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Health of singletons born after frozen embryo transfer until early adulthood: a Finnish register study

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STUDY QUESTION: Is the health of singletons born after frozen embryo transfer (FET) comparable to that of singletons born after fresh embryo transfer (ET) until early adulthood?

SUMMARY ANSWER: The health of singletons born after FET does not differ from that of singletons born after fresh ET.

WHAT IS KNOWN ALREADY: The differences in perinatal outcomes of children born after FET and fresh ET are well known. FET is associated with an increased risk of large-for-gestational-age but diminished risks of preterm birth (PTB), small-for-gestational-age and decreased perinatal mortality compared to fresh ET. However, knowledge on the long-term health after FET is scarce.

STUDY DESIGN, SIZE, DURATION: This retrospective register-based cohort study compares singletons born after FET (n = 1825) between the years 1995 and 2006 to those born after fresh ET (n = 2933) and natural conception (NC, n = 31 136) with a mean follow-up time of 18–20 years.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Singletons born after FET were compared to those born after fresh ET and NC regarding the frequencies of diagnoses in the main ICD-10 chapters (International Statistical Classification of Diseases and Related Health Problems, 10th revision), the number of outpatient visits and hospital admissions, and mortality. Adjustments were made for PTB, maternal age, parity, socioeconomic status based on mother's occupation and offspring sex. The study combines data from the Finnish Medical Birth Register, the Finnish Care Register for Health Care (CRHC) and the Cause-of-Death Register at Statistics Finland. The Student's *T*-test was used for continuous variables, and the Chi-square test was used for categorical variables. Cox regression was used to estimate crude and adjusted hazard ratios (HRs and aHRs, respectively). A general linear model was used to compare the means of outpatient visits, hospital admissions and lengths of hospital stays per person.

MAIN RESULTS AND THE ROLE OF CHANCE: No significant differences between the FET and fresh ET groups were found in the frequency of diagnoses in any of the ICD-10 chapters or in the parameters describing the need for hospital care. However, compared to the NC group, higher proportions in the FET group had outpatient visits in the hospital (93.5% vs 92.2%, aHR 1.23, 95% CI 1.17, 1.30) or hospital admissions (48% vs 46.5%, aHR 1.28, 95% CI 1.19, 1.37). Compared to the NC group, the FET group had elevated adjusted risks of diagnoses of infectious and parasitic diseases (aHR 1.24; 95% CI 1.11, 1.38), neoplasms (aHR 1.68; 95% CI 1.48, 1.91), diseases of the eye and adnexa, the ear or mastoid process (aHR 1.11; 95% CI 1.01, 1.21), the respiratory system (aHR 1.15; 95% CI 1.06, 1.23), the digestive system (aHR 1.17; 95% CI 1.05, 1.32), the skin or subcutaneous tissue (aHR 1.28; 95% CI 1.14, 1.43) and the genitourinary system (aHR 1.27; 95% CI 1.11, 1.45), as well as congenital malformations or chromosomal abnormalities (aHR 1.31; 95% CI 1.14, 1.50) and symptoms, signs or abnormal clinical or laboratory findings (aHR 1.25, 95% CI 1.16, 1.34).

LIMITATIONS, REASONS FOR CAUTION: Only hospital-based inpatient and outpatient care is covered by the CRHC register, excluding milder cases diagnosed elsewhere. We were not able to study the effect of ART treatments and subfertility separately in our setting. In addition, although our cohort is reasonably sized, even larger cohorts would be needed to reliably study rare outcomes, such as cancer.

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WIDER IMPLICATIONS OF THE FINDINGS: For many ICD-10 chapters, we present the first published data on the long-term outcome of singletons born after FET. The results on FET versus fresh ET are reassuring, whereas the results on FET versus NC warrant further investigation.

STUDY FUNDING/COMPETING INTEREST(S): Finnish government research funding was obtained for this study. Funding was also obtained from the Finnish Medical Society Duodecim, the Päivikki and Sakari Sohlberg Foundation, Orion Research Foundation, Finnish Society of Obstetrics and Gynaecology (research grants to A.M.T.) and Finnish government research funding. The funding sources were not involved in the planning or execution of the study. The authors have no competing interests to declare.

TRIAL REGISTRATION NUMBER: N/A.

Key words: frozen embryo transfer / FET / ART / long-term health / outcome

Introduction

The health of children born after assisted reproduction is of major interest since already up to 6% of children born in European countries are the result of ARTs (Wyns *et al.*, 2020). Frozen embryo transfers (FETs) are on a steep rise and comprise 32.6% of all ART treatment cycles in Europe. Delivery rates are higher for FET cycles per thawing than for fresh embryo transfer (ET) cycles per oocyte aspiration (Wyns *et al.*, 2021). In Finland, nearly 50% of ART children are born after FET (THL, 2019).

