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ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Long-term development of 12- and 15-year-old offspring after maternal cancer diagnosis during pregnancy: a prospective multicentre cohort study

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Background: Evidence is lacking on the long-term effects of prenatal exposure to maternal cancer and its treatment on adolescent neurocognitive, cardiac, and physical health.

Methods: In a multicentre cohort study, children aged 12 and/or 15 years, prenatally exposed to maternal cancer (treatment), underwent clinical, echocardiographic, and neurocognitive evaluations. Standardized assessments were used, and associations between neurocognitive outcomes and covariates were examined using one-way and multivariable analysis of variance. Further analyses examined the need for extra support and the impact of chemotherapy exposure on puberty onset.

Results: Of 166 children, 122 were exposed to chemotherapy, 17 to surgery alone, 14 to radiotherapy, 1 to trastuzumab, 1 to rituximab, and 21 to no treatment. Cardiac function was within normal ranges, with a median ejection fraction of 56.7% (z-score: −1.6) and two cases showed mild systolic dysfunction (ejection fraction <50%). Neurocognitive outcomes, including intelligence, memory, and attention, were also within normal limits. Nine children, however, had lower verbal memory scores linked to chemotherapy exposure ($\beta = -0.52$, $P = 0.044$). Visuospatial memory was negatively correlated with maternal death ($\beta = -0.55$, $P = 0.019$), and attention was influenced by prematurity ($\beta = 0.034$ per gestational week, $P = 0.020$) and male sex ($\beta = -0.17$, $P = 0.024$). Extra support was needed in 21 children, primarily associated with lower intelligence, attention, and executive function scores, as well as prematurity. Pubertal development was within standard ranges, with no significant associations found between chemotherapy exposure and puberty onset.

Conclusion: Overall, no significant disruptions were found in the neurocognitive, cardiac, or physical development of adolescents prenatally exposed to maternal cancer and its treatment. Observed vulnerabilities, such as lower verbal memory and attention scores, were primarily linked to prematurity and maternal death rather than maternal cancer or its treatment. Ongoing monitoring is recommended to understand long-term outcomes into adulthood.

Key words: young adolescent, development, long-term, maternal cancer, child

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INTRODUCTION

The diagnosis of cancer during pregnancy is a rare but increasingly prevalent occurrence, because of the growing trend of delaying childbirth and the increased incidental discovery of pre-symptomatic cancers through advanced techniques in standard prenatal care.[1,2] Advances in cancer treatment strategies during pregnancy have led to a growing population of offspring prenatally exposed to maternal cancer and its treatment. Consequently, there is increased attention to the long-term outcomes of these children. The critical period from conception to age 2 years, known as the first 1000 days of life, plays a pivotal role in shaping an individual's physical and cognitive development.[3]

Prenatal exposure to maternal cancer is associated with increased risk for adverse obstetric and paediatric outcomes.[4] Therefore, ethical and clinical decisions regarding treatment plans must be grounded in a comprehensive understanding of the tumour stage, treatment options, and maternal prognosis, while also considering the long-term paediatric outcomes associated with these high-risk pregnancies.

As part of the International Network on Cancer, Infertility, and Pregnancy (INCIP), our research group has published reports showing reassuring general health, neurocognitive, and cardiac outcomes in children aged 1.5, 3, 6, and 9 years who were prenatally exposed to maternal cancer and its treatment.[5-9] At age 6 years, however, these children scored lower on verbal intelligence and visuospatial long-term memory compared with children born after uncomplicated pregnancies, matched for age, sex, country, language, and gestational age at birth.[8] Furthermore, chemotherapy during pregnancy was associated with poorer emotional regulation.[10] Despite generally normal cognitive and behavioural development in 9-year-old exposed offspring, compared with test-specific norms of the general population, prematurity consistently emerged as a predictor of poorer cognitive outcomes across cross-sectional reports up to age 9 years.[7-9]

Furthermore, maternal death has repeatedly emerged as a potential contributor to various challenges in neurocognitive and behavioural development, both in the general literature and in offspring prenatally exposed to maternal cancer, underscoring the potential (psychosocial) impact of a cancer diagnosis during pregnancy on child development.[5,9] Additionally, previous studies have demonstrated that chemotherapy-induced gonadal damage, such as ovarian insufficiency or amenorrhea, as well as endocrine and pubertal disorders, can manifest during treatment and may persist long after the treatment period.[11] Notably, alkylating agents like cyclophosphamide and taxanes exhibit significant adverse effects on ovarian function.[12]

So far, the long-term neurocognitive and health outcomes of adolescents born to pregnant women with cancer have not been described in a standardised manner. The question remains whether children born after a pregnancy complicated by maternal cancer are at risk of impairments in neurocognitive development, cardiac functioning, complex behavioural and executive functions, or sexual development beyond the age of 9 years. Therefore, this cross-sectional cohort study aims to describe the cognitive, behavioural, cardiac, puberty, and health outcomes of 12- and 15-year-old children who were prenatally exposed to maternal cancer and its treatment.

