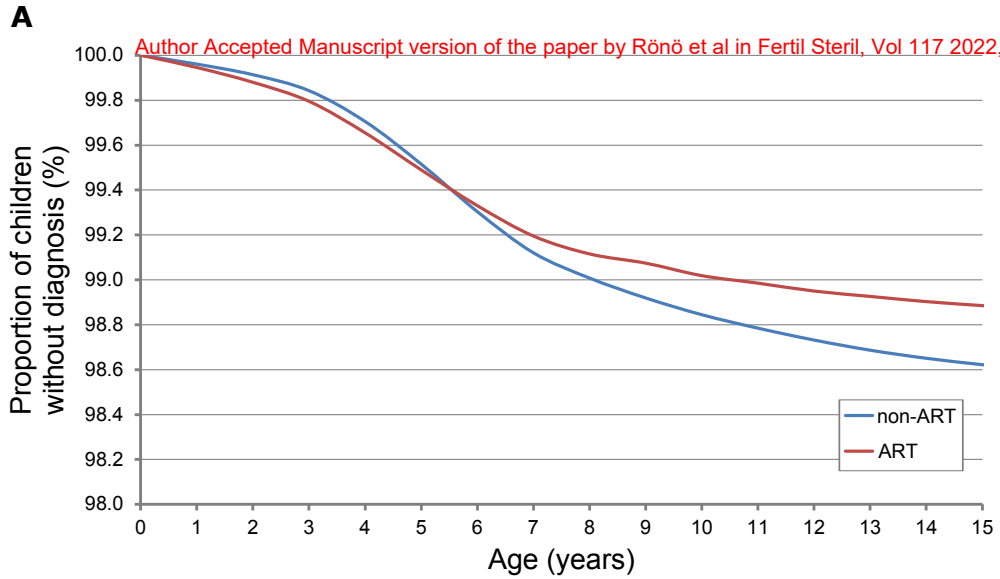
Table 3 Neurodevelopmental diagnoses for Danish, Norwegian, and Swedish singleton live births after the use of assisted reproductive technology (ART) by method of fertilization[a]

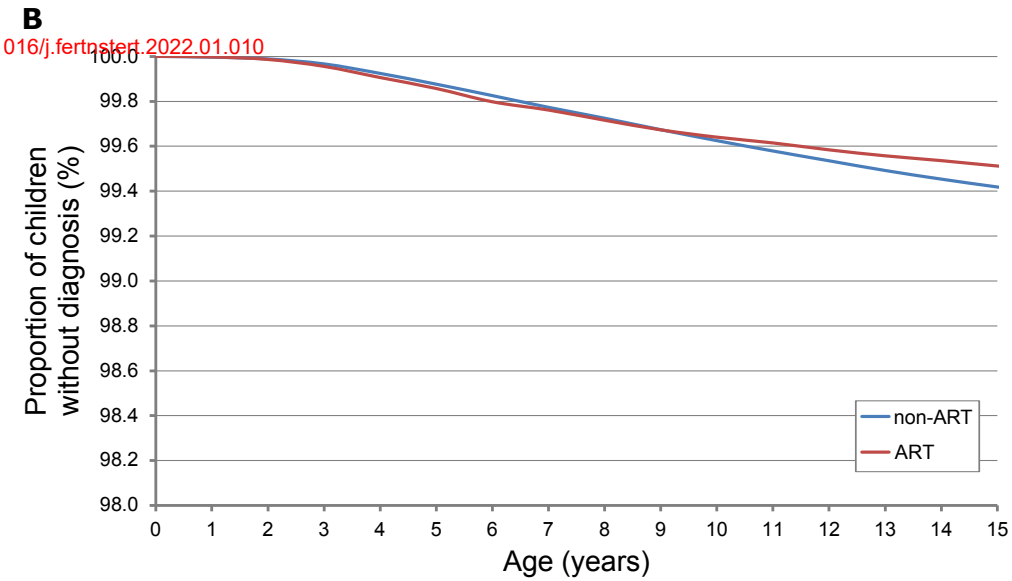
	Type of ART				Crude HR[b] (95% CI)	aHR[b] (95% CI)
Method of fertilization	**ICSI, n (%) n=37 504**	**IVF, n (%) n=52 160**	**ICSI, n/1000 person years; 252 840 person years**	**IVF, n/1000 person years; 370 715 person years**		
Learning and motor functioning disorders (F80–83)	239 (0.6)	316 (0.6)	0.9	0.9	1.19 (1.01–1.41)	1.07 (0.90–1.27)
Autism spectrum disorders (F84)	176 (0.5)	304 (0.6)	0.7	0.8	1.06 (0.88–1.27)	0.97 (0.84–1.13)
Attention-deficit hyperactivity disorders and conduct disorders (F90–92)	317 (0.8)	511 (1.0)	1.3	1.4	1.18 (1.03–1.36)	1.03 (0.84–1.22)
Tic disorders (F95)	63 (0.2)	77 (0.1)	0.2	0.2	1.40 (1.01–1.94)	0.90 (0.73–1.11)
Type of embryo transfer	**Frozen, n (%) n=18 563**	**Fresh, n (%) n=76 194**	**Frozen, n/1000 person years; 101 949 person years**	**Fresh, n/1000 person years; 562 663 person years**		
Learning and motor functioning disorders (F80–83)	115 (0.6)	459 (0.6)	1.1	0.8	1.38 (1.13–1.70)	0.93 (0.77–1.13)
Autism spectrum disorders (F84)	75 (0.4)	416 (0.5)	0.7	0.7	1.22 (0.95–1.56)	1.18 (0.84–1.65)
Attention-deficit hyperactivity disorders and conduct disorders (F90–92)	115 (0.6)	749 (1.0)	1.1	1.3	1.18 (0.97–1.44)	0.88 (0.68–1.15)
Tic disorders (F95)	20 (0.1)	126 (0.2)	0.2	0.2	1.08 (0.67–1.73)	0.76 (0.47–1.24)