Large cohort studies and meta-analyses have described the perinatal results. Singletons born after FET have a higher mean birthweight and a higher risk of large-for-gestational-age (LGA) compared to children born after fresh ET (Pelkonen *et al.*, 2010; Maheshwari *et al.*, 2018; Sha *et al.*, 2018; Terho *et al.*, 2021). In turn, the risks of preterm birth (PTB) and small-for-gestational-age (SGA) (Maheshwari *et al.*, 2018; Sha *et al.*, 2018) as well as perinatal mortality (Sha *et al.*, 2018) are decreased for FET children compared to fresh ET children. Compared to children born from natural conception (NC), FET singletons have increased risks of LGA and PTB (Elias *et al.*, 2020).

Long-term health data on children born after FET are scarce. Most studies have presented results on ART, fertility treatments or IVF compared to NC, and the possible effects of FET remain unclear (Wainstock *et al.*, 2019; Wijs *et al.*, 2021; Pettersson *et al.*, 2022). In addition, previous studies have concentrated on outcomes of selected separate diagnoses, such as cancer (Spector *et al.*, 2019; Zhang *et al.*, 2020). Our previous study (Pelkonen *et al.*, 2015) described widely the health results until the age of three and found the health of singleton children to be similar between FET and fresh ET groups, with ART children having slightly increased risks of hospital admission compared to NC children. The aim of this study is to provide a long-term follow-up until the age of 18 on singletons born after FET, based on Finnish high-quality population-based register data.

Materials and methods

Study population

The population of the present study includes preterm and term liveborn singletons born after FET ($n = 1825$) and fresh ET ($n = 2933$) between the years 1995 and 2006 in Oulu and Helsinki city areas in Finland. A 10% sample of NC controls ($n = 31\,136$) from the same birth years, matched for area of residence, was obtained from the Finnish Medical Birth Register (FMBR). This study is a continuation of previous studies by our study group covering the perinatal health (Pelkonen *et al.*, 2010), major congenital anomalies (Pelkonen *et al.*, 2014) and somatic health of children born after FET and fresh ET until the age of 3 (Pelkonen *et al.*, 2015). This register-based cohort study combines data from the FMBR, as well as the Finnish Care Register for Health Care (CRHC) and the Cause-of-Death Register at Statistics Finland.

The Finnish Institute for Health and Welfare (THL) is responsible for the FMBR and the CRHC registers. The FMBR includes data on live births and on stillbirths of fetuses with a birth weight of at least 500 g or gestational age of at least 22 weeks, as well as data on the mothers. Data sources of the FMBR include maternity hospitals and neonatal units, the Finnish Central Population Register kept by the Digital and population data services agency and Statistics Finland. The CRHC covers hospital and other inpatient care, and outpatient visits in public hospitals for the purpose of statistics, research and planning. Care providers submit the mandatory care notifications on a yearly basis. The care notifications include data on the personal identity number of the patient, reason for seeking care, admission and discharge, diagnoses, procedures and interventions (THL, 2021).

The Cause of Death Register is maintained by Statistics Finland, and it produces yearly statistics on causes of death and mortality based on death certificates complemented with data on deaths from the Population Information System of the Digital and population data services agency (Official Statistics of Finland (OSF): Causes of death, 2022).

Data linkage between registers is possible using the unique personal identity numbers assigned to each Finnish citizen immediately at birth or upon immigration. The personal identity numbers are extensively used throughout the society: in healthcare, social welfare system, school system, banking etc. All data were pseudonymized after the register linkage and before analyses.

Study permission and ethical approval

Study permission was granted by Findata, the Social and Health Data Permit Authority. Separate ethical approval was not needed since the study was based on register data and no registered person was contacted.

Outcomes and statistical methods

The frequencies of diagnoses in the main ICD-10 chapters (International Statistical Classification of Diseases and Related Health Problems, 10th revision) were compared between the study groups,

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with the first occurring diagnosis in each chapter counted per person, not taking repeated events into account. Crude hazard ratios (HRs) and adjusted hazard ratios (aHRs) were calculated for each main ICD-10 diagnosis chapter for FET versus fresh ET, FET versus NC and fresh ET versus NC. Adjustments were made for PTB, maternal age, parity, socioeconomic status (SES) based on mother's occupation and offspring sex.

In addition, the proportion of persons with outpatient visits and hospital admissions in each study group were compared. Outpatient visits in the hospital, hospital admissions and the lengths of hospital stay (days) per person were compared between the FET, fresh ET and NC groups. Mortality rates for each study group were calculated.

Background characteristics were described as mean and SD for continuous variables and as count and percentage for categorical variables. The Student's *T*-test was used for continuous variables, and the Chi-square test was used for categorical variables. Cox regression was used to estimate HRs and aHRs. The follow-up started at birth and ended in the first appearance of the selected outcome, death or end of follow-up, 31 December 2020. A general linear model was used to compare the means of outpatient visits, hospital admissions and lengths of hospital stays per person.