MATERIAL AND METHODS

Study participants

In the INCIP Child-Follow up study, a multicentre study, offspring from all pregnant women diagnosed with cancer at participating centres (Figure 1) were systematically invited to enrol, regardless of prognosis or cancer type. Recruitment was conducted prospectively and retrospectively across these sites, with children undergoing standardised follow-ups at predefined ages (1.5, 3, 6, 9, 12, 15, and 17/18 years). In this report, only children aged 12 and 15 years, prenatally exposed to maternal cancer with or without oncological treatment, were included. Children were assessed between 16 August 2007 and 6 June 2024 at six referral centres in Belgium (University Hospitals Leuven), New Jersey, USA (Cooper University Health Care), the Netherlands (Princess Máxima Center for Pediatric Oncology), Czechia (University Hospital Kralovske Vinohrady), and Italy (Fondazione IRCCS San Gerardo dei Tintori, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico). Maternal oncological, obstetrical, and neonatal data were collected from medical records for each mother—child pair. These data encompass information about the child's sex, gestational age at birth, birthweight, obstetrical and neonatal outcomes, maternal cancer stage and (sub)type, treatment (type, dosage, and timing) during pregnancy, and maternal outcome. Figure 1 summarises the study design and recruitment. Ethical approval was obtained by all participating centres. Written informed consent was obtained from all participating parents, and written informed assent from all participating children. The study is registered with ClinicalTrials.gov (NCT00330447).

Additionally, selection bias may be present, as participants were mainly recruited from tertiary care centres specialising in treating cancer during pregnancy, potentially underrepresenting mothers from lower socioeconomic backgrounds. To mitigate this, we offered flexible testing locations, compensation, and maintained regular contact with families through events and communications.

Methods of neurocognitive testing

All children were prospectively assessed using a validated comprehensive age-appropriate neurocognitive battery, assessing intelligence (IQ), attention, memory, and behaviour. Primary outcomes were the full scale intelligence quotient (FSIQ) from the Wechsler Intelligence Scale For Children (WISC[13-16]) and composite measures for visuospatial memory from the children's memory scale (CMS[17]), verbal memory from the Auditory Verbal Learning Test

