FACULTEIT PSYCHOLOGIE EN
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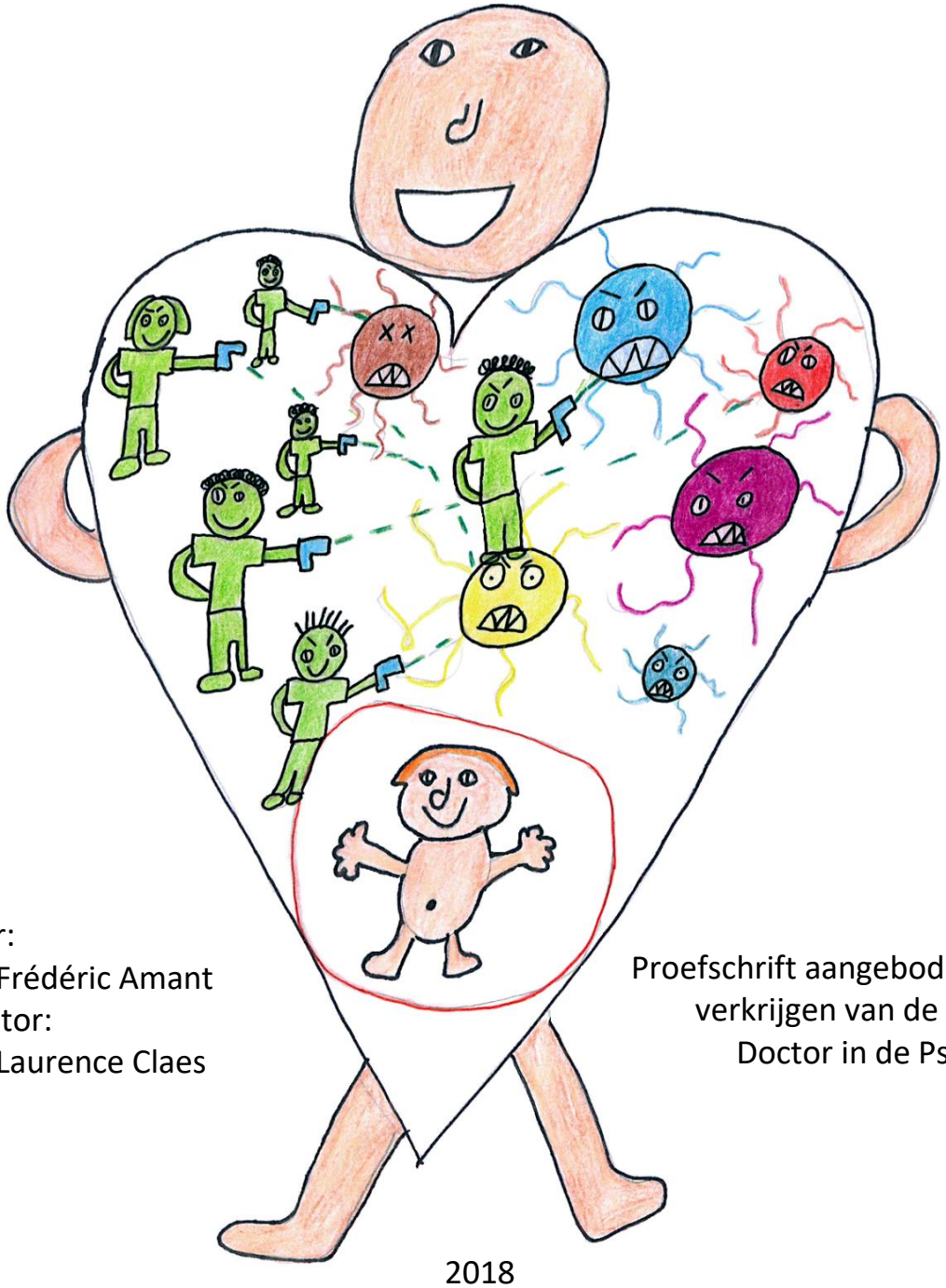
Onderzoekseenheid Klinische Psychologie

Cancer during pregnancy

Impact on neuropsychological child development and on the couple's distress and coping

Tineke Vandenbroucke



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Tineke Vandenbroucke: Cancer during pregnancy: Impact on neuropsychological child development and on the couple's distress and coping

Supervisor: Prof. dr. Frédéric Amant

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Cancer is diagnosed in about 1 in 1000 pregnant women. The treatment of cancer during pregnancy is challenging because two lives have to be considered in therapeutic decision making. A primordial concern is the possible impact of maternal cancer, the associated stress, diagnostic imaging and treatments on the developing fetus. Many physicians remain reluctant to start cancer treatment during pregnancy because of the lack of evidence on short- and long-term safety for the fetus. Moreover, a cancer diagnosis during pregnancy may be considered as an emotional challenge for the expecting parents. To date, there is a lack of knowledge about the concerns and distress these women and their partners experience, how they deal with these concerns and who is at risk for high levels of distress.

The PhD project focuses on two lines of research:

In the first line of research, we investigate the cognitive development and behavior of children born to mothers diagnosed with and treated for cancer during pregnancy. This part consists of four chapters. In **Chapter 2**, we review the available literature with regard to the outcome of children born from pregnancies complicated by maternal cancer. In **Chapter 3**, we investigate the effects of maternal cancer diagnosis and treatment during pregnancy on the general cognitive development of children in infancy and early toddlerhood (at the age of 1.5 and 3 years)**. Chapter 4** presents a study on the effects of maternal cancer diagnosis and treatment during pregnancy on the development of intelligence, attention, memory and behavior problems in early childhood (at the age of 6 years). In **Chapter 5**, an interim analysis of the effects of maternal cancer diagnosis and treatment during pregnancy on the development of intelligence, attention, memory and behavior problems in middle childhood (at the age of 9 years) is presented.

In the second line of research, we investigate the impact of the diagnosis and treatment of cancer during pregnancy on the psychological distress and use of cognitive coping strategies in pregnant women and their partners (**Chapter 6**).

In **Chapter 7**, the main results of our studies are summarized and discussed. The strengths and limitations of our studies are addressed, suggestions for future research are provided and clinical implications and recommendations are formulated.