All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute).

Results

Background characteristics

The background characteristics for the study groups are presented in Table I. Mothers in the FET group were older (mean 34.3 years) compared to those of the fresh ET group (33.9 years) and were less often primiparous (34.8%) compared to those of the fresh ET group (52.3%). The number of PTBs in the FET group was lower (6.4%) compared to the fresh ET group (8.5%), and the percentage of LGA was significantly higher for FET (3.9%) compared to fresh ET (2.1%). The mean follow-up time was shorter for FET (18.8 years) compared to fresh ET (19.5 years) and NC (20.5 years).

Diagnoses (ICD-10 chapters)

Table II presents the results on the frequency of diagnoses in the main ICD-10 chapters. No significant differences were found between the FET and fresh ET groups. However, the FET group had modestly elevated adjusted risks for diagnoses in several ICD-10 chapters compared to the NC group: A + B (infectious and parasitic diseases, aHR 1.24; 95% CI 1.11, 1.38), C + D00–D48 (neoplasms, aHR 1.68; 95% CI 1.48, 1.91), H (diseases of the eye and adnexa and the ear and mastoid process, aHR 1.11; 95% CI 1.01, 1.21), J (diseases of the respiratory system, aHR 1.15; 95% CI 1.06, 1.23), K (diseases of the digestive system, aHR 1.17; 95% CI 1.05, 1.32), L (diseases of the skin and subcutaneous tissue, aHR 1.28; 95% CI 1.14, 1.43), N (diseases of the genitourinary system, aHR 1.27; 95% CI 1.11, 1.45), Q (congenital malformations and chromosomal abnormalities, aHR 1.31; 95% CI 1.14, 1.50) and R (symptoms, signs and abnormal clinical and laboratory findings, aHR 1.25, 95% CI 1.16, 1.34). Adjustments were made for PTB, maternal age, parity, SES and offspring sex (Table II).

Hospital visits and admissions

More than 90% of persons in each study group had outpatient hospital visits, and almost 50% had hospital admissions. There were no significant differences between the FET and fresh ET groups in the number of outpatient hospital visits or hospital admissions. However, when compared to the NC group (92.2%), the proportion of persons with outpatient visits in the hospital was higher in the FET group (93.5%; $P < 0.001$; aHR 1.23, 95% CI 1.17, 1.30). For hospital admissions, an aHR of 1.28 (95% CI 1.19, 1.37) was found for FET versus NC. Adjustments were made for PTB, maternal age, parity, SES and offspring sex (Table III).

No significant differences between the FET and fresh ET groups were found in the mean number of outpatient visits, hospital admissions or days in hospital per person. Compared to the NC group, the FET group was associated with increased hospital admissions per person, 1.34 (95% CI 1.21, 1.48) vs 1.15 (95% CI 1.12, 1.19), difference between means 0.19 (95% CI 0.05, 0.32) (Table IV).

Mortality

The numbers of deaths were 7 (0.4%) for FET, 26 (0.9%) for fresh ET and 175 (0.6%) for NC ($P = 0.042$ for FET vs fresh ET, $P = 0.317$ for FET vs NC and $P = 0.028$ for fresh ET vs NC; data not shown).

Discussion

This Finnish register-based study shows that the general health of singletons born after FET and fresh ET is comparable up to early adulthood. However, as compared to those born after NC, singletons born after both FET and fresh ET had slightly increased risks of hospital visits and admissions, as well as elevated risks of diagnoses in several main ICD-10 chapters.

Our previous study conducted on the same population compared the health outcomes until the age of 3. Compared to the NC group, ART children (FET and fresh ET) had a slightly increased risk of hospital admission; aOR 1.10, 95% CI 1.02–1.19, adjusted for year of birth, PTB, maternal age, parity and SES. No significant differences between the FET and fresh ET groups were found in the risk of hospital admission or for any of the ICD-10 chapters (Pelkonen *et al.*, 2015). These findings persist in the present study. In contrast with our results, a US study found FET (n = 2101) to be associated with increased odds of infectious disease, and respiratory and neurologic conditions compared to fresh ET (Hwang *et al.*, 2019). The size of the FET cohort was similar to ours. However, the exact length of follow-up was not reported but was short, limited to 'infancy', which limits the comparability of the results with ours.