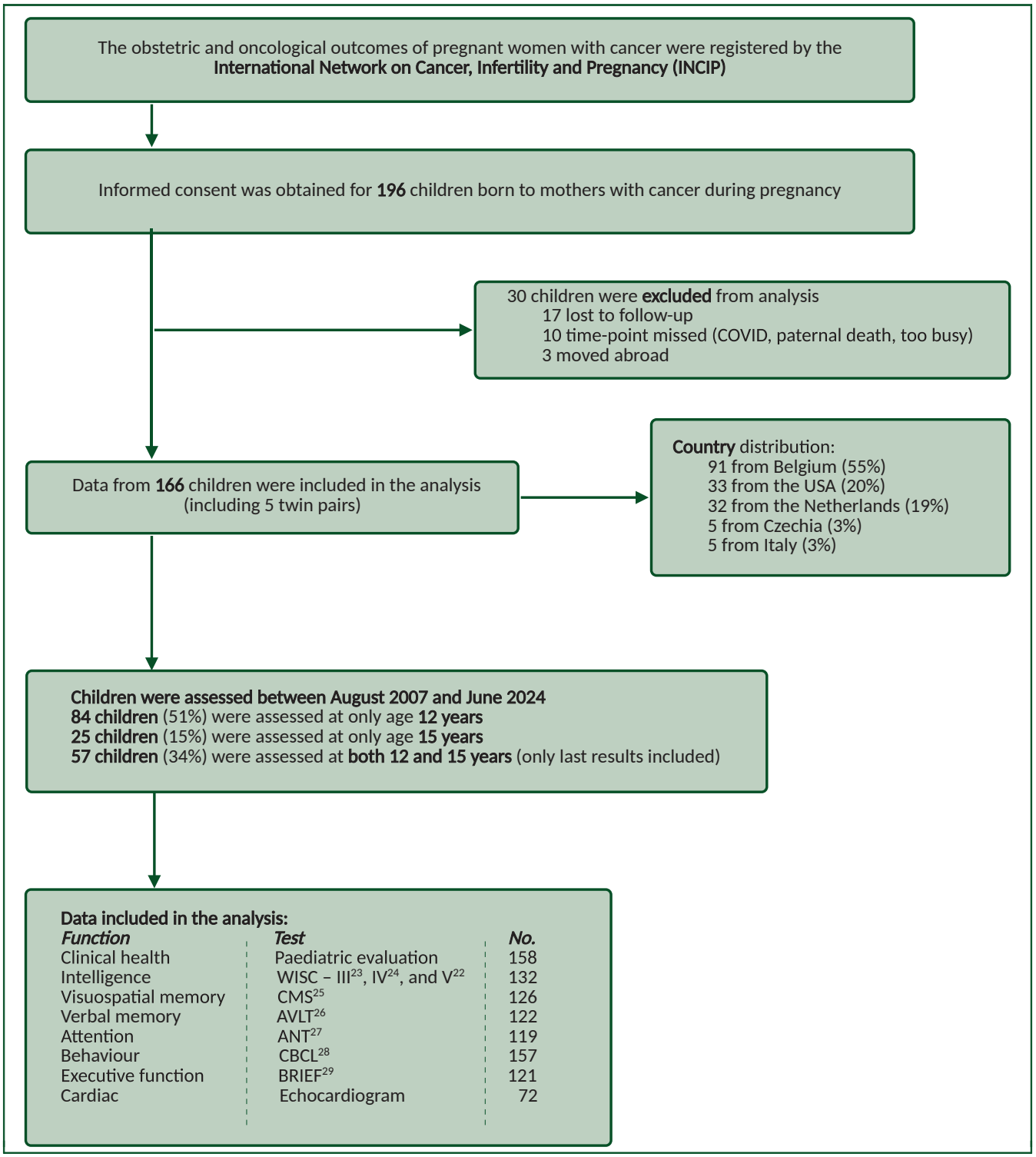

Figure 1. Study design and recruitment.
ANT, Amsterdam Neuropsychological Tasks; AVLT, Auditory Verbal Learning Test; BRIEF, Behaviour Rating Inventory of Executive Function; CBCL, Child Behaviour Checklist; CMS, Children's Memory Scale; WISC, Wechsler Intelligence Scale for Children.

(AVLT[18]), and attentional functioning from the Amsterdam Neuropsychological Tasks (ANT[19]), as well as the total scores for behavioural problems from the Child Behavior Checklist (CBCL[20]) and executive functioning problems from the Behavior Rating Inventory Of Executive Function (BRIEF[21]). Secondary outcomes included all other neurocognitive test scores, including IQ index scores, memory and attention sub-scores, and secondary behavioural and executive functioning questionnaire scores. All tests were administered in the child's native language. To allow objective interpretation of observed score differences, we report results in the context of established clinically

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meaningful ranges and standard deviations derived from test validation studies. For example, WISC defines a standard score with a mean of 100 and a standard deviation of 15; a difference of 10 points is generally considered a moderate effect, and a difference of 15 points or more is typically regarded as clinically relevant.[14-16] Similar interpretative guidelines are available for the CBCL and BRIEF questionnaires.[21,22]

Methods of cardiac evaluation

A standard paediatric echocardiography was carried out according to the standards of the American Society of Echocardiography guidelines.[23] The z-scores relative to body surface area were calculated using the formulae described in literature.[24-27] See Supplementary Appendix (p 2), available at https://doi.org/10.1016/j.annonc.2025.04.011, for further details of the methods (and definitions of outcomes) of cardiac evaluation.

Methods of general health and puberty assessments

A clinical neurological and general paediatric examination was conducted to screen the children's general health. Additionally, parents were invited to complete a (observational, non-validated) questionnaire on the general health of their child, their educational level, changes in family composition, and the age of their child at various pubertal milestones, including pubic hair development, voice change and facial hair growth in males, and breast development and the onset of menarche in females.

Data and statistical analysis

All neurocognitive and behavioural measures were converted to numerical data, with raw scores standardised using normative data adjusted for age and country. Similarly, raw echocardiographic variables were standardised using published normative data for both the whole cohort and a sub-cohort of children with prenatal exposure to anthracyclines.

Given the utilisation of different versions of the intelligence test (WISC), Verbal Comprehension Index (VCI) and verbal IQ (VIQ) scores were combined, giving priority to VCI when both were available (particularly from WISC-III), to provide a measure of verbal intelligence. Similarly, Perceptual Organization Index (POI), Perceptual Reasoning Index (PRI), Visuospatial Index (VSI), and Performance IQ (PIQ; when POI, PRI, and VSI were unavailable) were aggregated to provide a measure of performance intelligence. To represent outcomes from the other neurocognitive assessments (CMS, AVLT, ANT, CBCL, BRIEF), all standardised scores were converted to z-scores. Composite visuospatial memory, verbal memory, and attention scores were created by averaging the sub-scores from the CMS, AVLT, and ANT, respectively.

Linear mixed effects models were used to investigate the effect of age on primary outcomes in children who were tested at both 12 and 15 years of age, in a complete-case analysis manner.

Relationships were investigated between the primary outcomes (FSIQ, CMS composite score, AVLT composite score, ANT composite score, CBCL total score, BRIEF total score, separately) and various factors, including sex (female, male), gestational age at birth, chemotherapy exposure (yes, no), radiotherapy exposure (yes, no), edition of the intelligence test, maternal and paternal education level, as well as the occurrence of maternal death (before and after 2 years of age). This was done using multivariable analysis of variance with type II sum of squares, with the best-fit model selected via Bayesian information criterion.

Linear regression analyses were conducted to determine the association between need for extra (neurocognitive) support—such as school assistance or speech therapy—and primary outcomes and gestational age at birth. Fisher's exact tests were conducted to determine the relationships between need for extra support and maternal death and maternal treatment type during pregnancy. Linear regression analyses were also conducted to investigate the relationship between age at various puberty-related physical changes and prenatal exposure to specific chemotherapy agents (taxanes, cyclophosphamide, and platinum agents).

