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ORIGINAL ARTICLE *Reproductive epidemiology*

Early childhood respiratory tract infections according to parental subfertility and conception by assisted reproductive technologies

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STUDY QUESTION: Are children conceived by ART or born to subfertile parents more susceptible to upper or lower respiratory tract infections (URTI, LRTI)?

SUMMARY ANSWER: ART-conceived children had a higher frequency of and risk of hospitalization for respiratory infections up to age 3, which was only partly explained by parental subfertility.

WHAT IS KNOWN ALREADY: Some studies report increased risks of infections in children conceived by ART. Results for URTIs and LRTIs are inconclusive, and the contribution of underlying parental subfertility remains unclear.

STUDY DESIGN, SIZE, DURATION: We included 84 102 singletons of the Norwegian Mother, Father and Child Cohort Study (MoBa) born between 1999 and 2009. Mothers reported time-to-pregnancy at recruitment and child history of, frequency of and hospitalization for, respiratory infections when the child was 6, 18 and 36 months old by questionnaires. Subfertility was defined as having taken 12 or more months to conceive. The Medical Birth Registry of Norway (MBRN) provided information on ART. URTI included throat and ear infections, while LRTI included bronchitis, bronchiolitis, respiratory syncytial virus and pneumonia.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We used log-binomial regression to estimate risk ratios (RR) and 95% CI of any respiratory tract infection and hospitalization, and negative-binomial regression to calculate incidence rate ratios (IRR) and 95% CI for number of infections. We compared children conceived by ART, and naturally conceived children of subfertile parents, to children of fertile parents (<12 months to conceive) while adjusting for maternal age, education, BMI and smoking during pregnancy and previous livebirths. We accounted for dependency between children born to the same mother.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 7334 (8.7%) singletons were naturally conceived by subfertile parents and 1901 (2.3%) were conceived by ART. Between age 0 and 36 months, 41 609 (49.5%) of children experienced any URTI, 15 542 (18.5%) any LRTI and 4134 (4.9%) were hospitalized due to LRTI. Up to age 3, children conceived by ART had higher frequencies of URTI (adjusted IRR (aIRR) 1.16; 95% CI 1.05–1.28) and hospitalizations due to LRTI (adjusted RR (aRR) 1.25; 95% CI 1.02–1.53), which was not seen for children of subfertile parents. Children conceived by ART were not at higher risks of respiratory infections up to age 18 months; only at age 19–36 months, they had increased risk of any LRTI (aRR 1.16; 95% CI 1.01–1.33), increased frequency of LRTIs (IRR 1.22; 95% CI 1.02–1.47) and a higher risk of hospitalization for LRTI (aRR 1.35; 95% CI 1.01–1.80). They also had an increased frequency of URTIs (aIRR; 1.19; 95% CI 1.07–1.33). Children of subfertile parents only had a higher risk of LRTIs (aRR 1.09; 95% CI 1.01–1.17) at age 19–36 months.

LIMITATIONS, REASONS FOR CAUTION: Self-reported time-to-pregnancy and respiratory tract infections by parents could lead to misclassification. Both the initial participation rate and loss to follow up in the MoBa limits generalizability to the general Norwegian population.

WIDER IMPLICATIONS OF THE FINDINGS: ART-conceived children might be more susceptible to respiratory tract infections in early childhood. This appears to be only partly explained by underlying parental subfertility. Exactly what aspects related to the ART procedure might be reflected in these associations need to be further investigated.

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Key words: MoBa / MBRN / respiratory infections / ART outcome / subfertility / child health

Introduction

Among all deliveries in Norway in 2021, 4.5% were conceived using ART; and globally an estimated one in four couples need assistance to conceive (Mascarenhas *et al.*, 2012; Banker *et al.*, 2021). The association of ART with adverse pregnancy, maternal and perinatal outcomes is well established (Pinborg *et al.*, 2013; Qin *et al.*, 2016; Elias *et al.*, 2020). Consequently, several studies have described an increased risk of hospitalization during the neonatal period among children conceived by ART (Finnstrom *et al.*, 2011; Hwang *et al.*, 2018). According to the 'fetal origins of disease hypothesis', environmental influences in pregnancy can influence health in later life (Barker, 2007). This it is hypothesized that epigenetic changes induced by ART may affect long-term health (Carpinello *et al.*, 2018).

Whether children conceived by ART are at higher risk of respiratory infections is still unclear (Kettner *et al.*, 2015). A recent Swedish register-based study found that children conceived by ART had higher odds for infections and diseases of the respiratory system (Pettersson *et al.*, 2022). Older studies show inconsistent results on the association of ART and childhood infections. Two smaller cohort studies reported significantly increased odds for pneumonia (Koivurova *et al.*, 2003; Knoester *et al.*, 2008), whereas others did not show increased risks (Pinborg *et al.*, 2003; Källén *et al.*, 2005; Klemetti *et al.*, 2006; Ludwig *et al.*, 2009) or showed increased risks only for particular subgroups (Källén *et al.*, 2010; Hwang *et al.*, 2018). A higher prevalence of upper (URTI) and lower respiratory tract infections (LRTI) in children conceived by ART was confirmed in a European cohort study (Bonduelle *et al.*, 2005).

Most of the current evidence has examined risk of hospitalization for respiratory tract infections in children conceived by ART. The studies therefore rarely include less severe infections which are treated in primary care, or which did not require contact with health-care services. Whether risk of respiratory infections among children conceived by ART varies according to different medically assisted fertilization methods is unclear (Ludwig *et al.*, 2009; Wainstock *et al.*, 2019). Only a few studies have attempted to clarify whether any of the increased risk observed reflects a role of factors related to the underlying parental subfertility (Sutcliffe *et al.*, 2014; Hwang *et al.*, 2018; Waynforth, 2018; Wainstock *et al.*, 2019). Our aim therefore was to assess the risk of URTI and LRTI according to parental subfertility and conception by ART.