There are a few studies describing the risk of neoplasms and cancer of children born after FET. No increased cancer risk was found for FET (n = 33 899) versus fresh ET in a large US cohort with a mean follow-up of 4–6 years (Spector *et al.*, 2019). In accordance with this, a meta-analysis (Zhang *et al.*, 2020) found no difference in cancer risk between FET and fresh ET (relative risk (RR) 1.28, 95% CI 0.96–1.69). However, they described an increased risk of cancer for FET versus NC (RR 1.37, 95% CI 1.04–1.81) (Zhang *et al.*, 2020). In the present study, borderline significant differences were seen in the incidence of diagnoses of neoplasms (ICD-10 chapters C + D00–D48) between

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Table I Background characteristics of the study population.

Variable	FET n = 1825	Fresh ET n = 2933	NC n = 31 136	*P* FET vs fresh ET	*P* FET vs NC	*P* fresh ET vs NC
Maternal age, y, mean (SD)	34.3 (4.0)	33.9 (4.3)	30.0 (5.4)	**0.009**	**<0.001**	**<0.001**
Missing, n (%)	2 (0.1)	0 (0)	71 (0.2)			
Primiparous, n (%)	635 (34.8)	1535 (52.3)	9893 (31.8)	**<0.001**	**0.007**	**<0.001**
Missing (%)	2 (0.1)	1 (0.0)	105 (0.3)			
Smoking, n (%)	130 (7.1)	194 (6.6)	4707 (15.1)	0.498	**<0.001**	**<0.001**
Missing, n (%)	24 (1.3)	43 (1.5)	774 (2.5)			
Maternal SES				0.629	**<0.001**	**<0.001**
Upper white collar worker, n (%)	581 (31.8)	912 (31.1)	6460 (20.7)			
Lower white collar worker, n (%)	798 (43.7)	1254 (42.8)	11 873 (38.1)			
Blue collar worker, n (%)	166 (9.1)	286 (9.8)	3971 (12.8)			
Other or missing, n (%)	280 (15.3)	481 (16.4)	8832 (28.4)			
ICSI, n (%)	536 (29.4)	965 (32.9)	NA	**0.011**	NA	NA
Preterm births, n (%)	117 (6.4)	250 (8.5)	1341 (4.3)	**0.008**	**<0.001**	**<0.001**
Extremely preterm, <28 GW, n (%)	5 (0.3)	14 (0.5)	73 (0.2)	0.279	0.736	**0.013**
Caesarean sections, n (%)	518 (28.4)	818 (27.9)	5151 (16.5)	0.712	**<0.001**	**<0.001**
Missing, n (%)	0 (0)	0 (0)	5 (0.0)			
Offspring male sex, n (%)	926 (50.7)	1500 (51.1)	15 945 (51.2)	0.787	0.696	0.943
Birth weight, g, mean (SD)	3554 (579)	3423 (594)	3544 (544)	**<0.001**	0.437	**<0.001**
SGA, n (%)	55 (3.0)	126 (4.3)	992 (3.2)	**0.025**	0.683	**0.001**
LGA, n (%)	72 (3.9)	62 (2.1)	909 (2.9)	**<0.001**	**0.012**	**0.012**
NICU, n (%)	49 (2.7)	77 (2.6)	525 (1.7)	0.901	**0.002**	**<0.001**
Birth year				**<0.001**	**<0.001**	**<0.001**
1994–1997	241 (13.2)	567 (19.3)	9937 (31.9)			
1998–2000	421 (23.1)	820 (28.0)	6895 (22.1)			
2001–2003	533 (29.2)	773 (26.4)	6944 (22.3)			
2004–2006	630 (34.5)	773 (26.4)	7289 (23.4)			
Missing, n (%)	0 (0)	0 (0)	71 (0.2)[a]			
Follow-up time, y, mean (SD)[b]	18.8 (3.3)	19.5 (3.6)	20.5 (4.0)	**<0.001**	**<0.001**	**<0.001**

Independent samples *T*-test and Chi-square test.
FET, frozen embryo transfer; ET, embryo transfer; NC, natural conception; y, year; SES, socioeconomic status; NA, not applicable; GW, gestational week; SGA, small-for-gestational-age; LGA, large-for-gestational-age; NICU, treatment in neonatal intensive care unit.
[a]Incomplete personal ID code.
[b]Follow-up from birth until 31 December 2020 or death.
Bold indicates statistical significance at $P < 0.05$.

FET, fresh ET and NC. When restricting the analysis to malignant neoplasms (ICD-10 chapter C), no significant differences were seen. The overall incidence of malignant neoplasms was low in all groups: 7 (0.4%), 8 (0.3%) and 118 (0.4%) for FET, fresh ET and NC, respectively (data not shown). Since the incidence of childhood cancer is very low, large cohorts are needed to reach sufficient power to show differences between groups. This, as well as the different adjustments, may explain the conflicting results on cancer risk between different studies.

