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Original article

Cancer risk in children, adolescents, and young adults conceived by ART in 1983–2011

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ABSTRACT

STUDY QUESTION: Do children, adolescents, and young adults born after ART, including IVF, ICSI and frozen–thawed embryo transfer (FET), have an increased risk of cancer compared with children born to subfertile couples not conceived by ART and children from the general population?

SUMMARY ANSWER: After a median follow-up of 18 years, the overall cancer risk was not increased in children conceived by ART, but a slight risk increase was observed in children conceived after ICSI.

WHAT IS KNOWN ALREADY: There is growing evidence that ART procedures could perturb epigenetic processes during the pre-implantation period and influence long-term health. Recent studies showed (non-)significantly increased cancer risks after ICSI and FET, but not after IVF.

STUDY DESIGN, SIZE, DURATION: A nationwide historical cohort study with prospective follow-up was carried out, including all live-born offspring from women treated with ART between 1983 and 2011 and subfertile women not treated with ART in one of the 13 Dutch IVF clinics and two fertility centers.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Children were identified through the mothers' records in the Personal Records Database. Information on the conception method of each child was collected through the mother's medical record. In total, the cohort comprises 89 249 live-born children of subfertile couples, of whom 51 417 were conceived using ART and 37 832 were not (i.e. conceived naturally, through ovulation induction, or after IUI). Cancer incidence was ascertained through linkage with the Netherlands Cancer Registry for the period 1989–2019. Cancer risk in children conceived using ART was compared with risk in children born to subfertile couples but not conceived by ART (hazard ratio (HR)) and children from the general population (standardized incidence ratios (SIRs)).

MAIN RESULTS AND THE ROLE OF CHANCE: In total, 358 cancers were observed after a median follow-up of 18 years. Overall cancer risk was not increased in children conceived using ART, when compared with the general population (SIR = 0.96, 95% CI = 0.81–1.12) or with children from subfertile couples not conceived by ART (HR = 1.06, 95% CI = 0.84–1.33). Compared with children from subfertile couples not conceived by ART, the use of IVF or FET was not associated with increased cancer risk, but ICSI was associated with a slight risk increase (HR = 1.58, 95% CI = 1.08–2.31). Risk of cancer after ART did not increase at older ages (≥18 years, HR = 1.26, 95% CI = 0.88–1.81) compared to cancer risk in children not conceived by ART.

LIMITATIONS, REASONS FOR CAUTION: The observed increased risk among children conceived using ICSI must be interpreted with caution owing to the small number of cases.

WIDER IMPLICATIONS OF THE FINDINGS: After a median follow-up of 18 years, children conceived using ART do not have an increased overall cancer risk. Many large studies with prolonged follow-up are needed to investigate cancer risk in (young) adults conceived by different types of ART. In addition, international pooling of studies is recommended to provide sufficient power to study risk of specific cancer sites after ART.

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WHAT DOES THIS MEAN FOR PATIENTS?

This study examined whether children conceived using assisted reproductive technology, such as IVF, have an increased risk of developing cancer.

For subfertile couples contemplating whether to continue or start fertility treatment, there is currently only limited information available about possible long-term cancer risk in children conceived by such treatments.

This report is based on a large nationwide study with follow-up of children until a median age of 18 years. We observed that the risk of cancer in children born after assisted reproductive technology was not increased. However, in children born after intracytoplasmic sperm injection, a specific type of assisted reproductive technology where one single sperm cell is injected into one oocyte, the risk of cancer was slightly increased. This increased risk must be interpreted with caution as the number of children with cancer and born after intracytoplasmic sperm injection was rather small.

We conclude that the overall risk of cancer in children born after assisted reproductive technology is not increased. More research is needed to study the risk of specific types of cancer within certain subgroups.

Introduction

Since the introduction of ART in 1978, more than 10 million children have been conceived using ART and born over the intervening decades (European Medical Journal, 2018; Faddy *et al.*, 2018; Spaan *et al.*, 2019). Currently, an estimated 1 million children are expected to be conceived using ART and born every year after successful IVF, ICSI, and/or frozen–thawed embryo transfer (FET) procedures (European Medical Journal, 2018).

Each phase of the ART procedure is substantially different from natural conception (Buitendijk, 1999) and these processes occur in the same timeframe as epigenetic programming (Iliadou *et al.*, 2011). It seems plausible that ART could influence early stages of embryogenesis and thereby permanently influence the development and health of individuals conceived through these techniques. With the increasing number of children conceived using ART, even subtle increased health risks become important from a public health perspective (Roseboom, 2018).

Previous studies have shown that children born after conception through ART have a higher risk of adverse perinatal outcomes such as pre-term birth (Pinborg *et al.*, 2013; Berntsen *et al.*, 2019), a lower birthweight (Berntsen *et al.*, 2019), and congenital malformations (Davies *et al.*, 2012). In addition, there is evidence that ART may have long-term consequences for later health (Hart and Norman, 2013a,b). An increasing body of evidence suggests that ART may have consequences for cardiovascular and metabolic risk factors. In contrast, evidence regarding risk of cancer in children born after conception through ART is less consistent (Gilboa *et al.*, 2019; Hargreave *et al.*, 2019; Spaan *et al.*, 2019; Spector *et al.*, 2019; Sargisian *et al.*, 2022; Weng *et al.*, 2022). Some large population-based studies have observed an increased overall cancer risk after ART (Spector *et al.*, 2019; Weng *et al.*, 2022) while other studies did not (Hargreave *et al.*, 2019; Spaan *et al.*, 2019; Sargisian *et al.*, 2022). In addition, increased risk estimates have been observed for children born after FET (Hargreave *et al.*, 2019; Sargisian *et al.*, 2022) and non-significantly increased risks have been observed in children born after ICSI (Hargreave *et al.*, 2019; Spector *et al.*, 2019).