Materials and methods

The Norwegian Mother, Father and Child Cohort Study

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Pregnant women and their partners were recruited from all over Norway from 1998 to 2008 during their first ultrasound visit (Magnus *et al.*, 2006, 2016). Of all invited women, 41% consented to participate. More than 36 000 mothers participated with more than one child in the study. The cohort study is ongoing and includes around 114 000 children, 95 200 mothers and 75 200 fathers. The current study is based on version 12 of the quality-assured data files. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (#2014/404). Self-reported information from questionnaires administered to MoBa participants was linked to information from the birth registry using national personal identification numbers (Irgens, 1998, 2000). We included all live-born singletons with at least one answer to the questions assessing respiratory tract infections at 6 (Q4), 18 (Q5) or 36 (Q6) months for the age of the child (N = 86 589) (Fig. 1).

Information on parental subfertility and conception by assisted reproductive technologies

Information on whether the child was conceived by ART was available from the medical birth registry (MBRN), including information on different subgroups of ART such as *in vitro* fertilization or intracytoplasmic sperm injection, and information on the type of embryo transfer (fresh or frozen). At the time of recruitment, women reported the number of months it took to conceive. We defined subfertility as a time-to-pregnancy (TTP) of 12 or more months, following the definition by Zegers-Hochschild *et al.* (2017). Fertile parents were defined as those taking less than 12 months to conceive. We defined three exposure groups: (i) children of fertile parents (reference group), (ii) non-ART children of subfertile parents and (iii) children conceived by ART. Couples who stated that they had not planned their pregnancy were assigned to the fertile group.

Respiratory tract infections

The MoBa questionnaires included self-reported information on the occurrence of (yes or no), the frequency of (number) and the hospitalization (yes or no) for respiratory tract infections for the time intervals since the last questionnaire: 0–6 months reported at 6 months, 7–18 months reported at 18 and 19–36 months reported at 36 months. URTIs included throat infections with or without streptococci and ear infections. LRTIs included bronchitis, bronchiolitis, respiratory syncytial virus and pneumonia. To assess total frequency, the numbers given for

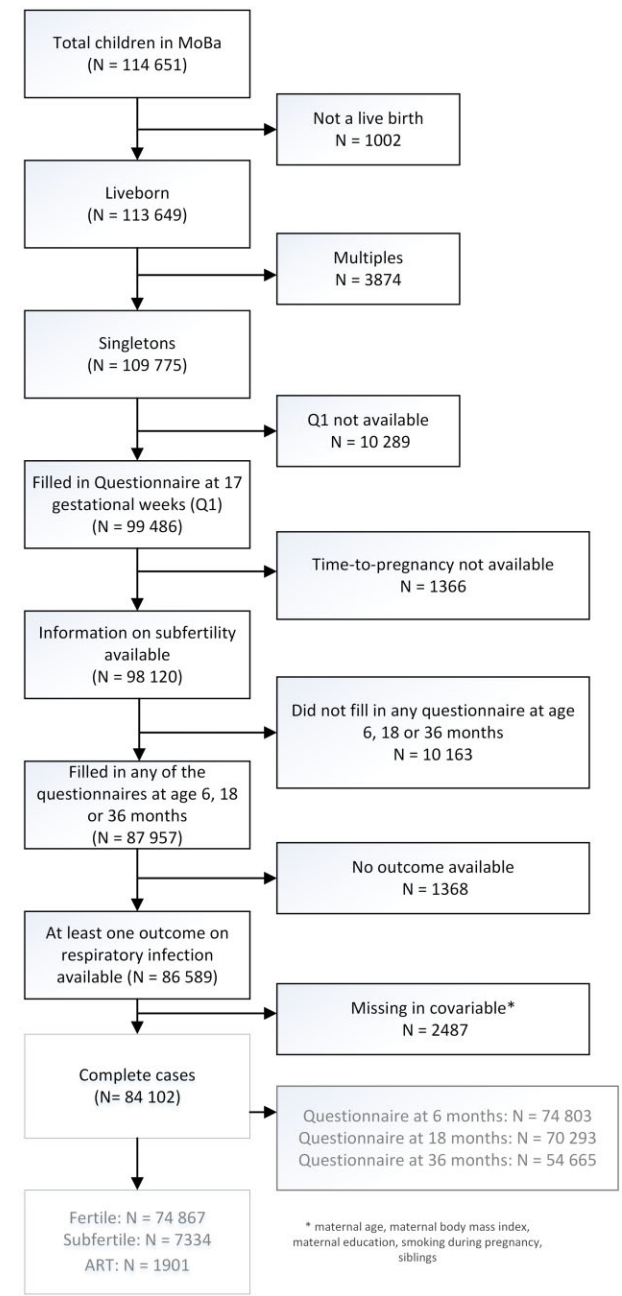

Figure 1. Population selection from the Norwegian MoBa Cohort. MoBa, Norwegian Mother, Father and Child Cohort. N, Number; Q1, first questionnaire at 15–17 gestational weeks.

any of the mentioned conditions were summed according to the diseases included in URTI or LRTI.

If the answers to the different questions on occurrence of, number of and hospitalization for infections were inconsistent, we used the answer given to one of the questions to fill in the others accordingly. If the number of infections was missing, but the occurrence or hospitalization was yes, we replaced the numbers of infection by the median of the reported values.

Covariates

We used self-reported information on maternal characteristics which could conceivably influence both parental fertility and offspring's risk of infection. This included maternal education (less than high school, high school, bachelor/up to 4 years of college, master or higher), smoking during pregnancy (no, stopped smoking before 15 gestational weeks, yes), pre-pregnancy BMI and number of livebirths before this birth (0, 1, 2, 3 or more). We also obtained information on early institutional childcare (care before age 12 months or no care before age 12 months) to explore potential effect modification.