A recent Swedish study suggested that the risk of type 1 diabetes is increased for FET (n = 11 211) compared to fresh ET and NC (aHR 1.52, 95% CI 1.08, 2.14 and aHR 1.41, 95% CI 1.05, 1.89, respectively). Adjustments were made for maternal age, smoking, parental country of birth, educational level, type 1 diabetes, IVF/ICSI and year of birth (Norrman *et al.*, 2020). In contrast, a Danish study found no association between ART (n = 8490) and type 1 diabetes, nor between FET (n = 715) and type 1 diabetes (Kettner *et al.*, 2016). In our study, no significant differences were found for endocrine, nutritional and metabolic diseases (ICD-10 chapter E) between the groups.

In the present study, no significant differences between FET, fresh ET and NC were found for ICD-10 chapter F (mental or behavioral disorders). In line with this, a recently published large Nordic cohort study found no significant differences in the risk of neurodevelopmental disorders between FET (n = 18 563) and fresh ET. However, ART was associated with a higher risk of learning and motor functioning disorders (aHR 1.17, 95% CI 1.11, 1.24) compared to NC (Rönö *et al.*, 2022). In addition, a recent population-based prospective study from Sweden found slightly increased risks of mood disorders and antidepressant use up to the median age of 18 when FET (n = 3636) was compared to fresh ET. However, the authors concluded that these

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Table II Frequency of main ICD-10 chapters in hospital visits and admissions.[a]

ICD-10 chapter	FET	Fresh ET	NC	*P* FET vs fresh ET	*P* FET vs NC	*P* Fresh ET vs NC	FET vs Fresh ET (1.0)		FET vs NC (1.0)		Fresh ET vs NC (1.0)	
							HR (95% CI)	aHR[b] (95% CI)	HR (95% CI)	aHR[b] (95% CI)	HR (95% CI)	aHR[b] (95% CI)
	n = 1825	n = 2933	n = 31 136									
A + B, Infectious and parasitic diseases, n (%)	382 (20.9)	627 (21.4)	5971 (19.2)	0.714	0.065	**0.004**	1.00 (0.88, 1.13)	1.01 (0.89, 1.14)	**1.18 (1.06, 1.31)**	**1.24 (1.11, 1.38)**	**1.17 (1.08, 1.27)**	**1.22 (1.12, 1.33)**
C + D00–D48, Neoplasms, n (%)	278 (15.2)	447 (15.2)	4597 (14.8)	0.994	0.584	0.488	**1.17 (1.01, 1.36)**	1.16 (1.00, 1.35)	**1.76 (1.55, 1.99)**	**1.68 (1.48, 1.91)**	**1.51 (1.37, 1.67)**	**1.44 (1.30, 1.60)**
D50–D89, Diseases of the blood and immune system, n (%)	141 (7.7)	241 (8.2)	2337 (7.5)	0.545	0.729	0.164	0.96 (0.77, 1.20)	0.95 (0.76, 1.18)	**1.23 (1.02, 1.47)**	1.20 (1.00, 1.45)	**1.27 (1.11, 1.46)**	**1.24 (1.07, 1.44)**
E, Endocrine, nutritional and metabolic diseases, n (%)	134 (7.3)	206 (7.0)	1988 (6.4)	0.678	0.105	0.178	1.06 (0.85, 1.32)	1.07 (0.86, 1.33)	**1.22 (1.03, 1.46)**	1.17 (0.97, 1.40)	1.14 (0.99, 1.32)	1.08 (0.93, 1.26)
F, Mental and behavioral disorders, n (%)	394 (21.6)	663 (22.6)	7769 (25.0)	0.412	**0.001**	**0.005**	1.00 (0.88, 1.13)	0.99 (0.88, 1.13)	0.95 (0.86, 1.05)	0.99 (0.90, 1.10)	0.95 (0.88, 1.03)	0.98 (0.90, 1.06)
G, Diseases of the nervous system, n (%)	110 (6.0)	192 (6.5)	2183 (7.0)	0.475	0.108	0.344	0.98 (0.78, 1.25)	0.97 (0.77, 1.23)	1.00 (0.82, 1.21)	1.01 (0.88, 1.30)	1.02 (0.88, 1.18)	1.07 (0.92, 1.25)
H, Diseases of the eye and adnexa and the ear and mastoid process, n (%)	551 (30.2)	924 (31.5)	9549 (30.7)	0.341	0.668	0.349	0.98 (0.88, 1.09)	0.97 (0.88, 1.08)	1.01 (0.93, 1.10)	**1.11 (1.01, 1.21)**	1.04 (0.97, 1.11)	**1.14 (1.07, 1.23)**
I, Diseases of the circulatory system, n (%)	49 (2.7)	81 (2.8)	955 (3.1)	0.875	0.356	0.357	1.07 (0.75, 1.53)	1.08 (0.76, 1.55)	1.08 (0.81, 1.43)	1.07 (0.80, 1.44)	1.01 (0.80, 1.26)	1.00 (0.79, 1.27)
J, Diseases of the respiratory system, n (%)	770 (42.2)	1266 (43.2)	12 819 (41.2)	0.510	0.398	**0.036**	1.00 (0.92, 1.10)	1.02 (0.93, 1.11)	**1.09 (1.01, 1.17)**	**1.15 (1.06, 1.23)**	**1.08 (1.02, 1.15)**	**1.13 (1.07, 1.21)**
K, Diseases of the digestive system, n (%)	321 (17.6)	547 (18.6)	5583 (17.9)	0.357	0.711	0.332	0.97 (0.84, 1.11)	0.97 (0.85, 1.12)	1.10 (0.98, 1.23)	**1.17 (1.05, 1.32)**	**1.13 (1.03, 1.23)**	**1.19 (1.09, 1.31)**
L, Diseases of the skin and subcutaneous tissue, n (%)	343 (18.8)	520 (17.7)	5141 (16.5)	0.354	**0.011**	0.090	1.11 (0.96, 1.27)	1.10 (0.96, 1.27)	**1.24 (1.12, 1.39)**	**1.28 (1.14, 1.43)**	**1.13 (1.03, 1.24)**	**1.15 (1.05, 1.27)**
M, Diseases of the musculoskeletal system and connective tissue, n (%)	246 (13.5)	463 (15.8)	4706 (15.1)	**0.030**	0.057	0.332	0.89 (0.76, 1.04)	0.89 (0.76, 1.04)	1.04 (0.91, 1.18)	1.02 (0.99, 1.04)	**1.15 (1.05, 1.27)**	**1.24 (1.12, 1.37)**
N, Diseases of the genitourinary system, n (%)	246 (13.5)	409 (13.9)	4196 (13.5)	0.651	0.057	0.478	1.03 (0.88, 1.21)	1.05 (0.89, 1.23)	**1.18 (1.04, 1.35)**	**1.27 (1.11, 1.45)**	**1.14 (1.03, 1.26)**	**1.23 (1.10, 1.37)**
Q, Congenital malformations and chromosomal abnormalities, n (%)	247 (13.5)	400 (13.6)	3159 (10.1)	0.919	**<0.001**	**<0.001**	1.00 (0.86, 1.17)	0.99 (0.84, 1.16)	**1.40 (1.23, 1.59)**	**1.31 (1.14, 1.50)**	**1.39 (1.25, 1.54)**	**1.28 (1.15, 1.43)**
R, Symptoms, signs and abnormal clinical and laboratory findings, n (%)	795 (43.6)	1236 (42.1)	12 710 (40.8)	0.335	**0.021**	0.164	1.08 (0.99, 1.19)	1.09 (1.00, 1.20)	**1.21 (1.12, 1.30)**	**1.25 (1.16, 1.34)**	**1.11 (1.04, 1.17)**	**1.14 (1.07, 1.21)**