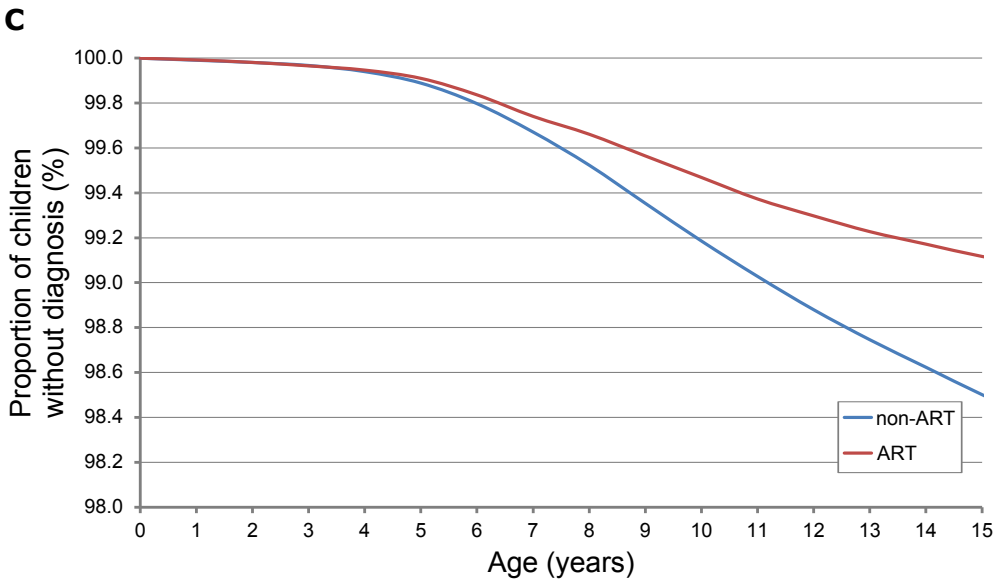
[a]Data available for 1995–2014 in Denmark, 1995–2015 in Sweden; and 2005–2015 in Norway