We obtained information on maternal age at delivery (continuous), child sex, preterm birth (<37 weeks of gestation), and delivery by caesarean section (yes or no) from the birth registry. We calculated birthweight percentiles using birthweight of all singleton births occurring during the MoBa recruitment period in Norway by gestational week and by sex. Birthweight percentiles below the 10th percentile were defined as small-for-gestational age and those higher than the 90th percentile as large-for-gestational age, with the groupings as follows: <10th percentile, 10–90th percentile, >90th percentile. Pregnancy outcomes were *a priori* hypothesized to act as potential mediators.

Statistical analysis

We examined the association of ART or subfertility with respiratory infections in early childhood by regression models according to the type of outcome. For the occurrence of any infection and hospitalization, we used log-binomial regression reporting relative risks (RR) and 95% CI. For the number of infections, we used a negative-binomial regression model to account for overdispersion, reporting incidence rate ratios (IRR) and 95% CI. We adjusted for maternal characteristics such as age (continuous), education, previous livebirths (continuous), pre-pregnancy BMI (continuous) and smoking during pregnancy. For the dependency between children born to the same mother, we used a robust cluster variance estimate. We present results from complete-case analysis, as only 2487 (2.9%) had missing information on one or more covariates (Fig. 1).

Adverse perinatal outcomes may result from parental fertility problems and at the same time may increase the risk for early childhood respiratory tract infections. To assess whether associations could be explained by these intermediate factors, we performed sensitivity analysis with additional adjustment for preterm birth, birthweight percentiles or delivery by caesarean section. Other factors, such as contact with other children, may increase the risk for RTI. We conducted additional sensitivity analyses by stratifying for the child sex and the child's day care attendance before 12 months of age and according to the mother's previous livebirths before the birth of the index child. Potential effect modification was assessed using multiplicative interaction terms and likelihood ratio test was used to test the combined effect of multiple interaction terms. We also conducted sensitivity analyses by excluding children of non-planned pregnancies. Additionally, we assessed the number of infections by grouping them into no infection, 1–2 infections and 3 or more infections, and compared these groups using a multinomial logistic model.

To assess the impact of differential over-reporting in subfertile parents and parents who conceived using ART, we randomly allocated 5% and 10% of the total of ART and subfertile cases to non-cases. The random assignment with regression was repeated 1000 times

using bootstrapping. We conducted all analysis using STATA V 16.0 (StataCorp, College Station, Texas, USA).

Results

A total of 84 102 singleton children were included in the analyses, of which 74 867 (89.0%) were born to fertile parents, 7334 (8.7%) were non-ART children of subfertile parents and 1901 (2.3%) children were conceived by ART (Fig. 1). In the fertile group, 78.9% conceived within 3 months and the median TTP was 2 months (IQR 1,4) whereas in the subfertile group, the median TTP was 18 months (IQR 13,24) ($P < 0.001$). Subfertile parents and ART parents were older and had fewer previous livebirths than fertile parents. Parents of children conceived by ART also smoked less and had higher education levels than fertile parents (Table I).

Complete information at 6, 18 and 36 months of age was available for 74 803, 70 293 and 54 665 children, respectively. Background characteristics of mothers and singletons according to participation in the three different follow-up questionnaires were similar (Supplementary Table SI).

Risk for URTI according to parental subfertility and conception by ART

Between 0 and 36 months, 41 609 (49.5%) of children experienced any URTI. At least one URTI was reported for 5173 (7.1%) children between 0 and 6 months, for 26 609 (38.2%) children between 7 and 18 months, for and 26 337 children (48.2%) between 19 and 36 months.

Non-ART children of subfertile parents did not have an increased risk of any URTI during the first 36 months of life (Fig. 2), nor any evidence of a higher frequency of URTI during this age period (Fig. 3), but children conceived by ART had a higher frequency of URTI (adjusted (a)IRR 1.16; 95% CI 1.05–1.28) (Fig. 3). No increased risk of any URTI for children conceived by ART was observed up to 36 months (Fig. 2) and no increased frequency of URTI was observed up to 18 months (Fig. 3). However, children conceived by ART had a slightly increased frequency of URTIs at 19–36 months (aIRR 1.19; 95% CI 1.07–1.33) (Fig. 3). We also observed a higher risk for three or more URTIs between 19 and 36 months of age as compared to no URTIs (Supplementary Table SII).

Risk for LRTI according to parental subfertility and conception by ART

A total of 15 542 (18.5%) children experienced any LRTI in the first 3 years of life, while 4134 (4.9%) children were hospitalized due to LRTI during this time period. At least one LTRI occurred in 3583 (4.9%) children between 0 and 6 months, 8757 (12.6%) children between 7 and 18 months and 7040 (13.2%) children between 19 and 36 months.

We observed no difference in the risk of any LRTI during the first 18 months of life in non-ART children compared to those with subfertile parents or ART conceived children (Fig. 2). A modest increased risk for any LRTI was observed between 19 and 36 months among non-ART children born to subfertile parents (aRR 1.09; 95% CI: 1.01–1.17) and a slightly higher risk was observed among children conceived by ART (aRR 1.16; 95% CI 1.01–1.33) (Fig. 2). No difference in the frequency of LRTI or hospitalization for LRTI was observed among non-ART conceived children of subfertile parents (Figs 3 and 4). Children conceived by ART had a higher frequency of LRTI (aIRR 1.22; 95% CI 1.02–1.47) and an increased risk for hospitalization (aRR 1.35 CI 1.01–1.80) for LRTI between 19 and 36 months (Figs 3 and 4). We also observed a higher risk for three or more LRTI at 19–36 months in children conceived by ART (Supplementary Table SII). Overall, from 0 to 36 months only a slightly increased risk for hospitalization due to LRTI (aRR 1.25; 95% CI 1.02–1.53) was found in children conceived by ART but not for children of subfertile parents. We observed no robust associations when we directly compared children conceived by ART to non-ART conceived children of subfertile parents (results not shown).