Chi-square test and Cox regression.

Only the first diagnosis per person is included in the analyses, repeated events are not taken into account.

ICD-10, International Classification of diseases, 10th revision; FET, frozen embryo transfer; ET, embryo transfer; NC, natural conception; HR, hazard ratio; aHR, adjusted hazard ratio.

[a]Any overnight visit is considered hospital stay.

[b]Adjusted for preterm birth, maternal age, parity, socioeconomic status and offspring sex (Cox regression takes follow-up time into account).

Bold indicates statistical significance.

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Table III Outpatient hospital visits and hospital admissions.[a]

Variable	FET	Fresh ET	NC	*P* FET vs fresh ET	*P* FET vs NC	*P* fresh ET vs NC	FET vs fresh ET (1.0)		FET vs NC (1.0)		Fresh ET vs NC (1.0)	
							HR	aHR[b]	HR	aHR[b]	HR	aHR[b]
	n = 1825	n = 2933	n = 31 136				(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Persons with outpatient visits, n (%)	1706 (93.5)	2732 (93.1)	29 717 (92.2)	0.656	**<0.001**	**<0.001**	1.04 (0.98, 1.11)	1.05 (0.99, 1.12)	**1.21 (1.15, 1.27)**	**1.23 (1.17, 1.30)**	**1.16 (1.12, 1.21)**	**1.17 (1.12, 1.22)**
Persons with hospital admissions, n (%)	876 (48.0)	1401 (47.8)	14 473 (46.5)	0.876	0.207	0.183	1.04 (0.95, 1.13)	1.07 (0.98, 1.16)	**1.16 (1.08, 1.24)**	**1.28 (1.19, 1.37)**	**1.11 (1.05, 1.17)**	**1.21 (1.14, 1.28)**

Independent samples *T*-test and Cox regression.
FET, frozen embryo transfer; ET, embryo transfer; NC, natural conception; HR, crude hazard ratio; aHR, adjusted hazard ratio.
[a]Any overnight stay is considered a hospital admission.
[b]Adjusted for preterm birth, maternal age, parity, socioeconomic status and offspring sex. Cox regression takes follow-up time into consideration.
Bold indicates statistical significance.