Tineke Vandenbroucke: Kanker tijdens de zwangerschap: Impact op de neuropsychologische ontwikkeling van het kind en op de stress en coping van het koppel

Promotor: Prof. dr. Frédéric Amant

Copromotor: Prof. dr. Laurence Claes

Kanker wordt vastgesteld bij ongeveer 1 op 1000 zwangere vrouwen. De behandeling van kanker tijdens de zwangerschap vormt een uitdaging omdat er bij het nemen van beslissingen met betrekking tot de behandeling rekening dient te worden gehouden met twee levens. Een van de belangrijkste bezorgdheden is de mogelijke impact van kanker, de daarbij behorende stress, diagnostische beeldvorming en behandelingen op de ontwikkelende foetus. Veel artsen staan weigerachtig tegenover het opstarten van een kankerbehandeling tijdens de zwangerschap, omwille van het gebrek aan evidentie over de veiligheid ervan voor het kind op korte en op lange termijn. Bovendien kan een kankerdiagnose tijdens de zwangerschap beschouwd worden als een emotionele uitdaging voor de toekomstige ouders. Op dit moment is er een gebrek aan kennis over de bezorgdheden en stress die deze vrouwen en hun partners ervaren, hoe zij hiermee omgaan en welke patiënten en partners risico lopen op het ervaren van hoge niveaus van stress.

Dit doctoraatsproject is gericht op twee onderzoekslijnen:

In de eerste onderzoekslijn gaan we na wat de impact is van een kankerdiagnose en –behandeling tijdens de zwangerschap op de cognitieve ontwikkeling en het gedrag van kinderen. Dit deel bevat vier hoofdstukken. In **hoofdstuk 2** wordt de beschikbare literatuur gereviewd. In **hoofdstuk 3** onderzoeken we de effecten van een kankerdiagnose en –behandeling tijdens de zwangerschap op de algemene cognitieve ontwikkeling van kinderen in de peutertijd en vroege kleutertijd (op de leeftijd van 1.5 en 3 jaar). **Hoofdstuk 4** stelt een studie voor omtrent de effecten van een kankerdiagnose en –behandeling tijdens de zwangerschap op de ontwikkeling van intelligentie, aandacht, geheugen en gedragsproblemen in de vroege kindertijd (6 jaar). In **hoofdstuk 5** wordt een interimanalyse uitgevoerd met betrekking tot de effecten van een kankerdiagnose en –behandeling tijdens de zwangerschap op de ontwikkeling van intelligentie, aandacht, geheugen en gedragsproblemen in de midden-kindertijd (9 jaar).

In de tweede onderzoekslijn gaan we na wat de impact is van een kankerdiagnose en –behandeling tijdens de zwangerschap op de aanwezigheid van psychologische stress en het gebruik van cognitieve coping strategieën bij zwangere vrouwen en hun partners (**hoofdstuk 6**).

In **hoofdstuk 7** worden de belangrijkste resultaten samengevat en kritisch bekeken. De sterktes en zwaktes van onze studies worden weergegeven, suggesties voor verder onderzoek worden geboden en klinische implicaties en aanbevelingen worden geformuleerd.

Dankwoord

They say they built the train tracks over the Alps, between Vienna and Venice, before there was a train that could make the trip. They built it anyway. They knew one day the train would come.

Uit 'Under the Tuscan sun'

Vijf jaar en 23 dagen geleden startte ik met het leggen van mijn spoor, met een duidelijk doel voor ogen, het behalen van een doctoraat in de psychologie. Vandaag sta ik hier voor jullie en kan ik met trots mijn spoor laten zien. Vandaag is de dag dat mijn trein gekomen is. Gelukkig was ik tijdens die vijf jaar omringd door heel wat helpende handen en supporters. Graag wil ik dan ook een aantal mensen bedanken.

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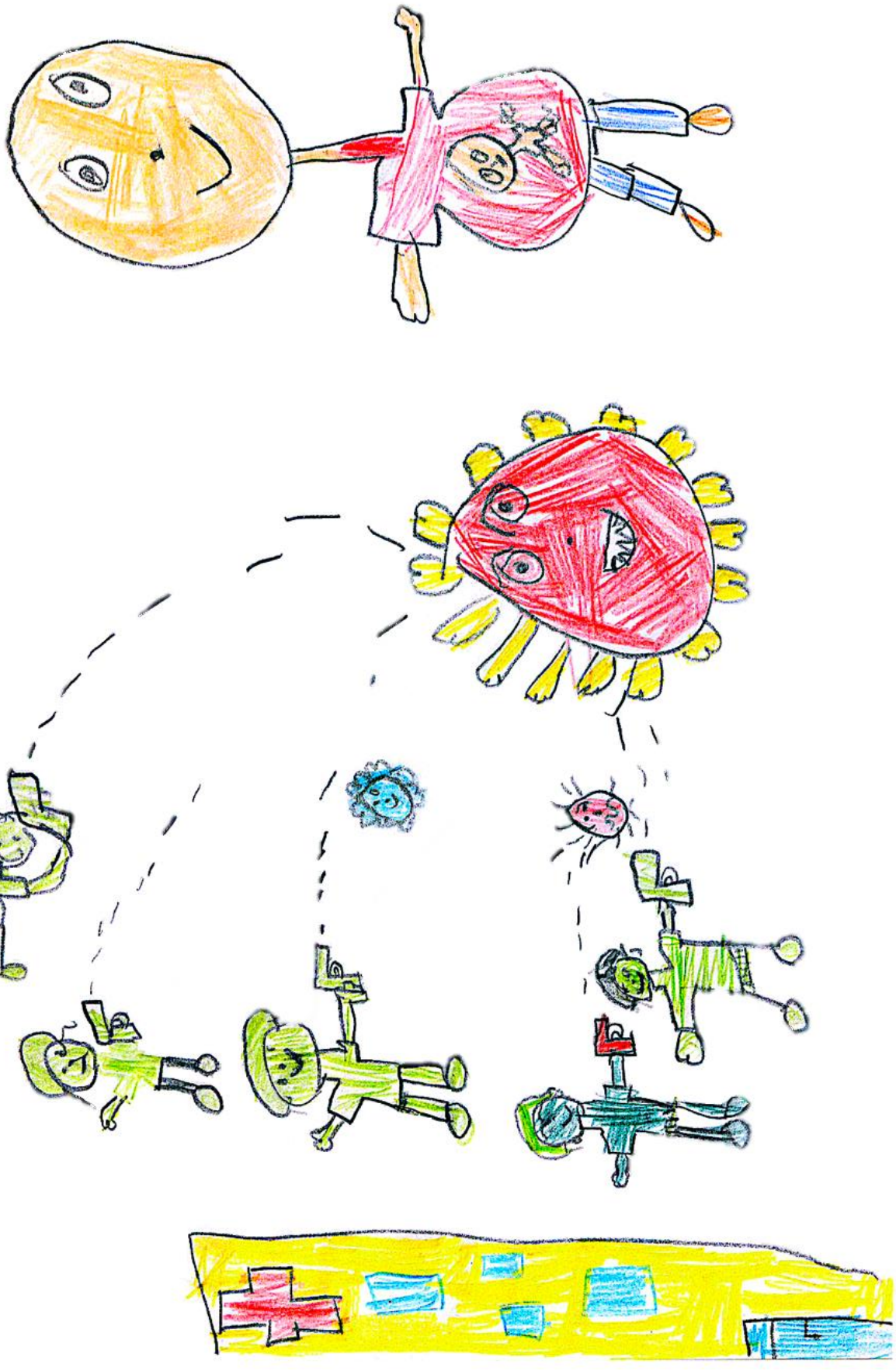