Sensitivity analyses

Excluding the non-planners from the reference group yielded similar results as the main analyses, and we did not identify increased risks associated with the fertilization method (ICSI or IVF) nor with the transfer type (fresh or frozen) (results not shown).

Adjustment for intermediate perinatal risk factors such as preterm birth, small- or large-for-gestational age and delivery by caesarean section showed a small attenuating effect on the associations between the occurrence of, the frequency of and hospitalization for LRTI at age 19–36 months among children conceived by ART (Table II).

Stratified analyses by the mother's status of having had a previous livebirth did show differences in the risk of any URTI up to 6 months, with a *P*-value for interaction of 0.034, but no differences between 7–18 or 19–36 months. For LRTI, no interaction was found for any infection nor hospitalization at any age (Supplementary Figs S1, S2 and S3). There was no significant interaction according to child sex (Supplementary Figs. S4, S5 and S6) nor with early day care attendance (results not shown).

Differential overreporting of infections in the subfertile and ART group would slightly attenuate the results and weaken the association observed between conception by ART and respiratory tract infection (Supplementary Fig. S7).

Discussion

We found some evidence of an increased frequency of URTI and hospitalization for LRTI during the first 3 years of life in children conceived by ART. We did not find evidence of increased risk for respiratory infections up to 18 months of age in non-ART children born to subfertile parents or children conceived by ART. However, children conceived by ART had more frequent URTIs and LRTIs at 19–36 months. They also had a higher risk of hospitalization for LRTIs from age 19 months onwards. These results seem only partially to be explained by characteristics associated with underlying parental subfertility, as the same associations were not found in children of subfertile parents. The increased risk of respiratory infections among children conceived by ART was also not completely explained by adverse perinatal outcomes such as preterm birth, small- or large-for-gestational age or delivery by caesarean section.

Table I Background characteristics by mode of conception.

	Fertile N = 74 867 N (%)/mean (SD)	Subfertile N = 7334 N (%)/mean (SD)	ART N = 1901 N (%)/mean (SD)
Maternal characteristics			
Age at delivery (years)	30.0 (4.5)	31.4 (4.6)	33.1 (3.8)
Age at delivery in groups			
<25	8187 (10.9%)	489 (6.7%)	19 (1.0%)
25–29	25 718 (34.4%)	2006 (27.4%)	330 (17.4%)
30–34	28 938 (38.7%)	2985 (40.7%)	859 (45.2%)
35 and older	12 024 (16.1%)	1854 (25.3%)	693 (36.5%)
Previous livebirths			
None	34 016 (45.4%)	4167 (56.8%)	1359 (71.5%)
1	27 719 (37.0%)	2299 (31.3%)	487 (25.6%)
2	10 892 (14.5%)	737 (10.0%)	44 (2.3%)
3 or more	2240 (3.0%)	131 (1.8%)	11 (0.6%)
Education (for mothers in education: aspired highest education)			
Less than high school	5505 (7.4%)	661 (9.0%)	132 (6.9%)
High school	17 748 (23.7%)	2076 (28.3%)	428 (22.5%)
Bachelor/up to 4 y college	32 400 (43.3%)	2982 (40.7%)	802 (42.2%)
Master or higher	19 214 (25.7%)	1615 (22.0%)	539 (28.4%)
Prepregnancy BMI (kg/m^2)			
<18.5	2192 (2.9%)	218 (3.0%)	41 (2.2%)
18.5–24.9	49 706 (66.4%)	4182 (57.0%)	1225 (64.4%)
25–29.9	16 397 (21.9%)	1783 (24.3%)	464 (24.4%)
30 or higher	6572 (8.8%)	1151 (15.7%)	171 (9.0%)
Smoking during pregnancy			
Did not smoke	57 772 (77.2%)	5375 (73.3%)	1661 (87.4%)
Stopped <15 gestational weeks	11 016 (14.7%)	1222 (16.7%)	149 (7.8%)
Smoked and did not stop	6079 (8.1%)	737 (10.0%)	91 (4.8%)
Characteristics of the Child			
Sex			
Male	38 332 (51.2%)	3789 (51.7%)	959 (50.4%)
Female	36 535 (48.8%)	3545 (48.3%)	942 (49.6%)
Gestational age			
Term	63 570 (95.6%)	6198 (94.6%)	1629 (92.1%)
<37 weeks	2621 (3.9%)	316 (4.8%)	116 (6.6%)
<32 weeks	289 (0.4%)	34 (0.5%)	22 (1.2%)
Missing	6 (0.0%)	1 (0.0%)	1 (0.1%)
Low birthweight (<2500 g)			
>=2500 g	72 973 (97.5%)	7104 (96.9%)	1811 (95.3%)
<2500 g	1885 (2.5%)	230 (3.1%)	90 (4.7%)
Missing	9 (0.0%)	0 (0.0%)	0 (0.0%)
Delivery by caesarean section			
No	65 055 (86.9%)	6022 (82.1%)	1510 (79.4%)
Yes	9812 (13.1%)	1312 (17.9%)	391 (20.6%)
Duration of breastfeeding			
Never breastfed	630 (0.8%)	75 (1.0%)	15 (0.8%)
<7 months breastfeed	11 215 (15.0%)	1298 (17.7%)	319 (16.8%)
7–12 months breastfed	37 424 (50.0%)	3487 (47.5%)	909 (47.8%)
>12 months breastfed	24 385 (32.6%)	2365 (32.2%)	631 (33.2%)
Missing	1213 (1.6%)	109 (1.5%)	27 (1.4%)