For all statistical tests, the assumptions were tested and confirmed. All analyses were conducted using a complete-case approach. Instances of missing data primarily arose due to practical limitations or time constraints encountered during the data collection process. Correction for multiple testing was carried out within each multivariable model (per primary outcome) but not across all analyses to prevent false-negative findings. Results are presented with 95% confidence intervals (CI).

RESULTS

Participant characteristics

A cohort comprising 166 children was examined, with 91 participants from Belgium, 33 from the USA, 32 from the Netherlands, 5 from Czechia, and 5 from Italy. Of these children, 84 (51%) were assessed only at age 12 years, 25 (15%) only at age 15, and 57 children (34%) at both ages. Linear mixed effects models, looking at the stability of outcomes across time in children for whom data are available at both 12 and 15 years, found no effect of age for any primary outcome. For the remaining analyses, only the latest results are included per child.

Participant characteristics are provided in Table 1. The data availability varied across tests, with the total number of participants for each test specified in Figure 1. Further details concerning maternal treatment can be found in Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2025.04.011, and details about drug use during pregnancy, fertility treatment, labour and delivery type, and congenital malformations can be found in Supplementary Tables S3-S6, available at https://doi.org/10.1016/j.annonc.2025.04.011.

Physical clinical examinations and neurologic examinations showed no neurological abnormalities, except for one child with spastic diplegia cerebral palsy (SDCP) born at 34

Table 1. Demographic characteristics of the participants

Characteristic	Children ($N = 166$)
Cancer treatment during pregnancy, *n* (%)	
Chemotherapy only	42 (25)
Radiotherapy only	1 (1)
Surgery only	17 (10)
Chemotherapy and surgery	70 (42)
Chemotherapy and radiotherapy	0 (0)
Radiotherapy and surgery	4 (2)
Chemotherapy, radiotherapy, and surgery	9 (5)
Targeted treatment	1 (1)
Targeted treatment, chemotherapy, and surgery	1 (1)
No treatment	21 (13)
Chemotherapeutic agent type, *n* (% of $n = 122$)[a]	
Anthracyclines	104 (85)
Cyclophosphamide	88 (72)
Antimetabolites	56 (46)
Taxanes	18 (15)
Vinca alkaloids	16 (13)
Platinum	15 (12)
Other	13 (11)
Mean age (SD), years	13.67 (1.63)
Mean GA (SD), weeks	36.05 (2.81)
Very preterm (<32 weeks)	11 (7%)
Moderately preterm (32.0-33.9 weeks)	23 (14%)
Late preterm (34.0-36.9 weeks)	61 (37%)
At term (≥37 weeks)	71 (43%)
Mean birth weight (SD), g	2658.66 (678.78)
Mean maternal age at delivery (SD), years	33.56 (4.86)
Admission to neonatal intensive care unit after birth, *n* (%)	75 (45)
Sex, *n* (%)	
Male	85 (51)
Female	81 (49)
Mother deceased, *n* (%)	
Before age 2 years	16 (10)
After age 2 years	9 (6)
Survived	136 (84)
Highest level of education parents, *n* (%)[b]	
Mother	
Primary school	6 (4)
Secondary school	44 (27)
Bachelor's degree	46 (29)
Master's degree or higher	33 (20)
Unknown	32 (20)
Father	
Primary school	6 (4)
Secondary school	53 (33)
Bachelor's degree	35 (22)
Master's degree or higher	31 (19)
Unknown	36 (22)

GA, gestational age; SD, standard deviation.

[a]Some mothers were treated with multiple chemotherapeutic agent types during pregnancy, thus resulting in a total percentage >100%.

[b]The highest level of education is presented according to the International Standard Classification of Education 2011, [36] and recorded into four classes as done by Meekes and colleagues.[37] A bachelor's degree is earned at both traditional universities and non-university institutions of higher education and requires between 3 and 4 years of full-time study. A master's degree is earned at university and requires 1-2 years of full-time study after a bachelor's degree.

weeks gestational age by C-section, and one twin pair born at 32 weeks gestational age by C-section, of which one child is known with severe intellectual disability and the other has a developmental disorder, both earlier described by our group.[6] The child with a severe intellectual disability was excluded from further cognitive and behavioural assessments, as these were not suitable for the child's level of functioning.

Cognitive development and behaviour

Across the entire cohort, and at both 12 and 15 years separately, we observed average scores for full scale intelligence (FSIQ), verbal intelligence, performance intelligence, processing speed, and working memory (Figure 2). Additionally, the average group outcomes for verbal and visuospatial memory, attentional function, and behavioural measures fell within normal ranges (Figure 3).

A total of 16 children (12%) of 132 with available data achieved an FSIQ score lower than 85 (low average) (z-score < -1, expected in ±15% of the population according to a normal distribution). This group includes the child with SDCP, who is also known with a psychomotor delay, as well as the twin pair previously described.

Univariate analyses with FSIQ as outcome variable revealed a relationship with both maternal [$F(3115) = 6.12$, $P = 0.00067$] and paternal education level [$F(3112) = 3.46$, $P = 0.019$]. In a multivariable analysis with both parental education levels as predictors, only maternal education level significantly explained part of the difference in FSIQ [$F(3109) = 3.74$, $P = 0.013$]. Children whose mother had at least a Master's degree scored higher than children whose mother's highest completion was either primary school ($\beta = 24.59$, 95% CI ± 17.22, $P = 0.0017$) or secondary school ($\beta = 13.68$, 95% CI ± 9.29, $P = 0.0012$). Clinically, this implies the need to consider parental education when assessing cognitive outcomes.