In our previous study, based on 21 246 children conceived after IVF, 3023 by ICSI, and 669 by FET, with a median follow-up of 21 years, slight increased risks of cancer, although not statistically significant, were found in children born after ICSI (hazard ratio (HR) = 1.52, 95% CI = 0.81–2.85) and FET (HR = 1.80, 95% CI = 0.65–4.95) (Spaan *et al.*, 2019). After this publication, four other large cohorts have published their results. In a Danish cohort, including 19 448 children conceived by IVF, 13 417 by ICSI, and 3356 by FET, with a mean follow-up of 11 years, the risk of cancer was significantly increased in children born after FET compared to naturally conceived offspring from subfertile couples (HR = 2.43, 95% CI = 1.44–4.11). The risk of cancer in ICSI-conceived children was HR = 1.31, 95% CI = 0.90–1.92 (Hargreave *et al.*, 2019). A Scandinavian cohort study, with data from Denmark, Finland, Norway, and Sweden, included 171 774 children conceived by ART (2.2%) and over 7.7 million children who were born after natural conception (Sargisian *et al.*, 2022). After a mean follow-up of 10 years, overall cancer risk was not increased after ART (HR = 1.08, 95% CI = 0.96–1.21), but risk of cancer was significantly increased in children born after FET (HR = 1.65, 95% CI = 1.24–2.19). Cancer risk after ICSI was not reported (Sargisian *et al.*, 2022). In a study from the USA, which included 275 686 ART children with median follow-up of 4.6 years, overall cancer risk was borderline significantly increased compared with the general population (HR = 1.17, 95% CI = 1.00–1.36) (Spector *et al.*, 2019). Risk of cancer in children born after ICSI was not significantly increased (HR = 1.29, 95% CI = 0.96–1.74) compared to children born after IVF. In a population-based Taiwanese study including 47 152 ART children, the overall risk of cancer was increased (HR = 1.42; 95% CI = 1.04–1.95) after a median follow-up of 6 years when compared to children from subfertile parents not conceived by ART. No association between use of FET and cancer was found. No data were available to allow research into the risk of cancer following ICSI conception (Weng *et al.*, 2022).

As the results from previous studies investigating risk of cancer in ART children are inconsistent, the aim of the current study was to investigate the risk of cancer in an expanded cohort of children born after conception through ART in 1983–2011. The study included a much larger group of children born after ICSI and FET than in our previous publication, as well as a comparison group of children conceived without the use of ART from

subfertile couples. This allowed for the investigation of cancer risk in children born after different types of ART (IVF, ICSI, and FET) with more statistical power.

Materials and methods

Study design and participants

OMEGA-offspring cohort

The OMEGA-offspring cohort consists of all live-born offspring from subfertile couples who were treated with ART between 1983 and 2011 in The Netherlands and all offspring of subfertile couples who were not treated with ART between 1980 and 2001 (Fig. 1). Couples were defined as subfertile if they were not able to conceive after 1 year or more of unprotected sex. The exposed group consisted of children conceived and born after ART in 1983–2011 while the comparison group included children conceived naturally (or after fertility drugs with/without IUI) born to subfertile women who did or did not receive ART treatment.

Original OMEGA-offspring cohort (ART treatments 1983–2000)

The original OMEGA-offspring cohort study included all live-born children of women treated with ART in 1983–2000. To obtain a large enough comparison group of children not born after ART, we identified women who were diagnosed with fertility problems shortly before ART became a routine procedure for subfertile patients, i.e. all live-born children of subfertile women never treated with ART in 1980–2000 were included (Fig. 1).The children of the women were identified through the Personal Records Database.

In brief, in the Netherlands, the personal record of a woman also includes information about her children. Information on subfertility treatments (including ART) and patient characteristics were retrieved from the clinic's (paper or electronic) records of the mothers from 12 Dutch IVF clinics and two regional fertility centers. Information on maternal characteristics and perinatal outcomes was available from the mothers' questionnaires (62% response). A more detailed description of the cohort is given in our previous paper (Spaan *et al.*, 2019) and in the Supplementary Data.

Expansion of the OMEGA-offspring cohort (ART treatments 2000–2010)

In 2018, the cohort was expanded with children born in 2000–2011 to women treated with ART in 2000–2010, in order to study with more power the risk of cancer in children born after ART, and especially the risk after ICSI and FET (Supplementary Table S1). In brief, all Dutch IVF clinics (n = 13, including the same 12 as in the original cohort plus one additional center) were requested to provide retrospective data regarding ART treatment cycles that led to a pregnancy between 1 January 2000 and 1 January 2011. Pregnancy was defined as the presence of hCG hormone tested in urine or blood samples following ART treatment. Information on patient characteristics and ART treatments was retrieved from the clinic's electronic patient records system. Information on maternal characteristics and perinatal outcomes was extracted from the Dutch Perinatal Registry. To create one dataset, including IVF data and perinatal data, the two databases were combined by probabilistic linkage, as described in detail previously (Pontesilli *et al.*, 2021).

In order to identify all children of the women, including those not conceived by ART (as a comparison group), a linkage based on birthdate and postal code(s) of the mother was performed with the Personal Records Database (Fig. 1). The overlap between children in the original cohort and the expanded cohort was excluded (n = 4441).

Assessment of conception method

The conception method of children from couples treated with or without ART between 1980 and 2001 (original cohort) was ascertained using information from the medical record and data regarding pregnancies (≥24 weeks) from the mother's questionnaires, and was described in more detail previously (Spaan *et al.*, 2019) and in the Supplementary Data.

For children from couples treated with ART between 2000 and 2011 (expanded cohort), the conception method was available from the clinic's electronic patient record of the mother. All children that resulted from a successful ART cycle were classified as born after the use of ART (and subdivided into IVF or ICSI and into fresh or FET). All children born to ART-treated couples

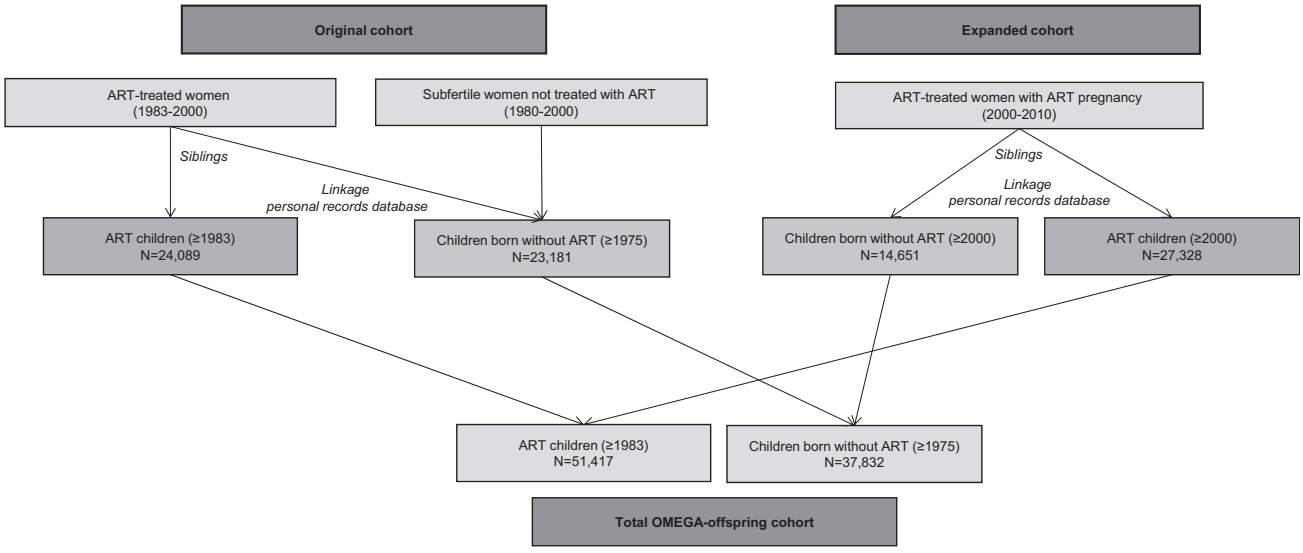

Figure 1. Structure of the OMEGA-offspring cohort. The OMEGA-offspring cohort consists of all live-born offspring from subfertile couples who were treated with ART between 1983 and 2011 in The Netherlands and all offspring of subfertile couples who were not treated with ART between 1980 and 2001.