(continued)

Table I Continued

	Fertile N = 74 867 N (%)/mean (SD)	Subfertile N = 7334 N (%)/mean (SD)	ART N = 1901 N (%)/mean (SD)
Age when care out of house started			
No nursery	18 435 (24.6%)	1772 (24.2%)	429 (22.6%)
≤12 months	9057 (12.1%)	882 (12.0%)	182 (9.6%)
>12 months	47 375 (63.3%)	4680 (63.8%)	1290 (67.9%)
Information of Questionnaire at 6 months			
No	8381 (11.2%)	785 (10.7%)	133 (7.0%)
Yes	66 486 (88.8%)	6549 (89.3%)	1768 (93.0%)
Information of Questionnaire at 18 months			
No	12 408 (16.6%)	1122 (15.3%)	279 (14.7%)
Yes	62 459 (83.4%)	6212 (84.7%)	1622 (85.3%)
Information of Questionnaire at 36 months			
No	26 436 (35.3%)	2449 (33.4%)	552 (29.0%)
Yes	48 431 (64.7%)	4885 (66.6%)	1349 (71.0%)

N, Number.

Important strengths of the study include the size of the cohort, the prospective data collection, our ability to examine the role of aspects related to underlying parental subfertility and information being available on a wide range of potential confounding and mediating factors. The self-reported information of respiratory tract infection by parents enabled us to capture infections that were less severe and did not result in contact with health-care services.

The study also has some limitations. We cannot exclude a potential bias due to selection to initial participation in MoBa or loss to follow-up. MoBa mothers are older and are less likely to smoke or to be a single mother, but more likely to use multivitamins and folic acid compared to all mothers who gave birth during the same period who did not choose to participate. Women with more than two previous births or a previous stillbirth are underrepresented (Nilsen *et al.*, 2009). Notably there are no differences in the frequency of ART children among participants in MoBa (2.8%) and among all children born during the MoBa recruitment period (2.6%) (Statistikkbank, 2022). However, there is a certain selection in the cases lost to follow-up over the course of the MoBa cohort study (Vejrup *et al.*, 2021). The proportion of children conceived by ART in our sample was 2.4%, 2.3% and 2.5% for the 6-, 18- and 36-months questionnaire, respectively. A further limitation is the use of self-reported TTP and of self-reported respiratory diseases in children. Studies have generally shown a good recall for TTP retrospectively (Radin *et al.*, 2015) and high completeness and reliability in parental reporting of respiratory diseases in small children (Kvestad *et al.*, 2006; Vissing *et al.*, 2012), especially for hospitalizations during the first 3 years of life (D'Souza-Vazirani *et al.*, 2005). Misreporting of numbers of infections is most likely. It is possible that parents who are subfertile or who conceive through ART have higher health awareness and recall better their children's experience of infections. Children conceived through ART are more often first born and an only child. Their parents more often belong to a higher social class (Goisis *et al.*, 2020). Both could be associated with better recall or over-reporting of infections (D'Souza-Vazirani *et al.*, 2005). Our simulated results suggest a potential overestimation of the associations observed in case of differential misclassification (Supplementary Fig. S7). We did not use the Norwegian patient registry or the Norwegian registry of primary healthcare to capture early childhood respiratory tract infections for MoBa children, as these registries started collecting data only in 2008 and 2006, respectively (Bakken *et al.*, 2020).

Our findings did not show an increase in respiratory tract infections during the first 18 months, in contrast to some studies observing differences in the perinatal period and in the first year of life (Finnstrom *et al.*, 2011; Hwang *et al.*, 2018). Our results show an increase of respiratory infections between 19 and 36 months, mainly for LRTI. This is in line with some other studies reporting higher risks for respiratory tract infections in singletons up to age 5, born following ART (Koivurova *et al.*, 2003; Bonduelle *et al.*, 2005; Källén *et al.*, 2005; Wainstock *et al.*, 2019). The most recent study found a higher risk for hospitalization for infections and respiratory diseases up to age 5 (Pettersson *et al.*, 2022).

We did not find any differences in the first 18 months. It is possible that parents do not report respiratory tract infections that might have occurred during a stay at the neonatal intensive care unit, as they might not recall this or may not refer to it in a self-reported questionnaire. Also breastfeeding is known to protect from respiratory tract infections, and in Norway, the breastfeeding prevalence until age 6 months and longer is high and, due to the maternity leave policies, care outside of families is very low during the first year. This might explain the overall low prevalence of URTIs and LRTIs in children under 6 months (Häggkvist *et al.*, 2010).

ART treatment can affect epigenetic programming during gameto- or embryo-genesis which might influence expression of genes relevant for immune responses (Horsthemke and Ludwig, 2005; Market-Velker *et al.*, 2010). Modifications in DNA methylation patterns had been