A univariate association was also found between FSIQ and 'maternal death' [$F(1129) = 4.74$, $P = 0.031$]. Children whose mother had died scored on average 7.26 (95% CI ± 3.33) points lower on FSIQ than children whose mother was alive at the time of the assessment. This association was no longer significant in multivariable analyses. Also, no difference was found between children whose mother died before or after 2 years of age.

A total of 12 children (10%) of 126 scored lower than average (z-score < -1) for visuospatial memory. Visuospatial memory was univariately associated with 'gestational age at birth' [$F(1121) = 4.72$, $P = 0.032$] and 'maternal death' [$F(1121) = 11.90$, $P = 0.00078$]. Gestational age at birth and maternal death, however, were highly correlated (Fisher's exact test, $P < 0.0001$), and thus possibly confounding. In a multivariable analysis, maternal death emerged as the stronger predictor [$F(2119) = 4.35$, $P = 0.015$]. In particular, children whose mother had died before the age of 2 years (i.e. in the critical 'first 1000 days' after conception) scored on average 0.55 (95% CI ± 0.48) points lower on the standardised visuospatial memory composite score than children whose mother was alive ($P = 0.019$). While statistically significant, this difference is relatively small and may not indicate strong clinical relevance.

A total of 9 children (7%) of 122 scored lower than average (z-score < -1) for verbal memory. Verbal memory was associated with prenatal exposure to 'chemotherapy' [$F(1120) = 4.13$, $P = 0.044$]. Children whose mothers were treated with chemotherapy during pregnancy scored on average 0.52 (95% CI ± 0.25) points lower on the

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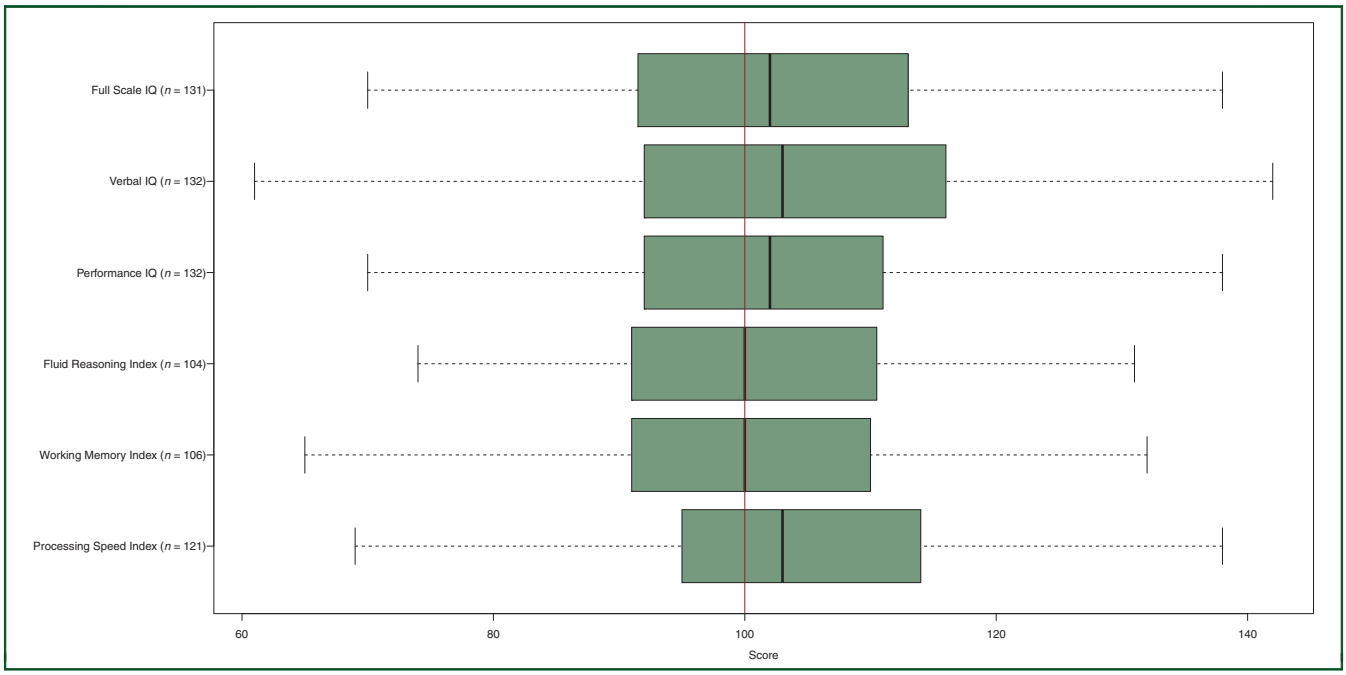

Figure 2. Means, standard deviations and ranges of intelligence scores at ages 12 and 15[a].
[a]VIQ and PIQ scores (from the WISC-III) were only included if VCI and POI scores, respectively, were not available.
PIQ, Performance IQ; POI, Perceptual Organization Index; VCI, Verbal Comprehension Index; VIQ, verbal IQ; WISC, Wechsler Intelligence Scale for Children.

standardised verbal memory composite scores than children not prenatally exposed to chemotherapy. When looking at the smaller subgroups of specific chemotherapy agents, taxane-exposed children had lower scores on verbal memory, although this association was not significant ($\beta = -0.74$, 95% CI $\pm$ 0.39, $P = 0.056$).