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Chapter 1

General introduction

Diagnosis and treatment of cancer during pregnancy

Parts of this introduction have been adapted from:

Vandenbroucke, T., Verheecke, M., Fumagalli, M., Lok, C., & Amant, F. (2017) Effects of cancer treatment during pregnancy on fetal and child development. *The Lancet Child and Adolescent Health, 1,* 302-310. DOI: 10.1016/S2352-4642(17)30091-3

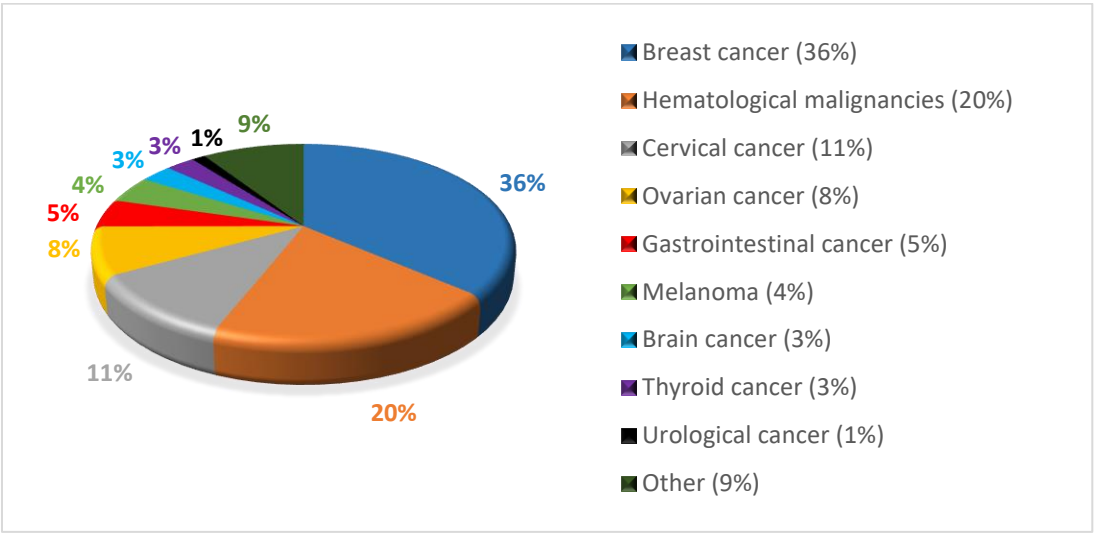
Vandenbroucke, T., Verheecke, M., Van Calsteren, K., Han, S. N., Claes L., & Amant, F. (2014). Fetal outcome after prenatal exposure to chemotherapy and mechanisms of teratogenicity compared to alcohol and smoking. *Expert Opinion on Drug Safety, 13,* 1653-1665. DOI: 10.1517/14740338.2014.965677

This chapter provides a general introduction to the topic of cancer during pregnancy. The epidemiology of cancer diagnosis during pregnancy, the possible treatment options and the follow-up of pregnancy and delivery are discussed. Finally, an overview of the dissertation is provided.

1. DIAGNOSIS OF CANCER DURING PREGNANCY

The prevalence of cancer diagnosed during pregnancy is estimated at 1 in 1000 pregnancies.[1,2] The most common cancer types diagnosed during pregnancy are the same as those found in non-pregnant women in the childbearing age: breast cancer, hematological malignancies, cervical cancer and ovarian cancer (Figure 1). As women in developed societies defer childbearing to the third or fourth decade of life, and the incidence of most malignancies rises with increasing age, the rare co-incidence of cancer and pregnancy is likely to become more common. Pregnancy is a period in which women regularly consult a medical doctor and/or midwife, have physical exams, blood analyses and ultrasound examinations. These examinations provide the opportunity for early diagnosis of major diseases like cancer. However, symptoms caused by a malignancy may mimic many common physiologic gestational symptoms such as nausea, fatigue, (relative) anemia, abdominal discomfort or changing breast consistency. Therefore, it is important to perform further technical examinations when complaints are persistent or worsening and physical exam is suspect for underlying disease. Improvements in diagnostic procedures have also led to a faster detection of cancer in pregnant women and therefore an increase in the detection of cases.

Figure 1. Distribution of cancer types diagnosed during pregnancy (N=1625)



Note: Data were retrieved from the cancer and pregnancy registry (June 2018) by the International Network on Cancer, Infertility and Pregnancy (INCIP).

2. CANCER TREATMENT DURING PREGNANCY

In the near past, the lack of safety data of cancer treatment during pregnancy for both mother and child generally withheld physicians from initiating cancer treatment during pregnancy. This commonly led to a delay in the treatment of the mother, termination of pregnancy or premature induction of delivery, with adverse consequences for mother and child. However, pregnancy itself has been shown not to have a negative impact on the maternal oncological outcome.[3] Also, termination of pregnancy does not seem to improve survival.[4] These data together with the preliminary findings discussed in the next chapter that cancer treatment during pregnancy may be relatively safe for the fetus, have changed the management of pregnant cancer patients towards the possibility of cancer treatment during pregnancy.