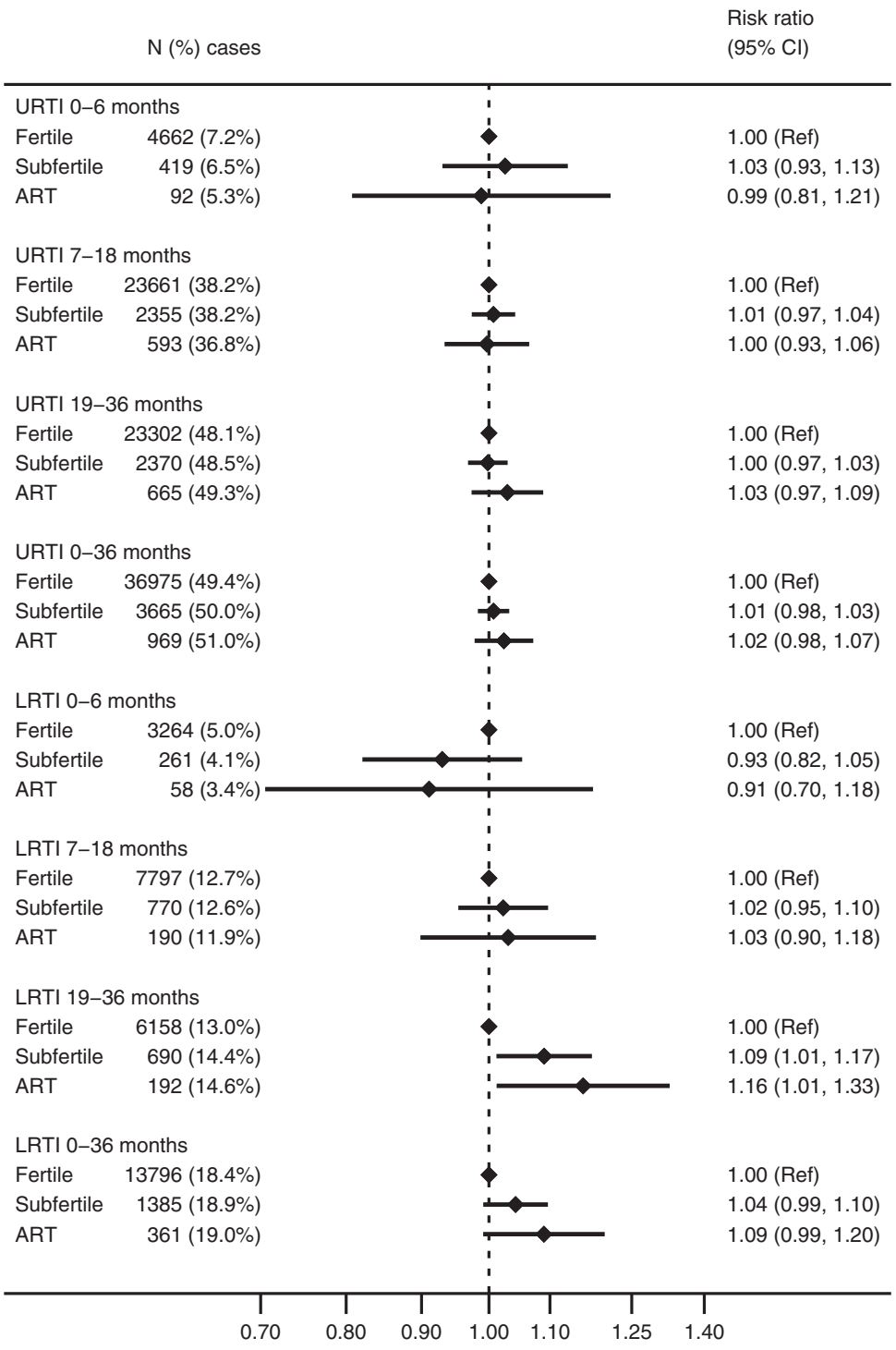

Figure 2. Risk of any respiratory tract infection in children born to fertile or subfertile parents or after conception by ART. Results are adjusted for maternal age, BMI, education, smoking during pregnancy and previous livebirths. LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; Ref, reference group; total N refers to the number of participants who filled in the specific questions on URTI/LRTI.

shown in ART conceived children, but the consequences are not yet understood (Mani *et al.*, 2020; Håberg *et al.*, 2022). Animal studies have demonstrated differences in the balance levels of T helper (Th) 1 and Th2 cells between naturally and ART conceived offspring and a generally less efficient immune response in ART offspring (Karimi *et al.*, 2017; Ahmadi *et al.*, 2020). Imbalances in Th1 and Th2 cells might