between 2000 and 2011 that did not result from a successful ART cycle were classified as conceived without the use of ART, i.e. naturally conceived, by hormonal stimulation, or IUI. Children born before 1 May 2000 or after 31 December 2011, i.e. that could not be born as a result of the included ART cycles in the expanded cohort, were excluded because their conception method was unknown (Supplementary Table S2). Additionally, adopted children were excluded (Fig. 2).

Assessment of cancer incidence and vital status

The OMEGA-offspring cohort was linked with the Netherlands Cancer Registry (NCR), under strict privacy regulations. The NCR is a national population-based registry, with 96–98% completeness from 1989 (Schouten *et al.*, 1993). For each cancer among OMEGA children until 1 November 2019, the NCR electronically provided information on date of diagnosis, topography, morphology, and stage (International Classification of Diseases for Oncology (ICD-O)). Deceased children were identified through linkage with the Central Bureau for Genealogy, which keeps electronic data about the vital status of all Dutch citizens from October 1994 onwards.

Assessment of possible confounders

Through the mother's record in the Personal Records Database the date of birth of the mother and the child was used to create the following three variables: maternal age, child's birth year, and multiple birth. Information about the sex of the child was not available through the mother's record. Therefore, sex was based on the first name(s) of the child, using information about popularity of first names among males and females obtained from The Corpus of Given Names in The Netherlands (online database that includes information about given names in the Netherlands). Information on parental subfertility cause was obtained from the medical records. If missing, it was supplemented from the women's questionnaire (only available for women in the original cohort).

Ethical approval

The participating IVF clinics and fertility clinics, the Institutional Review Board, legal counsel, and the disease registries gave permission for the performance of this study according to the General Data Protection Regulation. The dataset with the children's names has been encrypted by a Trusted Third Party (ZorgTTP).

Statistical analysis

Because of concerns about potential birth cohort effects on childhood cancer risk, children born before 1975 were excluded, providing a more equal age distribution between children born after the use of ART and those conceived without the use of ART, leaving 89 249 children in the analytical cohort (Fig. 2).

As the NCR did not fully cover the Netherlands before 1989, the observation time for each child started on 1 January 1989 or date of birth, whichever came last. Person-years of the observation were calculated until 1 November 2019, the date of first cancer, or the date of death, whichever came first. Children with a known cancer diagnosis or those who died before 1989 were excluded.

Cancer incidence in the OMEGA-offspring cohort was compared with that in the Dutch general population by determining the standardized incidence ratio (SIR), defined as the ratio of the observed and expected number of cancers in the study

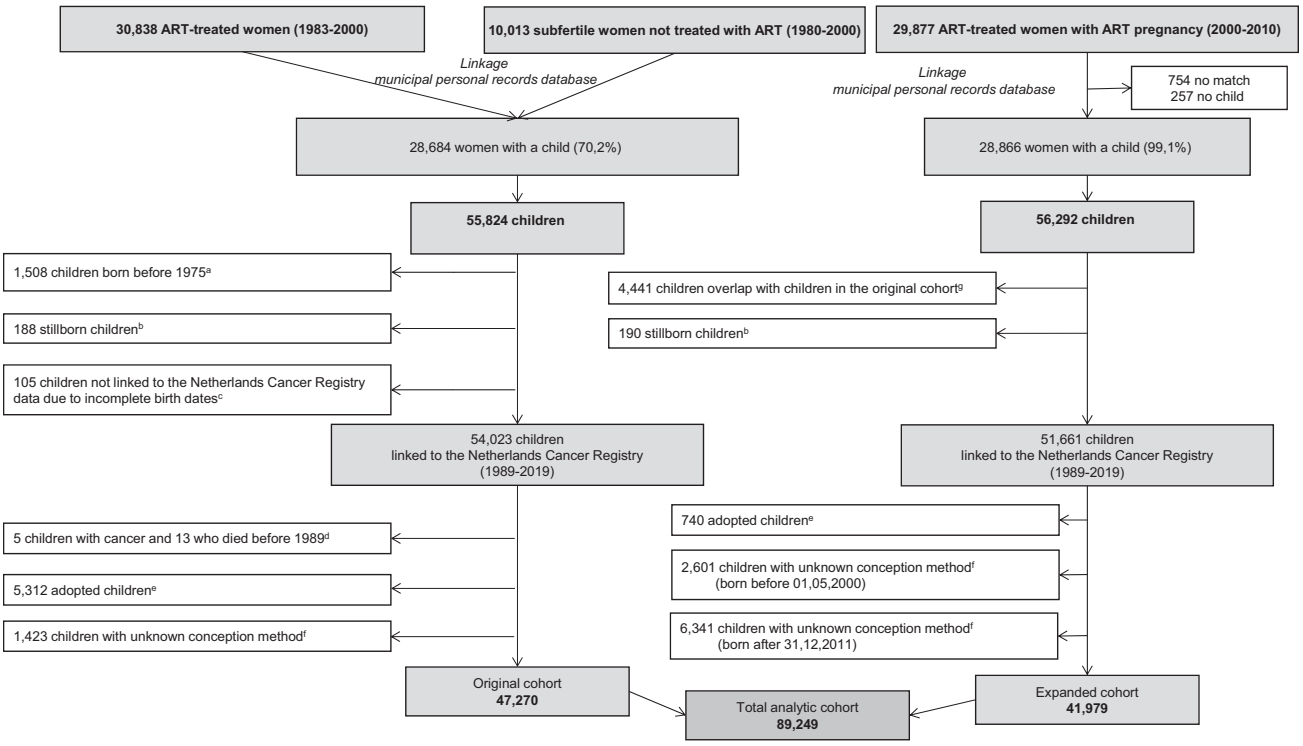

Figure 2. Identification of the OMEGA-offspring cohort. The OMEGA-offspring cohort consists of all live-born offspring from subfertile couples who were treated with ART between 1983 and 2011 in The Netherlands and all offspring of subfertile couples who were not treated with ART between 1980 and 2001. The following exclusions from the cohort were applied: [a]Children born before 1975; [b]Stillborns; [c]Children with incomplete birth dates; [d]Children with a cancer diagnosis or those who died before 1989; [e]Adopted children (i.e. not born in the Netherlands); [f]Children with an unknown conception method; [g]Children already identified in the OMEGA I–II cohort were excluded from the OMEGA-III cohort.

population. Expected numbers were calculated by applying the person-year distribution in the cohort to sex-, age-, and calendar year-specific cancer incidence rates from NCR.