Table IV Mean number of outpatient hospital visits, hospital admissions[a] and days in hospital per person.

Variable	FET	Fresh ET	NC	*P* FET vs fresh ET	*P* FET vs NC	*P* fresh ET vs NC	FET vs fresh ET	FET vs NC	Fresh ET vs NC
	n = 1825	n = 2933	n = 31 136				Difference between means (95% CI)	Difference between means (95% CI)	Difference between means (95% CI)
CRUDE									
Outpatient visits in hospital per person, mean (95% CI)	19.9 (18.1, 21.8)	21.7 (20.2, 23.1)	20.7 (20.3, 21.2)	0.116	0.345	0.226	−1.7 (−4.0, 0.6)	−0.8 (−2.7, 1.1)	0.9 (−0.6, 2.4)
Hospital admissions per person, mean (95% CI)	1.16 (1.04, 1.30)	1.22 (1.12, 1.32)	1.17 (1.14, 1.20)	0.542	0.955	0.376	−0.05 (−0.22, 0.11)	0.00 (−0.14, 0.13)	0.05 (−0.06, 0.16)
Days in hospital per person, mean (95% CI)	6.06 (4.23, 7.90)	7.87 (6.42, 9.31)	6.90 (6.45, 7.34)	0.287	0.341	0.454	−1.80 (−4.14, 0.54)	−0.83 (−2.72, 1.06)	0.97 (−0.55, 2.48)
ADJUSTED[b]									
Outpatient visits in hospital per person, mean (95% CI)	21.3 (19.4, 23.2)	22.2 (20.7, 23.7)	20.6 (20.2, 21.1)	0.418	0.491	0.051	−0.9 (−3.2, 1.4)	0.7 (−1.2, 2.6)	1.6 (0.0, 3.1)
Hospital admissions per person, mean (95% CI)	1.34 (1.21, 1.48)	1.32 (1.22, 1.43)	1.15 (1.12, 1.19)	0.838	**0.006**	**0.002**	0.02 (−0.15, 0.18)	**0.19 (0.05, 0.32)**	**0.17 (0.06, 0.28)**
Days in hospital per person, mean (95% CI)	6.92 (5.04, 8.80)	7.99 (6.49, 9.50)	6.85 (6.40, 7.29)	0.367	0.940	0.155	−1.07 (−3.41, 1.26)	0.08 (−1.87, 2.02)	1.15 (−0.44, 2.73)

Independent samples *T*-test and General linear model.
FET, frozen embryo transfer; ET, embryo transfer; NC, natural conception; HR, crude hazard ratio; aHR, adjusted hazard ratio.
[a]Any overnight stay is considered a hospital admission.
[b]Adjusted for birth year, preterm birth, maternal age, parity, socioeconomic status and offspring sex.
Bold indicates statistical significance.

differences were likely explained by differences in parental characteristics, such as subfertility (Wang *et al.*, 2022).

It has been reported in previous studies that the risk of asthma is increased for ART children compared to children born from NC (Carson *et al.*, 2013; Magnus *et al.*, 2019), but no data have been published specifically on FET and the risk of asthma. A recent meta-analysis of 14 high-quality studies verified the association of ART with an increased risk of asthma (RR 1.28, 95% CI 1.08, 1.51) (Wijs *et al.*, 2021). In the present study, the risk of respiratory diseases was increased for FET compared to NC. These diagnoses were mainly upper respiratory infections, allergic rhinitis, and asthma (data not shown). No significant differences were found between FET and fresh ET. These results seem to be in line with previous literature and further strengthen the association between asthma and assisted reproduction.

Several studies from an Israeli study group have described outcomes after IVF (n = 2603) in a local population-based cohort concerning separate diagnoses, with unfortunately no data on the use of FET. They have described increased risks of pediatric infections (Wainstock *et al.*, 2019), gastrointestinal (Shachor *et al.*, 2020), eruptive dermatological (Krieger *et al.*, 2018) and ophthalmic (Tsumi *et al.*, 2021) morbidities compared to NC. These findings appear to be in line with our results, where FET, as well as fresh ET, were associated with increased risks of hospital-based infectious diagnoses and diseases of the digestive system compared to NC. Additionally, in our study, increased risks of skin conditions were found for FET versus NC and fresh ET versus NC. Atopy and dermatitis were among the most frequent diagnoses in this chapter for FET (data not shown). However, no significant differences were found between FET and fresh ET.