2.1 Surgery

Surgery is an essential part of treatment for many cancer types and is feasible during all trimesters of pregnancy when precautions are taken. The most serious obstetrical risks of surgery in pregnancy are miscarriage, premature delivery, and fetal distress (i.e., decreased placental perfusion and fetal hypoxia).[5] Surgery-related risks of maternal hypotension, hypoxia, or stress pose a greater risk to the fetus than do anesthetic agents.[6] Therefore, maternal monitoring is crucial to prevent hypoxia, hypotension, and hypoglycemia, and is the best way to ensure fetal well-being.[7] Continuous feto-uterine monitoring by cardiotocography is possible during non-abdominal surgery, but should only be used when the fetus is viable.[8]

2.2 Chemotherapy

Physiologic changes during pregnancy can affect pharmacokinetics with respect to the distribution, metabolism, and excretion of systemic therapy, possibly leading to reduced drug exposure and effectiveness. Many drugs can cross the placenta, depending on their size, lipophilia, protein binding, ionization, and the presence in the placenta of protein drug transporters.[9,10] However, findings from animal studies showed that the concentrations of drugs are lower in the fetal plasma than in maternal plasma, supporting the protective role of the placenta.[9,10] The extent of this placental protection differs by chemotherapeutic agent, with a high passage of platin-based therapies (57% for carboplatin), but low passage of taxanes (1% for paclitaxel and not detectable for docetaxel) and anthracyclines (4% for epirubicin and 8% for doxorubicin).[9,10]

Chemotherapy is cytotoxic and interferes with cell growth. Therefore, the timing of chemotherapy, the number of cycles, and dose administered are crucial factors that contribute to fetal outcome. With insufficient knowledge of the safety of chemotherapy administration during organogenesis, systemic

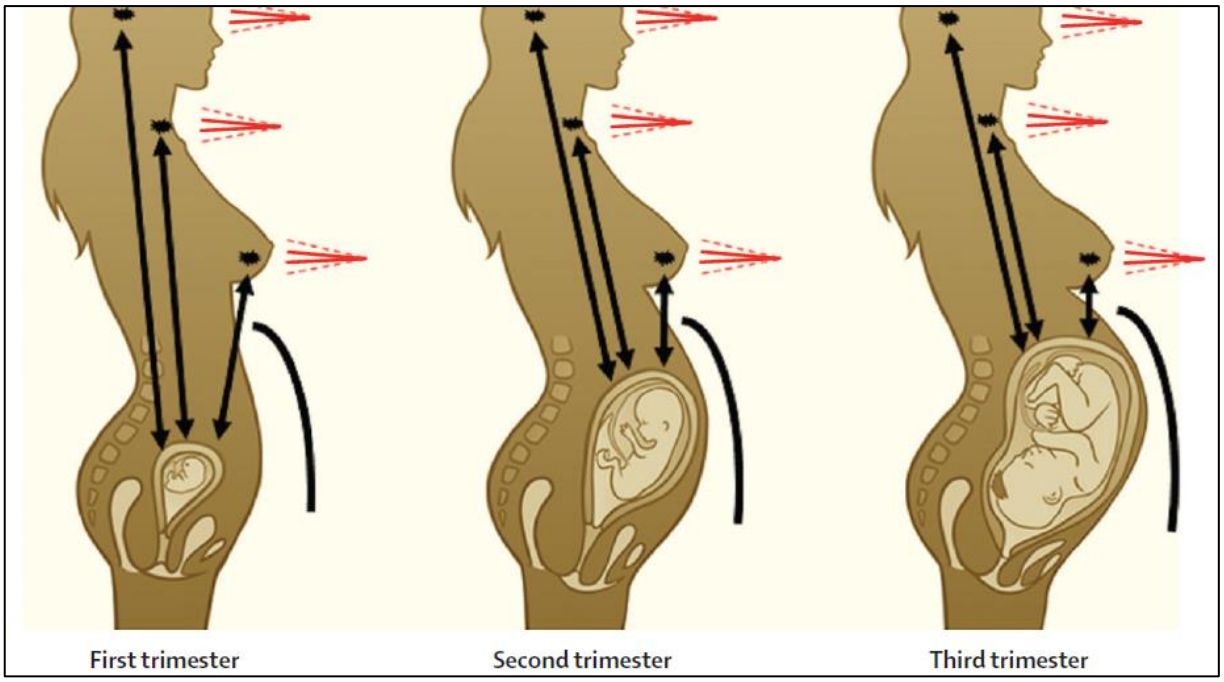
treatment remains experimental and contraindicated for the first trimester. From the second trimester on, data suggest that some chemotherapeutic agents can be administered without an increased risk of fetal malformations and without major malformations in the neonatal period and early childhood.[11,12] Nonetheless, the potential effects of chemotherapy need to be well considered, particularly because the development of the central nervous system starts in the fifth week of pregnancy and continues throughout pregnancy and after birth. Other potential risks of in utero exposure to chemotherapy during the second and third trimesters of pregnancy are low birth weight, subtle changes to the heart function, and premature delivery.[11-15]

There are a lot of different chemotherapeutic agents, all with their own potential impact on fetal development based on their working mechanism and adverse effects reported in adults and children diagnosed with cancer. Methotrexate has been associated with severe malformations, and therefore cannot be administered during pregnancy.[16] Four groups can be distinguished that are most frequently administered in pregnant cancer patients. First, anthracyclines (e.g., daunorubicin, doxorubicin, epirubicin, idarubicin) interfere with DNA replication by inhibiting topoisomerases, which are enzymes that regulate the overwinding or underwinding of the DNA so it can be copied. The main side effect of anthracyclines is cardiotoxicity.[17,18] Second, platinum-based antineoplastics (e.g., cisplatin, carboplatin) bind to and cause crosslinking of DNA, which leads to apoptosis. They may cause neurotoxicity when administered in high doses, resulting in peripheral neuropathies such as polyneuropathy.[19,20] Ototoxicity, especially hearing loss, has also been described.[20,21] Third, cyclophosphamide is an alkylating agent commonly used in breast and hematological malignancies. It directly damages the DNA to prevent reproduction of cancer cells. Adverse effects, especially when administered in high doses, may include permanent infertility.[22] Finally, taxanes (e.g., paclitaxel, docetaxel) inhibit mitosis by disrupting the microtubule function, which is essential to cell division. Dose-limiting toxicity of taxanes is predominantly sensory or sensorimotor axonal polyneuropathy.[19]

2.3 Radiotherapy

The biological effects of radiotherapy are incompatible with pregnancy because of the radiosensitivity of the rapidly growing embryo and fetus. However, these effects depend on gestational age and dose, and can be stochastic or deterministic. Stochastic effects occur by chance and do not have a threshold above which the effect is seen; the risk, but not severity, of these effects increases with treatment dose. By contrast, deterministic effects are characterized by a cause-effect association, and their severity increases with treatment dose once a particular threshold is reached. The dominant deterministic effect of preimplantation irradiation is early death of the conceptus.[23] During organogenesis in the first trimester, irradiation above the threshold of an absorbed dose of 100mGy