A total of 9 children (8%) of 119 scored lower than average (z-score < -1) for attention. Attention was associated with 'gestational age at birth' [F(1120) = 5.55, $P = 0.020$], 'maternal death' [F(1120) = 4.38, $P = 0.038$], and *sex* [F(1120) = 5.20, $P = 0.024$]. In a best-fit multivariable analysis, both gestational age at birth and sex significantly explained attentional functioning, with an increase by 0.034 (95% CI $\pm$ 0.014) points on the standardised attention composite score for every week increase in gestational age at birth, and boys scoring on average 0.17 (95% CI $\pm$ 0.078) points lower on than girls ($P = 0.024$). While these effects are statistically significant, their modest size implies that other factors may also contribute to attention outcomes.

For total behavioural problems (CBCL total score), 27 children (17%) of 157 scored lower than average (z-score < -1). Increased internalizing problems (subscale of the CBCL) were more common (35 children, 22%) than increased externalizing problems (15 children, 10%). Univariate analyses with the CBCL total score as outcome variable revealed a significant interaction with the 'informant' [F(3120) = 4.19, $P = 0.0074$]. Children scored on average 0.74 (95% CI $\pm$ 0.23) points lower when the questionnaire was completed by mothers compared with when filled in by partners ($P = 0.0078$). No other associations were found with the total behavioural problems score on the CBCL.

For total behavioural executive functioning problems (BRIEF total score), 20 children (17%) of 121 scored lower than average (z-score < -1). Increased metacognition problems were more common (20 children, 17%) than increased behavioural regulation problems (15 children, 12%). No associations were identified with the total executive problems score on the BRIEF.

Cardiac functioning

A total of 72 children underwent echocardiography of whom 53 (74%) were prenatally exposed to anthracyclines. Except for one patient with mild mitral regurgitation based on mitral valve prolapse, none of the echocardiograms was clinically reported to be abnormal. For none of the children, a decreased myocardial function was reported (median range).

Quantitative echo data can be found in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2025.04.011. M-mode measurements of cardiac structure were all within normal limits, except for one left ventricular end-diastolic diameter value with a z-score of -2.8. All fractional shortening values were above 28%. For biplane Simpson's ejection fraction, however, 19/63 (30%) patients had values slightly below 55%, with 13/63 (20%) having a z-score below -2. The median ejection fraction was 56.7%, with a z-score of -1.6. According to paediatric cardio-oncology guidelines, ejection fraction values below 50% are abnormal, while 50%-55% is considered borderline; thus, only two patients had an abnormal ejection fraction.[28] Median global longitudinal strain (GLS) was -19, with only 2/56 (4%) children having a GLS below -17 (Supplementary

Task or subtask	Tested variable	No.	Outcomes
Behaviour			
CBCL	Internalising problems	157	
	Externalising problems	157	
	Total problems	157	
BRIEF	Behavioural regulation	121	
	Metacognition	121	
	Global Executive	121	
Verbal memory			
AVLT	Learning	122	
	Immediate recall	122	
	Delayed recall	122	
Visuospatial memory			
CMS Dots	Learning	128	
	Immediate recall	126	
	Delayed recall	128	
Visuospatial memory span			
CMS Picture Locations		126	
Visuomotor reaction time			
ANT Baseline Speed	Total reaction time	121	
Response inhibition[a]			
ANT Go-NoGo	Hits reaction time	105	
	False alarms	105	
	Misses	105	
Selective attention			
ANT Focused Attention 4 Letters	Total reaction time	118	
	Distraction time	118	
	Distraction accuracy	119	
	Accuracy performance	119	
Divided attention			
ANT Memory Search Letters	Total reaction time	118	
	Percentage error	117	
	Memory search rate	118	
	Memory load accuracy	117	
Attention flexibility			
ANT Shifting Attentional Set Visual	Reaction time contrast	119	
	Error contrast	119	