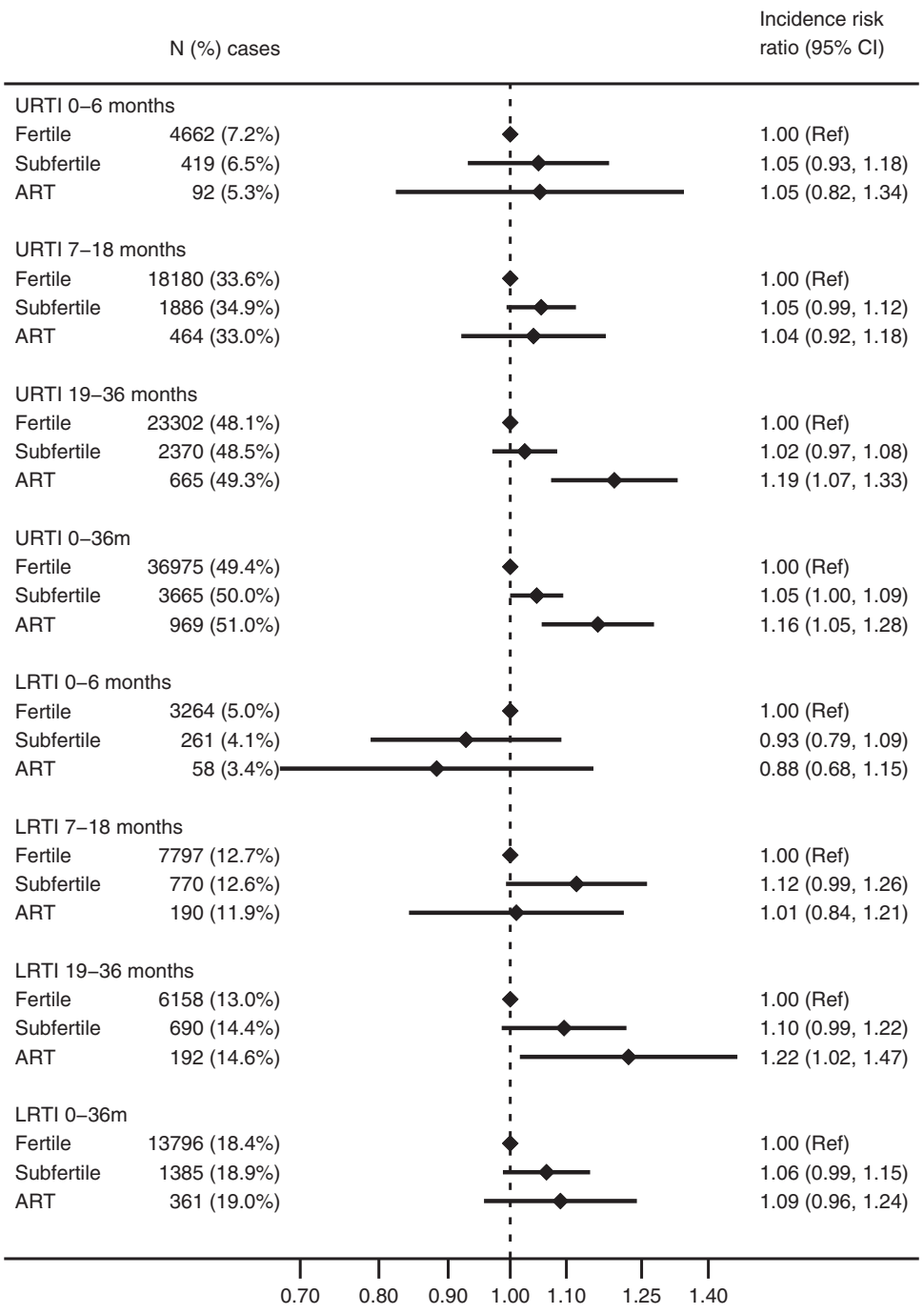

Figure 3. Incidence risk ratio of respiratory tract infections in children born to fertile or subfertile parents or after conception by ART. Results are adjusted for maternal age, BMI, education, smoking during pregnancy and previous livebirths. LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; Ref, reference group; Total N refers to the number of participants who filled in the specific questions on URTI/LRTI.

increase the risk of infectious diseases, as they are important in the defence towards intracellular or extracellular pathogens such as viruses and bacteria. A study in humans analysing peripheral blood showed different levels of cytokines between ART and naturally conceived children. However, this did not transfer to different frequencies of T cells or B cells or in an imbalance in Th1, Th2 and Th17, as it has is mice (Xu *et al.*, 2021). An increase in Th2 might also be associated with the higher prevalence of immune-related diseases in ART children. Asthma for instance has been shown to be more prevalent in children following ART (Carson *et al.*, 2013; Magnus *et al.*, 2019;

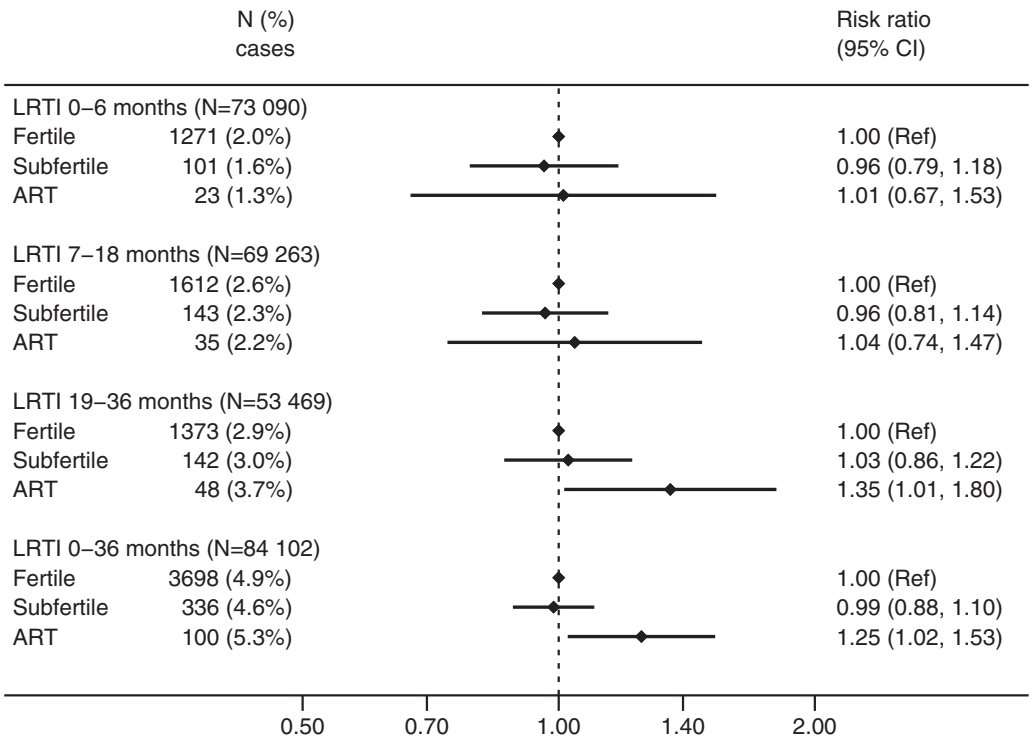

Figure 4. Risk of hospitalization due to lower respiratory tract infection in children born to fertile or subfertile parents or after conception by ART. Results are adjusted for maternal age, BMI, education, smoking during pregnancy and previous livebirths. LRTI, lower respiratory tract infection; Ref, reference group; Total N refers to the number of participants who filled in the specific questions on URTI/LRTI.