Figure 2. Fetal exposure to irradiation of the upper body parts



Note: The figure illustrates examples of brain, thyroid, and breast cancer. The highest dose of radiation is focused on the tumor (red solid lines), but scatter beams with low radiation dose (red dashed lines) divert away from the tumor. Curved black lines indicate abdominal shielding, and double arrows indicate the distance from the radiation field to the fundus.

increases the risk of malformations.[24] The fetal central nervous system continues to develop after the major organogenesis phase and can be impaired by exposure to prolonged irradiation. The neuronal plasticity and natural redundancy can compensate to some extent for irradiation damage. Findings from animal studies and data from atomic bomb survivors show a high sensitivity of the central nervous system to radiation up to 15 weeks of gestation.[25] Irradiation of an older fetus can lead to growth restriction and functional organ defects. A stochastic effect of radiotherapy is the increased risk of all types of childhood cancers, especially leukemia (3 to 4 per 1000 children).[23] This increase in risk is independent of the gestational age at exposure. Because of these uncertainties, radiotherapy is often postponed until the postpartum period. However, if a delay is detrimental for the mother, radiotherapy of upper body parts with fetal shielding is possible, especially in the first or second trimester, when the distance between the fetus and the field of irradiation is large, therefore reducing fetal exposure (Figure 2).[26] In the third trimester, this distance is very short in the case of breast cancer, resulting in increased fetal radiation exposure, but could be large enough to allow safe irradiation for brain or thyroid cancer. Because of the relation between effects on the fetus and distance from the target lesion, a phantom system (a model and specific software in which the fetal radiation dose can

be estimated before the treatment) and calculation of the estimated fetal exposure – taking into account the tumor type, radiotherapy dose, distance between the radiation field and the fetus, and type of shielding – are essential.[23] When fetal exposure is below the threshold of 100mGy, radiotherapy can be considered, although radiotherapy of the pelvis is not compatible with an ongoing pregnancy.[23]

2.4 Other treatments

Targeted therapy has become an important therapeutic option and its use is increasing steadily.[27] Data on the safety of these agents in pregnancy are overall scarce. Because of the small size, structure, metabolism and pharmacokinetics of these agents, they are potentially teratogenic and harmful for the fetus.[28]

Knowledge on the effects of hormonal therapy in pregnancy came from studies of women receiving adjuvant therapy for breast cancer. Although most children who had in utero exposure to tamoxifen (an estrogen antagonist) are healthy, tamoxifen is sometimes associated with fetal anomalies (e.g., ambiguous genitalia, craniofacial malformations, Goldenhar syndrome, and Pierre-Robin sequence).[29-32] Therefore, the use of tamoxifen is discouraged in pregnancy.

3. FOLLOW-UP OF PREGNANCY AND DELIVERY

Fetal maturation is a complex process. At different stages of development, different aspects can be influenced by external factors (e.g., teratogenic drugs, alcohol, smoking, maternal stress, altered nutrition), possibly with short- or long-term consequences for the child. A thorough follow-up of pregnancy in women with cancer is thus indispensable.

Before staging examinations or oncological treatment is started, fetal structural development and growth should be evaluated to exclude pre-existing anomalies.[33] The maternal and fetal condition, the administered treatment and the gestational age influence the preferred frequency of obstetrical control. At least monthly, a detailed fetal assessment should be performed by a maternal-fetal medicine specialist in order to follow fetal growth and detect possible teratogenic effects (congenital malformations or dysfunctions, fetal anemia). As babies are more frequently born preterm and small for gestational age (i.e., a birth weight below the tenth percentile for gender and gestational age matched controls), special attention is required for signs of preterm labor and fetal growth restriction.[12]

Moreover, the average age of pregnant women diagnosed with cancer is increased compared to the normal obstetric population. Therefore, special attention should be paid not only to the oncological

condition of the woman, but also to age-related pregnancy risks like hypertension, gestational diabetes and increased risk for fetal aneuploidy.

With regard to the timing of delivery, important fetal concerns have to be taken into account, such as acute side effects of cancer treatment, prematurity and extremely rarely fetal metastasis. Hematopoietic depression is a known side effect of chemotherapy. In order to avoid problems in the patient and the neonate (bleeding, sepsis, anemia), and to avoid drug accumulation in the fetus, an interval of two to three weeks should be respected between the last cycle of chemotherapy and the anticipated delivery.[33,34] Preferably, delivery should not be performed before 37 weeks of gestation.[35] Prematurity, including late prematurity (34-37 weeks), is associated with general health problems and cognitive and emotional developmental disorders on the short and on the long term.[11,36] Therefore, maximal efforts should be made to avoid unnecessary prematurity in patients where cancer treatment can be given during pregnancy. Documented reports of maternal malignancy metastases in the placenta are rare and also proven maternal metastasis to the fetus is exceptional.[37] However, each placenta should be thoroughly examined for metastasis, which, if present, should alert the clinician to monitor the infant for development of malignant disease.

4. OVERVIEW OF THE DISSERTATION

The dissertation consists of two main parts. **Part 1** describes the neuropsychological development and behavior of children born to mothers diagnosed with and treated for cancer during pregnancy. This part consists of Chapters 2 to 5. **Chapter 2** provides an introduction to neuropsychological development in this patient group. First, theoretical neuropsychological concepts are explained and normal cognitive development throughout childhood is discussed. Furthermore, prenatal risk factors for neurocognitive dysfunctions are explored, such as smoking and alcohol use in pregnancy, maternal stress, preterm birth and small for gestational age birth. Next, chemotherapy- and radiotherapy-induced neurotoxicity in children and adults with cancer are discussed, followed by a review of the available literature on the effects of prenatal exposure to cancer treatment. Finally, research questions and hypotheses are formulated. In **Chapter 3**, we investigate the effects of maternal cancer diagnosis and treatment during pregnancy on the general cognitive development of children in infancy and early toddlerhood (at the age of 1.5 and 3 years)**.** In **Chapter 4**, the effects of maternal cancer diagnosis and treatment during pregnancy on intelligence, attention, memory and behavior problems in early childhood (at the age of 6 years) are investigated. In **Chapter 5**, we provide an interim analysis of the effects of maternal cancer diagnosis and treatment during pregnancy on intelligence, attention, memory and behavior problems in middle childhood (at the age of 9 years). **Part 2** consists of one chapter, **Chapter 6**, in which we investigate the psychological distress and use of cognitive coping

strategies in pregnant women diagnosed with cancer and their partners. In **Chapter 7**, the main results of our studies are summarized and discussed. The strengths and limitations of our studies are addressed, suggestions for future research are provided and clinical implications and recommendations are formulated.