Multivariable Cox regression models, with attained age on the *X*-axis, were used to directly compare cancer risk between children conceived using ART and those conceived and born to subfertile couples without using ART, while adjusting for confounding. Confounders were identified as factors that changed the risk estimate for the exposure of interest by ≥10%. Based on *a priori* knowledge about risk factors for childhood cancer and perinatal factors associated with ART, we tested the following variables for confounding: parental subfertility cause, maternal age, and child's birth year. Effect modification of the association between ART and cancer risk was tested for parental cause of subfertility, sex, multiple birth, and different attained age groups. Missing data on sex was imputed with multivariate imputation by chained equations (van Buuren *et al.*, 1999). The variables adjusted for in the analysis are provided in the footnotes to each table.

Risk was assessed according to various ART aspects (IVF, ICSI, and FET (and IVF–FET and ICSI–FET)), follow-up period, and different cancer sites. Sensitivity analyses were performed to evaluate the influence of: inclusion of children born before 1989 (starting date NCR); inclusion of children from subfertile mothers never treated with ART in the comparison group (i.e. restricting the non-ART comparison group to children conceived without the use of ART from ART-treated women (sibling analysis)); non-independency caused by inclusion of siblings in the cohort; we excluded the second child with cancer in one sibship (i.e. only including the first child with cancer); and the expansion of the cohort (i.e. separate analysis for the original and expanded cohort). All tests were two-sided and a *P*-value below 0.05 was considered statistically significant. All statistical analyses were performed with Stata version 15.0 (StataCorp, 2017).

Results

Population characteristics

In total, the cohort comprised 51 417 children born after the use of ART and 37 832 children conceived without the use of ART. After a median follow-up of 17.8 years (interquartile range (IQR) = 12.1–24.6), 358 cancers were observed; 157 in the ART group and 201 in children conceived without the use of ART. Follow-up was shorter in children conceived using ART (median 16.3 years) than in children conceived without the use of ART (median 20.3 years) (Table 1). Age of mothers of children born after the use of ART was substantially older than those conceived without the use of ART. As expected, ART children had a shorter mean gestational age, lower mean birthweight, and were more often part of a multiple birth than children conceived without the use of ART.

Comparisons with the Dutch general population

Compared to the incidence rates in the general Dutch population, overall cancer risk was not increased in the entire OMEGA-offspring cohort (SIR = 0.95, 95% CI = 0.86–1.06), the ART group (SIR = 0.96, 95% CI = 0.81–1.12), or children conceived without the use of ART (SIR = 0.95, 95% CI = 0.83–1.09) (Table 2). Risks were also not increased in children conceived by ICSI and FET (SIR = 1.11, 95% CI = 0.80–1.51 and SIR = 1.22, 95% CI = 0.61–2.18, respectively) compared to the general population. Furthermore, the risk of cancer did not increase in any of the groups with an older attained age (Table 3).

Children born after the use of ART were at an increased risk of parotid gland cancer (SIR = 6.42, 95% CI = 1.32–18.77, based on ≤3 cases) compared to the general Dutch population. Risk of melanoma was non-significantly increased in children born after the use of ART (SIR = 1.66, 95% CI = 0.95–2.69, based on 16 cases), and not in children conceived without ART (SIR = 0.93, 95% CI = 0.58–1.41, based on 22 cases) (Table 2). ICSI-conceived children were at a significantly increased risk of melanoma (SIR = 4.67, 95% CI = 1.27–11.95, based on four cases) compared to the general population.

Comparisons with children conceived without the use of ART from subfertile couples

In comparison to children from subfertile couples conceived without the use of ART, the risk of cancer in children born after ART was not increased (age-adjusted HR = 1.03, 95% CI = 0.82–1.30). After adjustment for year of birth, the risk was also not increased (adjusted HR = 1.06, 95% CI = 0.84–1.33, Table 4). When stratifying ART into IVF and ICSI, IVF children were not at higher risk compared with children conceived without the use of ART (adjusted HR = 0.97, 95% CI = 0.76–1.23) but ICSI-conceived children were (adjusted HR = 1.58, 95% CI = 1.08–2.31) (Table 4). Cancer risk in children born after FET was slightly but nonsignificantly increased, both when compared to children not conceived by ART (HR = 1.61, 95% CI = 0.86–3.03) and when compared to children born after fresh embryo transfers (HR = 1.56, 95% CI = 0.83–2.91). The HRs for cancer in children born after IVF–FET and in children born after ICSI–FET were 1.28 (95% CI = 0.47–3.30) and 1.50 (95% CI = 0.68–3.29), respectively, compared to children not conceived by ART (Table 4). Analyses stratified according to attained age, sex, and multiple birth did not show different risks of cancer between ART children and those conceived without the use of ART (Table 5).

There were no significantly increased site-specific cancer risks in children born after the use of ART when compared with children conceived without the use of ART (Table 6). However, risk of melanoma was significantly increased in ICSI-conceived children compared with children conceived without ART (adjusted HR = 6.43, 95% CI = 1.59–25.94, based on 4 versus 22 cases). Additional adjustment for household income, as a surrogate for social economic status, did not alter the results. The risk of testicular carcinoma was not increased among ART boys (adjusted HR = 0.67, 95% CI = 0.30–1.50, based on 11 versus 20 cases).

Sensitivity analyses excluding children born before 1989 (starting date NCR) yielded a HR for ART conception versus conception without ART of 0.95 (95% CI = 0.74–1.21). Excluding children born from mothers never treated with ART resulted in comparable risk estimates for ART children versus children conceived without the use of ART (adjusted HR = 1.02, 95% CI = 0.78–1.34). To assess the influence of non-independency owing to the inclusion of siblings in our study, we performed an analysis restricted to the first child with cancer in a sibship. There were only three sibships with two cancer cases each in the cohort. Exclusion of the second child with cancer in these sibships did not alter the overall cancer risk (HR = 1.05, 95% CI = 0.84–1.32). Risk of cancer was also assessed separately in the original and expanded cohort; these risk estimates are shown in Supplementary Table S3.