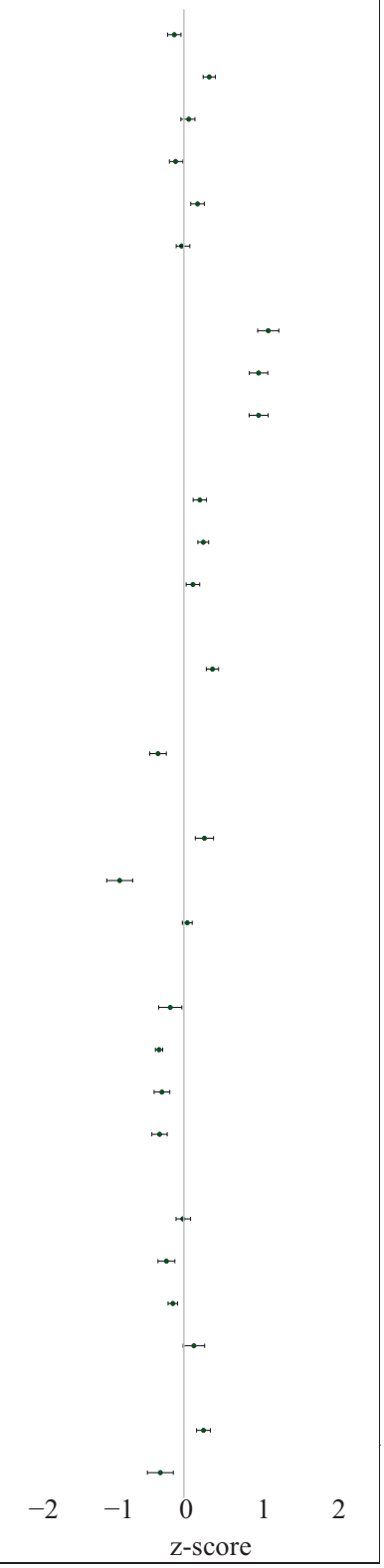

Figure 3. Cognitive (non-IQ) and behavioural outcomes. Points represent mean score, plus and minus confidence interval. For each child, the latest test results were included.

ANT, Amsterdam Neuropsychologic Task; AVLT, Auditory Verbal Learning Test; BRIEF, Behavior Rating Inventory of Executive Function; CBCL, Child Behavior Checklist; CMS, Children's Memory Scale.

[a]Response inhibition was only tested at age 12 years. The sample size (No.) is indicated for each measure. One child was excluded due to severe intellectual disability.

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Table S7, available at https://doi.org/10.1016/j.annonc.2025.04.011). Most diastolic function measures had median z-scores near 0, except for left atrial end-systolic volume, mitral E-wave deceleration time, and isovolumic relaxation time, with median z-scores of −1.65, 0.9, and −1.2, respectively. Median values and ranges were largely unchanged in the anthracycline-exposed sub-cohort, compared with the rest of the cohort.

Description of general health

Data on the general health were available for 158 children (95%). No childhood cancers were reported. A summary of medical problems is provided in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2025.04.011. Nine (6%) children had a diagnosis of attention-deficit hyperactivity disorder (ADHD), of whom three took supportive medication. One child (1%) had a diagnosis of autism spectrum disorder (ASD). Twenty-one children (13%) received extra (neurocognitive) support. Details of the types of support can be found in Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2025.04.011.

The need for extra support was negatively associated with 'FSIQ' ($\beta = -11.24$, 95% CI $\pm$ 3.89, $P = 0.0046$), 'attentional functioning' ($\beta = -0.27$, 95% CI $\pm$ 0.11, $P = 0.012$), 'behavioural functioning' ($\beta = -0.76$, 95% CI $\pm$ 0.17, $P < 0.0001$), and 'executive functioning' ($\beta = -0.63$, 95% CI $\pm$ 0.16, $P = 0.00014$). The need for support was also associated with 'gestational age at birth', with children in need of extra support born on average 1.91 (95% CI $\pm$ 0.64) weeks earlier than children not in need of extra support ($P = 0.0032$). This emphasizes the clinical relevance of identifying and supporting at-risk children as early as possible.

In the cohort assessed up to age 12 years, 15 children (9%), including 13 boys, had not yet entered puberty by that age. When examining puberty onset (based on parent-reported questionnaires), 2 out of 85 boys (1%) had not yet reached puberty by age 15 years. One had prenatal exposure to trastuzumab (between 11 and 26 weeks of gestation), and the other to 5-fluorouracil (between 29 and 33 weeks). The average age of reported onset for pubic hair development was 11.95 years (95% CI $\pm$ 1.32 years). In boys, the average age at the reported onset of facial hair development was 13.58 years (95% CI $\pm$ 1.67 years) and the average age at onset of voice change was 13.25 years (95% CI $\pm$ 1.14 years). In girls ($n = 81$), the average age at onset of breast development was 11.41 years (95% CI $\pm$ 1.07 years) and the average age at onset of menarche was 12.05 (95% CI $\pm$ 1.11 years). No significant associations were found between age at any puberty change and prenatal exposure to cyclophosphamide-, taxane-, or platinum-based chemotherapy agents. Furthermore, no associations were found between gestational age at start of chemotherapy exposure and age at puberty change. A detailed comparison of the characteristics between the chemotherapy-exposed group and the non-exposed group is provided in Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2025.04.011.

DISCUSSION

This multicentre cohort study fills a critical gap in understanding the long-term development of adolescents prenatally exposed to maternal cancer and its treatment. On average, children aged 12 and 15 years in this cohort exhibit normal cognitive, behavioural, cardiac, and physical functioning, with comparable rates of below-average scores to the general population, echocardiographic variables were within normal ranges, with no diagnoses of anthracycline-induced cardiomyopathy. Nevertheless, specific results related to prematurity, maternal death, and chemotherapy exposure merit attention.