PART 1

The impact of maternal cancer diagnosis and treatment during pregnancy on neuropsychological child development

Chapter 2

Cognitive development and behavior of children prenatally exposed to maternal cancer and its treatment: a review of the literature

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Parts of this chapter have been adapted from:

Vandenbroucke, T., Verheecke, M., Fumagalli, M., Lok, C., & Amant, F. (2017) Effects of cancer treatment during pregnancy on fetal and child development. *The Lancet Child and Adolescent Health, 1,* 302-310. DOI: 10.1016/S2352-4642(17)30091-3

Vandenbroucke, T., Verheecke, M., Van Calsteren, K., Han, S. N., Claes L., & Amant, F. (2014). Fetal outcome after prenatal exposure to chemotherapy and mechanisms of teratogenicity compared to alcohol and smoking. *Expert Opinion on Drug Safety, 13,* 1653-1665. DOI: 10.1517/14740338.2014.965677

This chapter provides an introduction to the cognitive development and behavior of children born from pregnancies complicated by maternal cancer. First, theoretical neurocognitive concepts, such as intelligence, memory, attention and executive functions will be explained and second, normal cognitive development throughout childhood will be described. Third, prenatal risk factors for neurocognitive dysfunctions will be explored, such as alcohol use and smoking in pregnancy, maternal stress, preterm birth and small for gestational age birth. Fourth, chemotherapy- and radiotherapy-induced neurotoxicity in children and adults with cancer will be discussed, followed by a review of the available literature on the effects of prenatal exposure to cancer treatment. Finally, research questions and hypotheses will be formulated.

1. INTELLIGENCE AND SPECIFIC NEUROCOGNITIVE FUNCTIONS

In this section, concepts of intelligence, memory, attention and executive functions will be explained and theoretical models of these neurocognitive functions will be presented.

1.1 Intelligence

Intelligence has been defined and conceptualized in many different ways. David Wechsler described intelligence as "the capacity of the individual to act purposefully, to think rationally, and deal effectively with his environment".[38] According to his definition, intelligence is an overall or global entity, which is multi-determined and multi-faced rather than an independent, uniquely-defined trait. Wechsler was the founder of the most used intelligence quotient (IQ) tests worldwide today to assess individual general intelligence: Wechsler Preschool and Primary Scale of Intelligence (WPPSI)[39], Wechsler Intelligence Scale for Children (WISC)[40] and Wechsler Adult Intelligence Scale (WAIS)[41]. These tests are composed of several subtests which constitute the Total or Full Scale IQ score (FSIQ). Depending on the specific test and edition, several IQ factors and index scores can be calculated, such as Verbal Intelligence (VIQ), Performance Intelligence (PIQ), Verbal Comprehension (VCI), Perceptual Organization (POI), Processing Speed (PSI), Working Memory (WMI), Perceptual Reasoning (PRI), Fluid Reasoning (FRI), Visual Spatial (VSI) index and General Language Composite (GLC). The IQ, index and subtest scores are corrected for age and are normally distributed (mean IQ or index score = 100, standard deviation (SD) = 15; mean standard subtest score = 10, SD = 3).[42] IQ scores have shown to be good predictors of academic performance.[43,44]

1.2 Memory

Learning and memory are fundamental aspects of cognitive development. Without a memory of the past, we cannot operate in the present or think about the future. Memory processes are essential for the effectiveness of other cognitive, affective and social processes. Nonetheless, functions such as language, attention and executive functions also play an important role in the success of learning and memory.

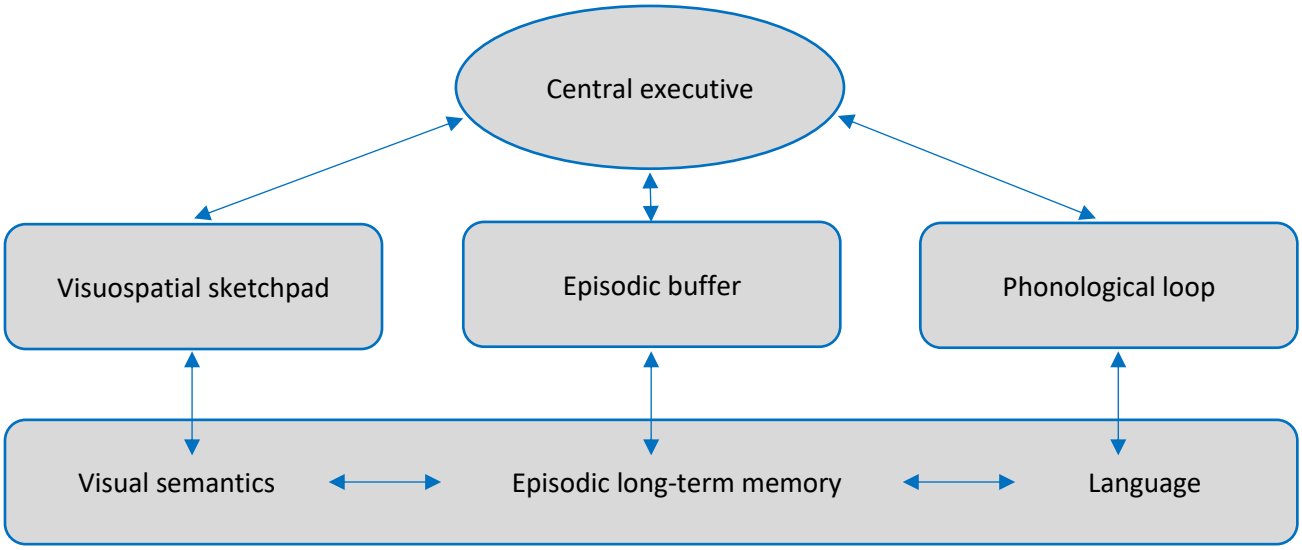
Memory is considered as an information processing model, composed of three interactive stages.[45] The first stage, *encoding*, is the initial registration of information. When information from sensory input is noticed, it needs to be changed into a form that the system can cope with, for example in a visual, auditory, sensory or semantic way. In the second stage, *storage*, the information is associated with previously stored information in the memory and in this way it can be stored in a relatively stable and long-lasting memory track. The third stage, *retrieval*, concerns the retrieval of stored information. The three stages are bounded by each other and affect one another. Failures can occur at any stage, leading to forgetting or to false memories.