Discussion

This large-scale study with a median of 18 years of follow-up showed that overall cancer risk in children born after the use of ART is not increased, either when compared with the general population or when compared with children born to subfertile

Table 1. Characteristics of the OMEGA-offspring cohort* by conception method.

	ART N = 51 417	Without ART[a] N = 37 832	Total N = 89 249
Median age at end of follow-up,[b] years (min–max)	16.3 (0.003–36.8)	20.3 (0.003–44.8)	17.8 (0.003–44.8)
Sex, No. (%)			
Male	24 916 (48.5)	18 398 (48.6)	41 314 (48.5)
Female	23 235 (45.2)	17 144 (45.3)	40 379 (45.2)
Unknown	3266 (6.4)	2290 (6.1)	5556 (6.2)
Year of birth, No. (%)			
1975–1989	1068 (2.1)	7908 (20.9)	8976 (10.1)
1990–1994	6.891 (13.4)	5908 (15.6)	12 799 (14.3)
1995–1999	9910 (19.3)	5687 (15.0)	15 597 (17.5)
2000–2004	11 586 (22.5)	7145 (18.9)	18 731 (21.0)
2005–2009	15 189 (29.5)	7699 (20.4)	22 888 (25.7)
≥2010	6773 (13.2)	3485 (9.2)	10 258 (11.5)
Age at end of follow-up,[b] years, No. (%)			
0–9	7874 (15.3)	4036 (10.7)	11 910 (13.3)
10–14	14 832 (28.9)	7662 (20.3)	22 494 (25.2)
15–19	11 460 (22.3)	6942 (18.4)	18 402 (20.6)
20–24	9791 (19.0)	5810 (15.4)	15 601 (17.5)
25–29	6514 (12.7)	5745 (15.2)	12 259 (13.7)
≥30	946 (1.8)	7637 (20.2)	8583 (9.6)
Gestational age (weeks) at birth, mean (SD)	38.2 (2.8)	39.2 (2.4)	38.5 (2.7)
Birthweight, gram, mean (SD)	3065 (758)	3295 (662)	3130 (739)
Birthweight, No. (%)			
<2000	3591 (7.0)	624 (1.7)	4215 (4.7)
2000–2999	13 197 (25.7)	3379 (8.9)	16 576 (18.6)
3000–3499	11 013 (21.4)	5024 (13.3)	16 037 (18.0)
3500–3999	8695 (16.9)	4527 (12.0)	13 222 (14.8)
≥4000	3657 (7.11)	2003 (5.3)	5660 (6.3)
Unknown	11 264 (21.9)	22 275 (58.9)	33 539 (37.6)
Part of multiple birth, No. (%)			
Singleton	36 182 (70.4)	35 206 (93.1)	71 388 (80.0)
Twin	14 273 (27.7)	2524 (6.7)	16 797 (18.8)
Triplet	934 (1.8)	102 (0.3)	1036 (1.2)
Quadruplet	28 (0.1)	0 (0.0)	28 (0.0)
Maternal age at birth of child, years, No. (%)			
<25	755 (1.5)	4108 (10.9)	4863 (5.5)
25–29	7417 (14.4)	8259 (21.8)	15 675 (17.6)
30–34	21 488 (41.8)	13 613 (36.0)	35 101 (39.3)
35–39	18 069 (35.1)	9828 (26.0)	27 897 (31.3)
≥40	3568 (6.9)	1873 (5.0)	5441 (6.1)
Unknown	120 (0.2)	151 (0.4)	271 (0.3)
Parental cause of subfertility,[c] No. (%)			
Male factor	15 343 (29.8)	6931 (18.3)	22 274 (25.0)
Tubal factor	7526 (14.6)	6609 (17.5)	14 135 (15.8)
Unexplained or other factors[d]	21 458 (41.7)	14 674 (38.8)	36 132 (40.5)
Unknown	7090 (13.8)	9618 (25.4)	16 708 (18.7)

[a] Includes children conceived by fertility drugs with/without IUI or naturally conceived children from subfertile couples.
[b] Follow-up ended at date of any cancer diagnosis or date of completeness of cancer registry, whichever came first.
[c] The causes of subfertility were categorized according to the factor that was identified as the most important one within a couple. If several diagnoses had been registered, without mention of the main diagnosis, the following order was applied: male factor, tubal factor, hormonal factor, other factor or unexplained for main diagnosis. Male factors include azoospermia, oligozoospermia, asthenozoospermia, and/or teratozoospermia. Tubal factor was reported for all types of tubal pathology. Hormonal factors include ovulation disorders, PCOS, and premature menopause; unexplained and other factors such as endometriosis and cervical factors.
[d] Other factors include factors such as endometriosis, cervical factors, and hormonal factors (such as ovulation disorders, PCOS, and premature menopause).
* The OMEGA-offspring cohort consists of all live-born offspring from subfertile couples who were treated with ART between 1983 and 2011 in The Netherlands and all offspring of subfertile couples who were not treated with ART between 1980 and 2001.

couples without the use of ART. Despite the reassuring results, an increased risk of cancer was observed in ICSI-conceived children, which was mainly driven by a higher risk of melanoma. However, as the number of melanoma cases was small, this finding may be due to chance and should be interpreted with the greatest caution. Furthermore, if this risk increase would be true, the absolute risk of developing melanoma after ART remains very low (<1%).

Results from the current study are in line with those from the two Scandinavian cohort studies to the extent that no increased overall cancer risk was observed after ART (Hargreave *et al.*, 2019; Sargisian *et al.*, 2022). However, our results are in contrast with two other large population-based cohorts that did report an increase of overall cancer risk after ART (Spector *et al.*, 2019; Weng *et al.*, 2022). The increased risk we observed in ICSI-conceived offspring compared to children conceived without the use of ART is consistent with risk estimates reported in other cohort studies (HR = 1.29, 95% CI = 0.96–1.74 (Spector *et al.*, 2019) and HR = 1.33, 95% CI = 0.94–1.89 (Hargreave *et al.*, 2019), although none of these reached statistical significance (Hargreave *et al.*, 2019; Spector *et al.*, 2019). Although our risk estimates for FET (HR = 1.61 and 1.56) are quite comparable with those observed in the Scandinavian studies (HR = 2.43 (Hargreave *et al.*, 2019), HR = 1.65 (Sargisian *et al.*, 2022)), our results were not statistically significant.

The varying outcomes across studies may be explained by differences in follow-up time (4.6 years (Spector *et al.*, 2019), 6.0 years (Weng *et al.*, 2022), 9.9 years (Sargisian *et al.*, 2022), and

Table 2. Risk of cancer according to conception method compared with the Dutch general population.