Major congenital anomalies of the present cohort were described in our earlier study based on the Finnish Register of Congenital Malformations. No significant differences were found between FET and fresh ET, but ART had a higher adjusted odds of a major congenital anomalies compared to NC (Pelkonen *et al.*, 2014). This finding persists in the present study regarding a diagnosis in ICD-10 chapter Q including both minor and major anomalies. Overall mortality was significantly lower for FET compared to NC, as well as NC compared to fresh ET. However, these results should be regarded with caution, as the absolute incidences of death are low.

In line with our previous study (Pelkonen *et al.*, 2015), in the current study, the FET and fresh ET groups had slightly higher percentage of outpatient visits and hospital admissions compared to the NC group. In addition, the FET and fresh ET groups had more diagnoses in ICD-10 chapter R (symptoms, signs, and abnormal clinical and laboratory findings) compared to the NC group. This may be indicative of ART children having more contact with health care, in accordance with a recent Swedish register-based study, which found ART to be a risk factor for more in- and outpatient visits and diagnoses in several ICD-10 chapters including chapter R, compared to NC, until the age of 5 (Pettersson *et al.*, 2022).

It remains partly unclear which mechanisms explain the small health differences between singletons born after ART and NC. Not only ART but also parental subfertility and less invasive fertility treatments, such as ovulation induction, associate with poorer outcome of the offspring concerning asthma and infectious diseases (Harju *et al.*, 2013; Magnus *et al.*, 2019; Wainstock *et al.*, 2019). Patient or embryo selection may be caused by the freeze-thaw process. One possible pathway to explain the differences between FET, fresh ET and NC are epigenetic changes, which may be induced by the laboratory procedures or by the different hormonal milieu of the uterus at the time of implantation. Differences in DNA methylation and gene expression have been shown in placental samples and/or cord blood between FET, fresh ET and NC (Estill *et al.*, 2016; Litzky *et al.*, 2017; Choux *et al.*, 2018; Barberet *et al.*, 2021; Caramaschi *et al.*, 2021). However, a recent study found no differences in whole blood methylation patterns in adolescents born after ART compared to NC, suggesting that these changes might be transient in nature (Penova-Veselinovic *et al.*, 2021).

In the analyses of the present study, we adjusted for PTB, which might conceal some of the positive effects of the diminished PTB and SGA risk of FET offspring. A separate analysis was carried out without adjusting for PTB, adjusting only for maternal age, parity, SES and offspring sex. However, no significant differences between FET and fresh ET were found for the need of hospital care or any of the ICD-10 chapter outcomes (data not shown).

The limitations of our study must be acknowledged. First, the CRHC covers hospital-based inpatient and outpatient care, excluding milder cases diagnosed in primary health care or the private sector. Thus, our results should be interpreted as representing only the more severe morbidity. Second, we were not able to study the effect of ART treatments and subfertility separately in our setting. In addition, although our cohort is reasonably sized, even larger cohorts would be needed to reliably study separate diagnoses included in the main ICD-10 chapters, or rare outcomes, such as cancer. It should be noted that only slow freezing was used in Finland when the children of this cohort were born, therefore these results may not be extrapolated to represent outcomes after vitrification. During our study period, a single embryo was transferred in the majority of ETs, and mainly natural cycles were used in FET, though unfortunately exact data were not available for statistical analysis.

A major strength of the study is the reliable register data. It is mandatory for public hospitals to report their discharge diagnoses, thus the CRHC coverage has been found to be accurate (Sund, 2012). Hospital care in Finland is almost exclusively offered by the public hospitals, especially for children, so these results should give an accurate description of the more severe morbidity in the population. Data linkages are feasible and reliable because of the personal identity numbers used widely in the Finnish society. In addition, we were able to adjust for several confounding factors deemed clinically relevant. However, there may be residual confounding that we were not able to control for. Finally, to our knowledge, our study offers the longest follow-up on the general health outcomes of a large FET cohort to date. For many ICD-10 chapters, we present the first published data on the long-term outcome of singletons born after FET.

In conclusion, this study gives further assurance that the health of singletons born after FET does not significantly alter from those born after fresh ET until early adulthood. Certain increased risks were found for FET compared to NC, which warrant further investigations. Similar results were found for fresh ET compared to NC. However, the magnitudes of the increased risks were small or modest at most. The ART cohort is still quite young for thorough investigation of diseases typically prevalent only in older population, such as cardiovascular disease or some cancers. In the future, large cohorts with sufficient follow-up time are needed to investigate the long-term health of ART offspring into adulthood.

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Data availability

Under Finnish privacy laws, the study permission and access to register data were granted specifically to the authors. Upon reasonable request, statistical code and data output may be available from the corresponding author.

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Authors' roles

All authors participated in the original study design. A.M.T. and M.G. analyzed the data, and A.M.T. was responsible for the preparation of the manuscript. All authors contributed to the revisions of the manuscript and approved the final version.

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Conflict of interest

There are no conflicts of interest to declare.

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