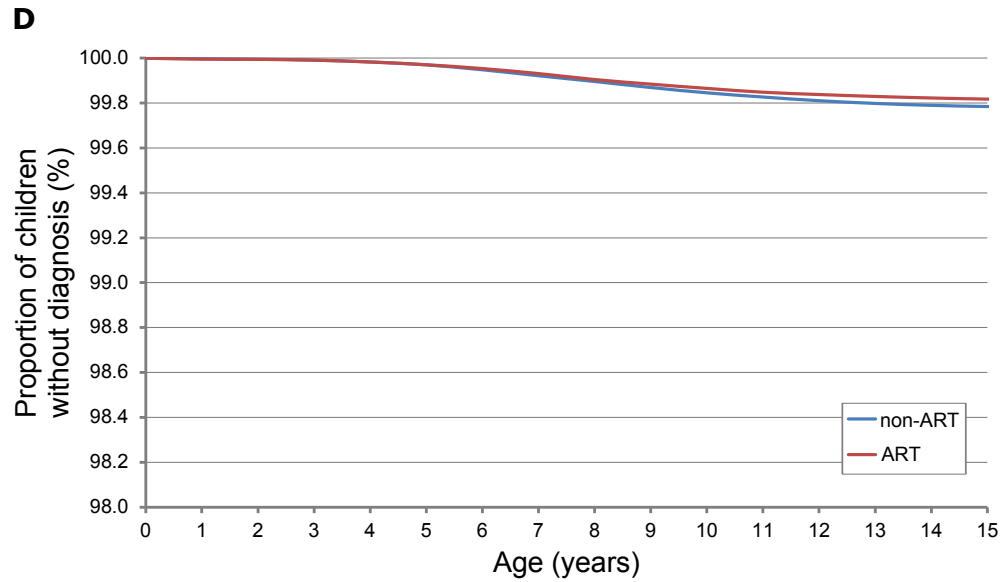
[b]Cox regressions; aHR adjusted for country, year of birth, sex, mother's age at delivery, parity, smoking during pregnancy, and maternal psychiatric morbidity

IVF = *in vitro* fertilization, ICSI = intracytoplasmic sperm injection, HR = Hazard Ratio, CI = Confidence Interval, y = years of follow-up









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Supplemental table 1 Neurodevelopmental diagnoses for Nordic singleton live births after the use assisted reproductive technology (ART) and without the use of ART (non-ART) in countries (Denmark, Finland, and Sweden) with data of maternal education available[2]

	ART n (%)	non-ART n (%)	ART n/1000 person years	non-ART n/1000 person years		
	n=99 262	n=4 305 367	804 823 person years	43 319 241 person years	Crude HR[b] (95% CI)	aHR[b] (95% CI)
Learning and motor functioning disorders (F80–83)	1226 (1.2)	65 516 (1.5)	1.5	1.5	1.01 (0.96–1.07)	1.18 (1.12–1.25)
Autism spectrum disorders (F84)	597 (0.6)	31 521 (0.7)	0.7	0.7	1.13 (1.04–1.23)	1.08 (0.99–1.17)
Attention-deficit hyperactivity disorders and conduct disorders (F90–92)	1128 (1.1)	85 975 (2.0)	1.4	2.0	0.81 (0.77–0.86)	1.05 (0.99–1.12)
Tic disorders (F95)	205 (0.2)	10 365 (0.2)	0.3	0.2	1.21 (1.06–1.39)	1.12 (0.97–1.29)

[a]Data available for 1995–2014 in Denmark and Finland, 1995–2015 in Sweden
[b]Cox regressions; aHR adjusted for country, year of birth, sex, mother's age at delivery, parity, smoking during pregnancy, maternal psychiatric morbidity, and highest maternal educational level at the end of follow-up
HR = Hazard Ratio, CI = Confidence Interval

Supplemental table 2 Neurodevelopmental diagnoses for Nordic singleton live births after the use assisted reproductive technology (ART) and without the use of ART (non-ART) in countries (Denmark and Sweden) with data of paternal psychiatric morbidity available[2]