Type of malignancy (International Classification of Diseases for Oncology)	ART		Without ART[a]		Total[b]	
	N = 51 417		N = 37 832		N = 89 249	
	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)
All first cancers[c] (C00–80)	157	0.96 (0.81–1.12)	201	0.95 (0.83–1.09)	358	0.95 (0.86–1.06)
Head and neck (C00–14)	5	4.45 (1.44–10.38)	≤3	0.84 (0.10–3.03)	≥5	1.99 (0.80–4.11)
Salivary glands (C07–08)	≤3	6.04 (1.25–17.65)	≤3	2.66 (0.32–9.61)	≥3	4.00 (1.30–9.35)
Parotid gland (C07)	≤3	6.42 (1.32–18.77)	≤3	3.02 (0.37–10.90)	≥3	4.43 (1.44–10.33)
Digestive organs (C15–26, C48.1, C48.2)	7	1.09 (0.44–2.24)	6	0.56 (0.21–1.23)	13	0.76 (0.41–1.31)
Liver, hepatoblastoma (C22)	≤3	0.77 (0.02–4.30)	≤3	1.24 (0.03–6.90)	≤3	0.95 (0.12–3.44)
Bone, joints and soft tissue[c] (C40–41)	16	0.70 (0.40–1.13)	22	1.05 (0.66–1.60)	38	0.87 (0.61–1.19)
Kaposi sarcoma (M9140)	≤3	0.00 (0.00–37.76)	≤3	9.50 (1.96–27.77)	≤3	7.26 (1.50–21.21)
Soft tissue	8	1.14 (0.49–2.24)	9	1.28 (0.59–2.43)	17	1.21 (0.70–1.93)
Bone and joint (C40–41)	7	0.91 (0.37–1.88)	12	1.73 (0.89–3.01)	19	1.30 (0.78–2.03)
Skin, melanoma (C44, C51, C60, C63.2, C80)	16	1.66 (0.95–2.69)	22	0.93 (0.58–1.41)	38	1.14 (0.81–1.57)
Breast (C50)	≤3	0.43 (0.01–2.37)	18	1.05 (0.62–1.65)	≥18	0.97 (0.59–1.52)
Female genital tract (C51–58)	4	0.87 (0.24–2.24)	15	1.20 (0.67–1.98)	19	1.11 (0.67–1.73)
Cervix uteri (C53)	≤3	2.65 (0.55–7.74)	11	1.85 (0.92–3.31)	≥11	1.98 (1.08–3.32)
Male genital tract (C60–62)	12	0.93 (0.48–1.62)	24	1.00 (0.64–1.49)	36	0.98 (0.68–1.35)
Testis (C62)	11	0.94 (0.47–1.68)	20	0.87 (0.53–1.35)	31	0.90 (0.61–1.27)
Urinary tract (C64)	8	0.94 (0.41–1.85)	6	0.73 (0.27–1.60)	14	0.84 (0.46–1.41)
Nephroblastoma (C64)	7	1.12 (0.45–2.30)	4	0.95 (0.26–2.44)	11	1.05 (0.53–1.88)
Eye and adnexa (C69)	8	1.56 (0.69–3.13)	≤3	0.28 (0.01–1.56)	≥8	1.05 (0.48–1.99)
Retinoblastoma (C69)	7	1.64 (0.66–3.37)	≤3	0.34 (0.01–1.99)	≥7	1.13 (0.49–2.23)
Brain and other parts of central nervous system (C70–72, C75.1, C75.3)	14	0.67 (0.37–1.12)	13	0.68 (0.36–1.63)	27	0.68 (0.45–0.98)
Brain malignant (C71)	14	0.88 (0.48–1.48)	13	0.92 (0.49–1.57)	27	0.90 (0.59–1.31)
Endocrine glands (C73–75.0, C75.8, C75.9)	≤3	0.68 (0.14–1.99)	4	0.57 (0.16–1.46)	≥4	0.61 (0.25–1.26)
Lymphohematopoietic malignancies	60	0.92 (0.70–1.19)	58	0.95 (0.72–1.23)	118	0.94 (0.78–1.12)
Hodgkin lymphoma	11	0.89 (0.45–1.60)	16	1.04 (0.60–1.69)	27	0.98 (0.64–1.42)
Mature T/NK cell lymphoma	≤3	1.43 (0.17–5.16)	4	2.62 (0.72–6.72)	≥4	2.05 (0.75–4.47)
Aggressive non-Hodgkin	5	0.79 (0.26–1.83)	≤3	0.14 (0.00–0.76)	≥5	0.44 (0.16–0.96)
Lymphoblastic leukemia	27	0.87 (0.58–1.34)	19	0.86 (0.52–1.34)	46	0.87 (0.64–1.16)
Acute myeloid leukemia	4	0.55 (0.15–1.41)	6	0.94 (0.34–2.05)	10	0.73 (0.35–1.35)
Myelodysplastic syndrome	4	3.62 (0.99–9.27)	≤3	0.00 (0.00–3.76)	≥4	2.09 (0.52–4.91)

SIR: standardized incidence ratio.
[a] Includes naturally conceived children and children conceived by fertility drugs (with/without intrauterine insemination) from subfertile couples.
[b] Total cohort, includes children born after the use of ART and without the use of ART from subfertile couples (and includes naturally conceived children and children conceived by fertility drugs (with/without IUI)).
[c] Only first cancers were included in the analyses.

Table 3. Risk of cancer according to conception method and attained age compared with the Dutch general population.[a]

	IVF		ICSI		Without ART[b]	
	N = 33 484		N = 17 933		N = 37 832	
	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)
Overall	115	0.91 (0.75–1.09)	42	1.11 (0.80–1.51)	201	0.95 (0.83–1.09)
Attained age (years)						
0–4	24	0.71 (0.46–1.06)	17	0.94 (0.55–1.50)	31	0.94 (0.64–1.33)
5–9	13	0.73 (0.39–1.24)	14	1.53 (0.84–2.57)	19	1.00 (0.60–1.57)
10–14	17	1.00 (0.58–1.60)	≤3	0.51 (0.11–1.49)	18	0.97 (0.57–1.53)
15–19	26	1.13 (0.74–1.65)	8	1.75 (0.84–2.57)	21	0.84 (0.52–1.28)
20–24	19	0.89 (0.54–1.39)			37	1.23 (0.87–1.70)
25–29	16	1.18 (0.68–1.92)			29	0.90 (0.60–1.30)
30–34					29	1.04 (0.90–1.50)
≥35					17	0.68 (0.40–1.09)

SIR: standardized incidence ratio.
[a] Only first cancers were included in the analyses.
[b] Includes naturally conceived children and children conceived by fertility drugs (with/without IUI) from subfertile couples.