A higher prevalence of parent-reported internalising behavioural problems (22.3%) was observed compared with the expected population prevalence (15.9%), though no associations were found with treatment factors. Reporting bias may contribute, as mothers reported lower psychosocial functioning scores on the questionnaires, as commonly found in general literature.[29-32] Maternal education strongly influenced cognitive outcomes, and maternal death, particularly within the child's first 1000 days, was associated with lower visuospatial memory, potentially reflecting broader psychosocial or neurodevelopmental vulnerabilities following early maternal loss. Although this finding may lack clinical significance, it underscores the need for cautious interpretation, replication in larger samples, and exploration of unmeasured factors, such as caregiving environment and psychosocial stress.[6,10]

Children prenatally exposed to chemotherapy scored slightly lower on verbal memory, although still within normal ranges. This result aligns with previous findings of lower verbal and visuospatial memory in 6-year-olds prenatally exposed to chemotherapy and children with prenatal taxane exposure.[8,33] Although specific chemotherapy agents did not significantly explain this effect, further research is necessary to explore mechanisms linking prenatal chemotherapy exposure to memory outcomes.

Gestational age at birth was another significant predictor of cognitive outcomes, with earlier gestational age associated with lower attention scores. This finding aligns with the broader literature on developmental risks associated with prematurity and highlights the compounded risks faced by children born preterm and exposed to maternal cancer and its treatment.[34] Consequently, close monitoring and early interventions are crucial for these children.

The need for extra support for the child was associated with lower intelligence, attention, executive function, psychosocial functioning, and prematurity. This likely reflects the proactive identification and intervention for developmental problems through participation in the child follow-up study. Commonly reported types of support included extra school guidance and psychological support for conditions such as ADHD and autism.

Puberty onset appears to be within normal ranges,[35] with no observed impact from alkylating chemotherapy exposure. Although this is reassuring, further follow-up of these children is necessary to assess the risk of specific fertility disorders, particularly for chemotherapy exposure before 20 weeks of gestation, which could affect oocyte production.[36] Therefore, although we did not find a significant association between gestational age at start of chemotherapy exposure with puberty onset, further follow-up for potential fertility issues, such as gonadal dysfunction and premature menopause, is necessary. Additional factors, such as birth weight, should also be considered, as they may influence reproductive health outcomes in these children.

Quantitative echocardiographic variables were mostly within normal limits, though slightly low values for Simpson's biplane ejection fraction (median 56.7% or median z-score −1.6) warrant attention. These could either be a first sign of subclinical left ventricular dysfunction or represent a methodological measurement difference between our centres and the published reference data. Besides, without a control group, we relied on published reference values. By using z-scores, we compared our cohort with these external references, rather than with a control group assessed by the same observer. It is also important to note that for many functional variables (Simpson's biplane, inflow and tissue Dopplers), reference populations are relatively small and z-score calculations are not established for wide ranges of children (e.g. for very high/low body surface area or different ethnicities). Further follow-up of the cohort is warranted, although it is reassuring that other measures of systolic function (fractional shortening, GLS, cardiac output, and visual review by the clinical cardiologist) were all normal. Furthermore, the sub-cohort that was exposed to anthracyclines, associated with cardiotoxicity, did not have worse values for systolic function compared with the non-exposed children.

While our study provides valuable insights, it has several limitations. Incomplete data on co-medication during pregnancy prevented assessment of confounding effects from drugs like glucocorticoids, antibiotics, and opioids. The international, longitudinal study design introduced heterogeneity due to different test versions, availability, participant attrition, and possible inter-centre differences in assessment. Besides, the outdated norms of the AVLT tests may affect the interpretation of the results. Also, the diverse sample, including children exposed to various treatments at different gestational stages, limits insight into specific prenatal exposures. Additionally, selection bias may be present, as participants were mainly recruited from tertiary care centres specialising in treating cancer during pregnancy. This may have led to the underrepresentation of mothers from a lower socioeconomic background, who have less access to specialized care and are generally less likely to participate in research. It is also important to acknowledge that, while correction for multiple testing was carried out within each multivariable model (per primary outcome), our study did not correct for multiple testing across all analyses. This could mean that some of our significant observations may be false positives. Given the sensitive nature of the study topic, however, we made the well-considered choice to prioritise avoiding the overlooking of potential significant associations, even though it may have increased the likelihood of false positives.

Future larger-scale longitudinal analyses can validate our results and explore underlying mechanisms. Addressing the specific needs of families affected by maternal mortality due to cancer and developing precise support interventions are crucial. Understanding the long-term impacts of different prenatal cancer treatments can inform guidelines for managing pregnancies complicated by cancer, ultimately improving outcomes for both mothers and their children.

Conclusions

This study provides important insights into the developmental trajectories of children exposed to maternal cancer and its treatment, contributing to the growing body of evidence on the long-term impacts of such exposures. While these children generally exhibit normal cognitive, behavioural, cardiac, and physical health outcomes, specific risk factors like maternal death, prematurity, and prenatal chemotherapy exposure require further investigation and targeted interventions.

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DISCLOSURE

The authors have declared no conflicts of interest.

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