	ART n (%)	non-ART n (%)	ART n/1000 person years	non-ART n/1000 person years		
	n=78 527	n=3 197 377	600 658 person years	31 642 433 person years	Crude HR[b] (95% CI)	aHR[b] (95% CI)
Learning and motor functioning disorders (F80–83)	481 (0.6)	23 278 (0.7)	0.8	0.7	1.07 (0.98–1.08)	1.17 (1.07–1.28)
Autism spectrum disorders (F84)	465 (0.6)	25 076 (0.8)	0.8	0.8	1.09 (0.99–1.93)	1.15 (1.05–1.27)
Attention-deficit hyperactivity disorders and conduct disorders (F90–92)	831 (1.1)	60 741 (1.9)	1.4	1.9	0.85 (0.79–0.91)	1.16 (1.08–1.25)
Tic disorders (F95)	131 (0.2)	7009 (0.2)	0.2	0.2	1.05 (0.89–1.25)	1.16 (0.97–1.38)

[a]Data available for 1995–2014 in Denmark and 1995–2015 in Sweden
[b]Cox regressions; aHR adjusted for country, year of birth, sex, mother's age at delivery, parity, smoking during pregnancy, maternal psychiatric morbidity, and paternal psychiatric morbidity
HR = Hazard Ratio, CI = Confidence Interval

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Supplemental table 3 Neurodevelopmental diagnoses for Nordic singleton live births after the use assisted reproductive technology (ART) and without the use of ART (non-ART) in countries (Norway and Sweden) with data of faters age available[2]

	ART n (%) n=65 246	non-ART n (%) 2 649 606	ART n/1000 person years 442 006 person years	non-ART n/1000 person years 22 916 390 person years	Crude HR[b] (95% CI)	aHR[b] (95% CI)
Learning and motor functioning disorders (F80–83)	560 (0.9)	26 091 (1.0)	1.3	1.1	1.13 (1.04–1.22)	1.17 (1.07–1.28)
Autism spectrum disorders (F84)	437 (0.7)	23 570 (0.9)	1.0	1.0	1.12 (1.02–1.23)	1.08 (0.98–1.19)
Attention-deficit hyperactivity disorders and conduct disorders (F90–92)	760 (1.2)	57 455 (2.2)	1.7	2.5	0.87 (0.81–0.94)	1.10 (1.02–1.19)
Tic disorders (F95)	139 (0.2)	7 210 (0.3)	0.3	0.3	1.12 (0.95–1.33)	1.10 (0.92–1.31)

[a]Data available for 2005–2015 in Norway and 1995–2015 in Sweden
[b]Cox regressions; aHR adjusted for country, year of birth, sex, mother's and father's age at delivery, parity, smoking during pregnancy, and maternal psychiatric morbidity
HR = Hazard Ratio, CI = Confidence Interval

Supplemental table 4 Associations of maternal covariates in adjusted Cox regression model with cumulative incidences of neurodevelopmental diagnoses in Nordic singleton live births (N = 5 076 444)[a]

	Learning and motor functioning disorders (F80-83) HR (95% CI)	Autism spectrum disorders (F84) HR (95% CI)	Attention-deficit hyperactivity disorders and conduct disorders (F90-92) HR (95% CI)	Tic disorders (F95) HR (95% CI)
Maternal age at delivery (years)	0.99 (0.99-0.99)	1.01 (1.00-1.01)	0.96 (0.96-0.96)	1.00 (0.99-1.00)
Parity (number of prior deliveries)	1.04 (1.03-1.05)	0.88 (0.87-0.89)	1.03 (1.03-1.04)	0.83 (0.81-0.85)
Smoking during pregnancy	1.26 (1.23-1.28)	1.25 (1.21-1.28)	1.80 (1.77-1.82)	1.16 (1.11-1.21)
Maternal psychiatric morbidity	1.67 (1.64-1.70)	2.58 (2.42-2.54)	2.59 (2.55-2.63)	2.01 (1.93-2.10)
Use of assisted reproductive technology	1.18 (1.11-1.24)	1.07 (0.99-1.16)	1.06 (0.99-1.12)	1.11 (0.97-1.27)

[a]Adjusted for country, year of birth and sex. Data available for 1995–2014 in Denmark and Finland, 2005–2015 in Norway, and 1995–2015 in Sweden
HR= Hazard Ratio, CI = Confidence Interval