11.3 years (Hargreave *et al.*, 2019) versus 17.8 years in our study), included treatment years, cohort size, comparison groups (general population (Hargreave *et al.*, 2019; Sargisian *et al.*, 2022; Spector *et al.*, 2019; Weng *et al.*, 2022) versus offspring from subfertile women conceived without the use of ART in our study and two other cohort studies (Hargreave *et al.*, 2019; Weng *et al.*, 2022)), and the availability of confounding variables. As ever more children are born through ICSI and FET, long-term cancer risk should be investigated in cohorts comprising larger numbers of children born after these techniques.

Compared with the general Dutch population, the risk of some cancer types was (non-)significantly increased among ART

children and children conceived without the use of ART. Except for melanoma, the small number of cases did not enable us to further explore the association with ART within the cohort. As melanoma incidence is higher among people with a high income (possibly owing to more frequent exposure to sunlight) (van der Aa *et al.*, 2011), we additionally adjusted for household income of the parents. The results did not change substantially, which might be explained by the fact that the children diagnosed with melanoma are relatively young and that risk factors, such as sun exposure, might not be very important yet. Therefore, early life exposures, including perinatal factors, might be of more importance. Information regarding perinatal exposures and risk of melanoma in offspring is scarce. Interestingly, in a cohort study among women who were exposed to diethylstilbestrol (DES) *in utero*, an increased risk of melanoma was found (risk of melanoma before age 40 years: SIR = 1.59; 95% CI = 1.08–2.26) (Verloop *et al.*, 2010). Although the biological mechanism is unknown, it is possible that conception by ART may also induce melanoma in later life. Before definitive conclusions can be drawn, more research is warranted into perinatal factors, including ART, and risk of melanoma.

The literature on the risk of melanoma after ART is scarce, possibly because most studies did not have sufficiently long follow-up to observe these tumours. Only one earlier study reported on the risk of skin cancer in young adults born to women evaluated for infertility (HR = 1.22, 95% CI = 0.94–1.60) (Hargreave *et al.*, 2013). Two other studies reported the number of observed melanomas (Kallen *et al.*, 2010) and skin cancers (Wainstock *et al.*, 2017) but the numbers were too small for statistical analyses. To further investigate the risks of cancer types frequently occurring at young adult ages, such as melanoma, many large studies with longer follow-up periods are needed.

Table 4. Risk of cancer according to specific conception methods; multivariable Cox regression analyses.

	Total no.	No. of cancers	Multivariably adjusted HR (95% CI)[a]
ART versus without ART[b]			
Without ART	37 832	201	1.00 (ref)
ART	51 417	157	1.06 (0.84–1.33)
IVF	33 484	115	0.97 (0.76–1.23)
ICSI	17 933	42	1.58 (1.08–2.31)
Fresh embryo transfer	47 049	146	1.04 (0.82–1.30)
FET	4368	11	1.61 (0.86–3.03)
IVF + Fresh	32 333	111	0.97 (0.76–1.24)
ICSI + Fresh	14 716	35	1.25 (0.85–1.85)
IVF + FET	1151	4	1.28 (0.47–3.30)
ICSI + FET	3217	7	1.50 (0.68–3.29)
Within ART group			
IVF	33 484	115	1.00 (ref)
ICSI	17 933	42	1.63 (1.11–2.40)
Type of embryo transfer (ART)			
Fresh	47 049	146	1.00 (ref)
FET	4368	11	1.56 (0.83–2.91)

FET: frozen–thawed embryo transfer; HR: hazard ratio.
Each bold row represents a separate regression analysis.
[a] Additionally adjusted for birth year. Parental subfertility cause and maternal age did not confound the results and were therefore not included as confounders.
[b] Includes naturally conceived children and children conceived by fertility drugs (with/without IUI) from subfertile couples.

Strengths and limitations

This study has some limitations. Firstly, as cancer in children and young adults is rare, the number of cancers was rather small for subgroup analyses, despite the large size and long follow-up of the cohort. As a consequence, the observed (non-)significantly increased risks must be interpreted with caution. Although our study had long-term follow-up (median 18 years, IQR = 12.1–24.6), the risks of cancer in older adults conceived by ART remain unclear. Furthermore, analyses according to type of fertility drug used could not be performed owing to little variation in addition

Table 5. Cancer risk for ART conceived children and adolescents versus children and adolescents not conceived by ART; multivariable Cox regression analyses.

	Overall cancer risk					
	ART		Without ART[a]			
	No. of cancers[b]	No. of children[b]	No. of cancers[b]	No. of children[b]	HR for ART versus without ART (95% CI)[c]	*P* value[d]
Attained age (years)						
<10	68	51 417	50	36 700	0.94 (0.65–1.36)	
10–19	52	43 543	39	33 796	1.24 (0.82–1.88)	0.32
≥20	37	17 241	112	19 190	1.04 (0.70–1.56)	0.71
Attained age (years)						
<14	85	51 417	65	37 832	0.95 (0.68–1.31)	
≥14	72	31 141	136	27 675	1.17 (0.86–1.61)	0.35
Attained age (years)						
<18	105	51 417	85	37 832	0.95 (0.71–1.26)	
≥18	52	21 995	116	21 682	1.26 (0.88–1.81)	0.22
Sex						
Male	82	26 583	108	19 527	1.01 (0.75–1.37)	
Female	75	24 834	93	18 305	1.11 (0.81–1.53)	0.65
Part of multiple birth						
Singleton	103	36 182	192	35 206	1.05 (0.81–1.36)	
Multiple	54	15 235	9	2626	0.93 (0.46–1.88)	0.75

HR: hazard ratio.
[a] Includes naturally conceived children and children conceived by fertility drugs (with/without IUI) from subfertile couples.
[b] Not all numbers add up to 100%, because of missing values.
[c] Cox regression analyses: models with age (in years) as time scale and adjusted for birth year. Analyses include 89 249 persons, 51 417 ART, and 37 832 without ART. Parental subfertility cause and maternal age did not confound the results and were therefore not included as confounders.
[d] *P* value of interaction terms.

Table 6. Risk of selected malignancies according to conception method; multivariable Cox regression analyses.