The storage of information relies on the functioning of different memory systems. Atkinson and Shiffrin considered memory as a serial process.[46] According to their theory, sensory information is first processed by the sensory memory system. Then, the processed information is sent to the short-term memory, which is a temporary storage system where a small amount of information can be stored for a short period. Last, the information is stored in the long-term memory, which is considered as the permanent storage of information. Memories from the short-term memory system are transformed into permanent memories in the long-term memory system through a process of consolidation. The theory has now become strongly nuanced. Learning is no longer considered as a serial process and different subsystems can be distinguished within the sensory, short-term and long-term memory systems.[47-49]

Short-term memory and working memory are sometimes used interchangeably. However, while short-term memory refers to the temporary storage of information, working memory requires the active manipulation of short-term stored information. The currently most accepted model of working memory was developed by Alan Baddeley (see Figure 1).[47,48] In his model, working memory is composed of three components that are driven by a central control system, which he called the *central executive*. It acts as a supervisory system that controls cognitive processes to make sure that the storage is actively working, to intervene in case of maladaptive functioning and to prevent from distractions. It controls the two main subsystems: the *visuospatial sketchpad* and the *phonological loop*. In the visuospatial sketchpad, visual and spatial information is integrated in a mental representation (visualization) that is temporarily stored and edited. Speech-related information is

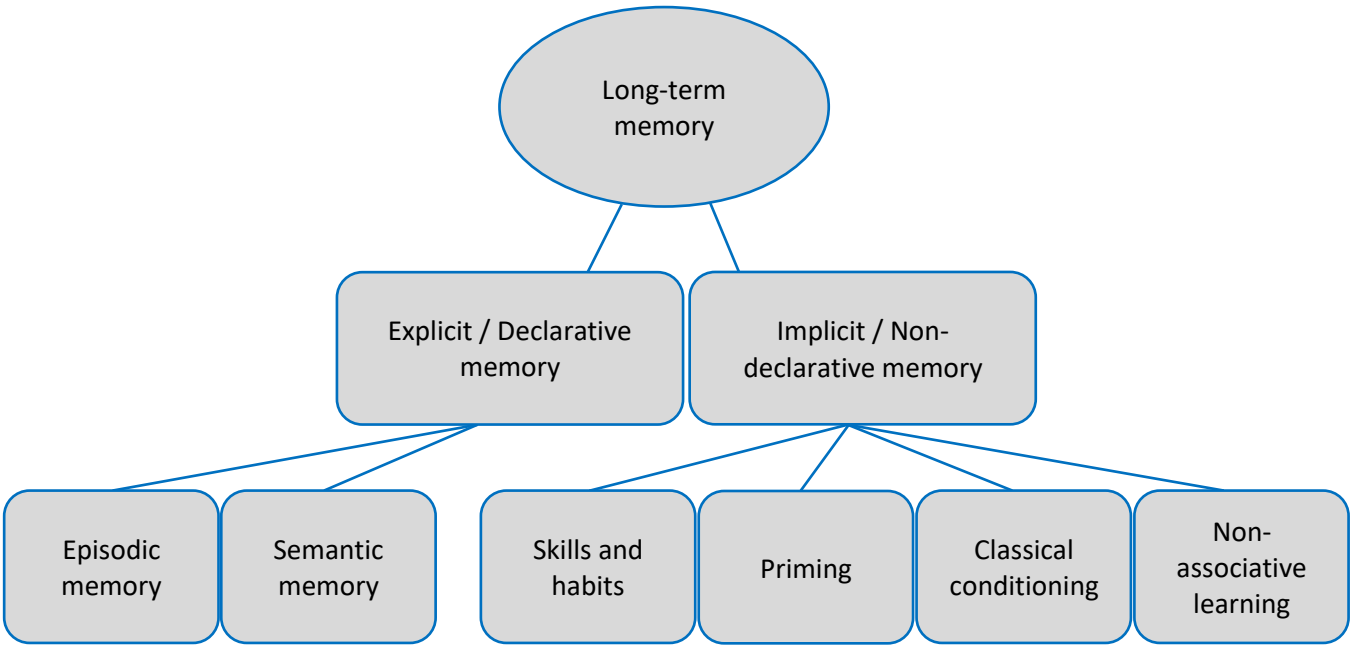
temporarily stored in the phonological loop by means of subvocal rehearsal. In 2000, the *episodic buffer* was added as a fourth component to the model. The episodic buffer is a system that stores different aspects of information in a multidimensional code and that acts as a connection between the active subsystems of working memory and between working memory and long-term memory.

Figure 1. Baddeley's model of working memory (2000)



Squire developed a model of long-term memory in 1992.[49] According to his model, long-term memory can be split into two interacting memory systems: *explicit* or *declarative memory* and *implicit* or *non-declarative memory*. The declarative memory system is engaged in the storage of facts and events and consists of two subsystems: *episodic memory* and *semantic memory*. Personal experiences that are bounded to a specific timing and place are stored in the episodic memory, for example a car-accident. In the semantic memory, general information is stored about the meaning of words and concepts and about the world we live in, for example if something is eatable or not. The non-declarative memory system is involved in procedural learning, such as learning how to ride a bike or the development of handwriting. Several types of learning may lead to implicit memories, such as skills and habits, priming, classical conditioning and non-associative learning.