Tsabouri *et al.*, 2021) as has atopic respiratory conditions, atopic disorders and allergies (Halliday *et al.*, 2014; Wijs *et al.*, 2021) but the increased risk of asthma has not transferred into adolescence and young adulthood (Halliday *et al.*, 2019). Maternal subfertility itself has been associated with higher prevalence of asthma in the offspring (Harju *et al.*, 2013; Magnus *et al.*, 2019). During early childhood, respiratory diseases are difficult to distinguish from early signs of asthma, such as wheezing or snoring. Asthma and wheezing are linked to the functioning and susceptibility of the respiratory tract and a higher incidence of LRTIs below age 3 is associated with an increased risk of asthma at school age (Nafstad *et al.*, 2000; van Meel *et al.*, 2022). Most children later diagnosed with asthma have persistent wheezing and symptoms before age 3 (Subbarao *et al.*, 2009). Also, a bidirectional relationship between asthma and otitis media has been described (Kim *et al.*, 2021). Children with otitis media seem to be at an increased risk of developing asthma later (MacIntyre and Heinrich, 2012). Higher risks of an increased frequency of LRTIs and URTIs including otitis media in our study could hence be linked to a higher prevalence of asthma in this population later (Magnus *et al.*, 2019).

A second potential explanation for an increased risk of infections among children conceived by ART includes changes in the microbiome (de Steenhuijsen Piters *et al.*, 2020). Reduced diversity and decreased relative abundance of Bacteroidetes were identified in the microbiome of newborns conceived by ART (Lu *et al.*, 2020). The microbiome has also been shown to be associated with disease susceptibility and at the same time its development is dependent on perinatal factors and breastfeeding (Rutayisire *et al.*, 2016; Princisval *et al.*, 2021). Early-life exposure to microbes is inversely associated with later susceptibility towards respiratory diseases (Nino *et al.*, 2021).

A third potential explanation for an increased risk of infections among ART children include the adverse pregnancy outcomes. Children conceived by ART and non-ART conceived children born to subfertile parents are more likely to be delivered by caesarean section, to be born preterm or to have a low birthweight (Messerlian *et al.*, 2013; Qin *et al.*, 2016; Vannuccini *et al.*, 2018). Preterm born children are more vulnerable to respiratory infections due to impaired lung development (Bolton *et al.*, 2015). Perinatal risk factors notably did not completely explain our findings as we still observed an increased frequency of URTI at 19–36 months, whereas the association with LRTI was weakened after additional adjustment for these interacting factors (preterm, birthweight percentile, delivery by caesarean section).

Sociobiological factors might also play a role in the observed associations. The experience of infertility and fertility treatment is often stressful for couples and previous treatment failure, and feelings of insufficiency or biological malfunction might affect the childcare and parenting style (Hammarberg *et al.*, 2008) but not necessarily investment in the child (Gameiro *et al.*, 2011). Parents who conceived using ART might be overcautious about their child's health. This might render them more likely to take their child to the doctor for any respiratory symptoms. A similar mechanism has been seen regarding the matter

Table II Results of sensitivity analysis including intermediate perinatal risk factors (mediation by preterm birth, birthweight percentiles or caesarean section).

	Number of URTI 19–36 m		Any LRTI 19–36 m		Number of LRTI 19–36 m		Hospitalization due to LRTI 19–36 m	
	Adjustment 1 IRR (95% CI)	Adjustment 2 IRR (95% CI)	Adjustment 1 RR (95% CI)	Adjustment 2 RR (95% CI)	Adjustment 1 IRR (95% CI)	Adjustment 2 IRR (95% CI)	Adjustment 1 RR (95% CI)	Adjustment 2 RR (95% CI)
Fertile	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Subfertile	1.02 (0.97–1.08)	1.02 (0.97–1.08)	1.09 (1.01–1.17)	1.08 (1.01–1.17)	1.10 (0.99–1.22)	1.09 (0.98–1.21)	1.03 (0.86–1.22)	1.02 (0.86–1.21)
ART	1.19 (1.07–1.33)	1.19 (1.07–1.32)	1.16 (1.01–1.33)	1.14 (1.00–1.31)	1.22 (1.02–1.47)	1.20 (1.00–1.44)	1.35 (1.01–1.80)	1.31 (0.98–1.74)

IRR, incidence risk ratio; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; Ref, reference group; RR, risk ratio.
Adjustment 1: Estimates adjusted for maternal age, education, body mass index, smoking during pregnancy and previous livebirths.
Adjustment 2: Estimates adjusted for maternal age, education, body mass index, smoking during pregnancy and previous livebirths, preterm birth (<37 gestational weeks), birthweight percentiles (small-for-gestational age (<10th percentile); normal 10–90th percentile, large-for-gestational age (>90th percentile)) and caesarean section (yes or no).

of preventive testing during ART pregnancies and is referred to as the precious baby effect (Minkoff and Berkowitz, 2005). We could not see any differences in breastfeeding duration or day care attendance between the different groups, which reduces the concern that different parenting strategies are reflected in the associations we observed.

Our results indicating only a very modest increased risk of respiratory tract infections may be reassuring for parents who are subfertile or who conceive using ART. However, follow-up for asthma may be considered in case of worsening or longer lasting infections or recurrent respiratory problems.

Conclusion

Our results indicate that children conceived by ART have a higher frequency of infections and increased risk of hospitalization for respiratory tract infection during early childhood. These results were not fully explained by characteristics influencing the underlying parental subfertility.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

Researchers who want access to MoBa datasets for replication should apply by sending an e-mail to datatilgang@fhi.no. The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Access to data sets requires approval from The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa (Folkehelseinstituttet, 2022).

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Authors' roles

V.R.M., M.C.M. and S.E.H. conceived and developed the study, M.C.M. provided access to data, V.R.M. conducted the analysis and M.C.M. supervised the analysis. V.R.M. wrote the first draft. All authors interpreted the data, gave critical feedback, contributed to writing, and approved the final manuscript.

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Conflict of interest

All authors declare no conflict of interest.

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