	ART N = 51 417	Without ART[a] N = 37 832
Leukemia[b]		
No. of cancers	31	25
Multivariably adjusted HR (95% CI)[c]	1.15 (0.77–1.71)	1.0 (reference)
Lymphoblastic leukemia		
No. of cancers	27	19
Multivariably adjusted HR (95% CI)[c]	1.31 (0.70–2.45)	1.0 (reference)
Lymphoma[d]		
No. of cancers	19	23
Multivariably adjusted HR (95% CI)[c]	1.20 (0.60–2.41)	1.0 (reference)
Breast		
No. of cancers	≤3	18
Multivariably adjusted HR (95% CI)[c]	0.70 (0.07–6.52)	1.0 (reference)
Cervix		
No. of cancers	7	6
Multivariably adjusted HR (95% CI)[c]	1.73 (0.40–7.54)	1.0 (reference)
Testis		
No. of cancers	11	20
Multivariably adjusted HR (95% CI)[c]	0.67 (0.30–1.50)	1.0 (reference)
Kidney		
No. of cancers	7	6
Multivariably adjusted HR (95% CI)[c]	1.02 (0.32–3.28)	1.0 (reference)
Brain		
No. of cancers	14	14
Multivariably adjusted HR (95% CI)[c]	1.28 (0.56–2.93)	1.0 (reference)
Melanoma		
No. of cancers	16	22
Multivariably adjusted HR (95% CI)[c]	1.55 (0.72–3.34)	1.0 (reference)

HR: hazard ratio.
[a] Includes naturally conceived children and children conceived by fertility drugs (with/without IUI) from subfertile couples.
[b] Acute myeloid leukemia and lymphoblastic leukemia.
[c] Additionally adjusted for birth year. Parental subfertility cause and maternal age did not confound the results and were therefore not included as confounders.
[d] Hodgkin lymphoma and non-Hodgkin lymphoma.

to a large proportion of missing data. Additionally, for 10 365 children, the conception method was unknown, mainly for children in the expanded cohort, therefore they were excluded from our main analysis. However, in sensitivity analyses including these children as either ART-conceived or conceived without the use of ART, the results were comparable, rendering bias caused by exclusion of these children unlikely. Furthermore, the cohort includes children born from 1975 onwards, while cancer registration was incomplete before 1989. Therefore, accrual of person-years and childhood malignancies started in 1989. In sensitivity analyses, exclusion of children born before 1989 did not affect the results in a meaningful way. Selection bias and misclassification bias are therefore highly unlikely. Residual confounding might be present owing to unmeasured differences (such as paternal age) between children born after the use of ART and children conceived without the use of ART. However, an analysis only including siblings from ART children in the comparison group showed comparable results, rendering such bias unlikely. Furthermore, the risk of cancer at young ages may run in families and some ART-conceived children may have had parents who became infertile after cancer treatment. Unfortunately, we had no complete data on the prevalence of cancer among parents, only among the mothers in our original cohort. Data from our original cohort showed that only 0.46% of the women had cancer prior to their subfertility treatment. This is in line with the prevalence of cancer in women from the general Dutch population, rendering bias owing to a higher proportion of parents with cancer less likely. Lastly, results are largely based on ART treatments performed in 1983–2010. Therefore, it is uncertain how the study results generalize to more contemporary ART treatments.

The strengths of the current study include a long and complete follow-up, a comparison group of children from subfertile couples conceived without the use of ART, and detailed information on potential confounders. Selection bias is minimized because the Personal Records Database yielded complete information about all children from women included in the OMEGA study, and cancer incidence in the children was obtained through the national population-based NCR.

In conclusion, after a median follow-up of 18 years, children born after the use of ART did not have an increased overall cancer risk. Our observation of an increased risk among ICSI-conceived children must be interpreted with caution owing to the small number of cases. Many large studies with prolonged follow-up are needed to investigate cancer risk in (young) adults conceived by different types of ART. In addition, international pooling of studies is recommended to provide sufficient power to study the risk of specific cancer sites after ART.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals in the study. The data will be shared on reasonable request to the corresponding author.

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Authors' roles

M.S., F.E.v.L., T.J.R., M.G., and C.B.L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M.S., F.E.v.L., T.J.R., M.G., C.B.L. Acquisition, analysis, or interpretation of data: M.S., F.E.v.L., T.J.R., M.G., C.B.L., M.P., A.C.J.R., A.W.v.d.B.D., C.W.B., M.M.v.d.H.E., E.H.K., R.S., M.K., F.J.M.B., J.S.E.L., L.M.M., E.J.P.v.S., P.M.R., L.A.J.v.d.W., B.J.C., M.H.J.M.C., D.D.M.B., L.R., J.M.J.S., D.C., A.E.P.C., M.G., R.J.T.v.G.,

J.C.M.D., M.M.E.v.R., W.v.I., C.J.C.M.H., and P.A.M.M. Drafting of the manuscript: M.S., F.E.v.L., T.J.R., M.G., and C.B.L. Critical revision of the manuscript for important intellectual content: F.E.v.L., T.J.R., M.G., C.B.L., M.P., A.C.J.R., A.W.v.d.B.D., C.W.B., M.M.v.d.H.E., E.H.K., R.S., M.K., F.J.M.B., J.S.E.L., L.M.M., E.J.P.v.S., P.M.R., L.A.J.v.d.W., B.J.C., M.H.J.M.C., D.D.M.B., L.R., J.M.J.S., D.C., A.E.P.C., M.G., R.J.T.v.G., J.C.M.D., M.M.E.v.R., W.v.I., C.J.C.M.H., and P.A.M.M. Statistical analysis: M.S., F.E.v.L., T.J.R., M.G., and C.B.L. Obtained funding: M.S., F.E.v.L., T.J.R., M.G., C.B.L., C.W.B., A.W.v.d.B.D., and M.M.v.d.H.E. Administrative, technical, or material support: M.S., F.E.v.L., T.J.R., and M.P. Study supervision: F.E.v.L., T.J.R., M.G., and C.B.L.

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Conflict of interest

The authors declare no competing interests.

Appendix

The OMEGA-offspring steering group includes E.H. Kostelijk and R. Schats (Amsterdam UMC, Free University Amsterdam, Amsterdam), M. Kortman and F.J.M. Broekmans (University Medical Center Utrecht, Utrecht), J.S.E. Laven and L.M. Moolenaar (Erasmus University Medical Center, Rotterdam), E.J.P. van Santbrink and P.M. Rijnders (Reinier de Graaf Hospital, Voorburg), L.A.J. van der Westerlaken (Leiden University Medical Center, Leiden), B.J. Cohlen and M.H.J.M. Curfs (Isala, Zwolle), D.D.M. Braat and L. Ramos (Radboud University Medical Center, Nijmegen), J.M.J. Smeenk and D. Consten (St Elisabeth Hospital, Tilburg), A.E.P. Cantineau (University of Groningen, University Medical Center Groningen, Groningen), M. Goddijn (Amsterdam UMC, University of Amsterdam, Amsterdam), R.J.T. van Golde and J.C.M. Dumoulin (Maastricht University Medical Center, Maastricht), M.M.E. van Rumste (Catharina Hospital, Eindhoven), W. van Inzen (IVF Center Medisch Centrum Kinderwens, Leiderdorp), C.J.C.M. Hamilton (Jeroen Bosch Hospital, Den Bosch), and P.A.M. Meeuwissen (Admiraal de Ruyter Hospital, Vlissingen).

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