Figure 2. Squire's model of long-term memory (1992)



1.3 Attention and executive functions

Attention and executive functions are strongly related to each other. The term *attention* refers to different processes involved in the detection and selection of sensory information from the environment in order to further process this information.[50] Several types of attention can be distinguished.[51] *Alertness* is the admissibility of the brain for information. *Sustained attention* is defined as the capacity to maintain an active attentional attitude for a task, goal or behavior, notwithstanding there being little inherent stimulation of the task to maintain the attention. *Selective attention* refers to the efficiency with which information can be filtered to detect relevant information and to neglect irrelevant or distracting information. *Divided attention* is the capacity to perform two tasks at once and to divide the attention on these tasks or to direct the attention to two different aspects of the same task.[51]

Executive functions are a collection of processes that are responsible for guiding, directing, and managing cognitive, emotional and behavioral functions, particularly during active, novel problem solving.[52] Executive functions can be divided into specific subdomains, including the ability to initiate behavior, inhibit competing actions or stimuli, select relevant task goals, plan and organize a means to solve complex problems, shift problem-solving strategies flexibly when necessary, and monitor and evaluate behavior. In this dissertation, the main executive functions under study are working memory (discussed above), response inhibition and attentional control. *Response inhibition* refers to the ability to stop automatic thoughts and behaviors in time if necessary. *Attentional control* and *attentional*

switching consist of the capacity to coordinate different skills or to make an adequate plan to solve a problem.[51]

2. NORMAL NEUROCOGNITIVE DEVELOPMENT

Neurocognitive development finds its origins in pregnancy with the development of the central nervous system (CNS) in the embryo. The CNS starts to develop in the fifth week of pregnancy and has its origin in the neural plate by thickening of the ectoderm.[53] Thereafter, when the neural groove is formed and closed, it becomes the neural tube. The development of the CNS proceeds throughout pregnancy and continues after birth. Some cerebral structures such as the striatum, the cerebellum and the brain stem are functionally sufficiently developed at birth, which enables the start of implicit learning.[54,55] Moreover, the development of the hippocampus occurs mainly prenatally. At 24 weeks gestational age, the hippocampus of the fetus resembles already that of an adult.[56]

As different definitions and conceptualizations of intelligence exist, different theories of normal development of intelligence and general cognitive abilities have been proposed. An important question relates to the stability of intelligence. Research has shown that the stability of intelligence increases with age. Intelligence measured before the age of 5 years only moderately correlates to intelligence at older age, but from the age of 11-12 years, correlations of 0.80 with adult intelligence have been found.[57,58] However, intelligence does not develop synchronically in all domains. For example, task performances that rely on fluid intelligence (i.e., inductive and deductive reasoning, non-verbal conceptualization and flexibility) reach their top relatively early in development and decrease faster at older age, compared to task performances that rely on crystalized intelligence (such as vocabulary, facts and reading comprehension).[59]

The development of memory starts early in life. At the age of 5 to 6 months, babies are already able to remember information for a short delay of 1 to 2 seconds and this delay increases up to 10 seconds at the age of 1 year.[60] Throughout development, working memory improves with age, depending on structural and functional changes in the brain. The capacity of working memory equals adult capacities at the age of 15 years. Also for long-term memory, research has found early developmental evidence. Implicit memory has been investigated in infants, showing that repeated presentation of stimuli may lead to early memories that can be stored for substantial time periods. Infants are already able to make new and relatively permanent associations between objects and facts and between stored representations of objects and objects that are physically present.[61] Declarative memory is thought to develop rapidly from the age of 1 year into adolescence. According to Siegler, four factors contribute to the improvements in memory.[62] First, the capacity and efficiency of working memory increase throughout development. Second, children start to make use of memory strategies, such as semantic

clustering, and use them more efficiently with age. Third, older children can make use of increasing semantic knowledge, which enables them to associate newly acquired information to information that is already stored. Fourth, children develop a so-called *meta-memory*, which allows them to learn about the functioning of their own memory systems.

Attention and executive functions undergo qualitative changes throughout development. Children become faster and more accurate in all cognitive tasks and are able to concentrate for longer intervals.[63] When it comes to alertness, children experience more difficulties than adults to be constantly alert. They also use less signals from the environment to regulate their alertness, such as an approaching car. At the age of 2 years, most children are not yet able to distinguish relevant from non-relevant information and to direct attention specifically to relevant information. Selective attention starts to mature around the age of 4 years and proceeds rapidly until the age of 7 years.[64] However, the capacity of children to divide attention to different aspects of a task already resembles that of adults.[63] Children of 6 to 8 years show more difficulties with response inhibition than older children. Starting from that age, differences in task performances become smaller between different age groups, but improvements up to adult level are remarked until adolescent ages.[65] On tasks measuring cognitive flexibility, children of 3 to 4 years experience more difficulties to change strategies that have worked in the past but are no longer appropriate, even though they can admit that the strategy is no longer correct.[66] At the age of 8 years, children are capable to adapt strategies flexibly, but they can still improve. At 12 years, performances of children on cognitive flexibility tasks are comparable to those of adults.[67]

3. PRENATAL RISK FACTORS FOR NEUROCOGNITIVE DYSFUNCTION

It is clear that prenatal development plays an important role in postnatal neurocognitive development. In this section, the possible impact of several prenatal risk factors for neurocognitive dysfunction will be discussed, more specifically the impact of substance abuse (alcohol and smoking), maternal stress, premature birth and small for gestational age birth.

3.1 Alcohol use

When alcohol is present in maternal blood, it easily crosses the placenta and the fetal blood-brain barrier.[68] Several mechanisms through which alcohol can affect the fetus have been described.[69] First, the breakdown of ethanol by the liver results in acetaldehyde, a toxic chemical consisting of small molecules that can easily cross the placenta and accumulate in the fetal brain. Second, ethanol itself can lead to an alteration of growth regulatory factors that inhibit or stimulate cell proliferation in the body. Third, alcohol increases the generation of free oxygen radicals and reactive oxygen

intermediates, which may lead to damage of proteins and lipids in the cells and consequently increased apoptosis. Finally, high levels of ethanol were found to inhibit alcohol dehydrogenase-catalyzed retinol oxidation, which normally results in retinoic acid, a signaling mechanism for embryonic development.[70] Alcohol abuse during pregnancy can lead to Fetal Alcohol Syndrome (FAS) in the child, a condition characterized by physical and mental retardation, craniofacial anomalies and minor joint abnormalities.[69] More specifically, FAS is associated with prenatal and postnatal growth restriction, neurodevelopmental abnormalities (e.g., developmental delay, mental retardation, learning difficulties with math and visual spatial materials, microcephaly), dysmorphic face characteristics (e.g., small eyes, epicanthic folds, long hypoplastic philtrum, thin upper lip, midfacial hypoplasia) and associated congenital anomalies (e.g., hemangiomas, cardiac defects, minor joint and limb abnormalities, genital abnormalities, single palmar creases, ptosis, strabismus).[71] Moreover, cardiac malformations are common in children with FAS, specifically ventricular septal defects, pulmonary artery hypoplasia and interruption of aortic arch type A.[69]

Heavy drinking, defined as 5 or 6 alcohol units per occasion and a minimum average intake of 1 to 3 drinks a day, results in FAS rates between 2 to 4%.[72] Hence, only a minority of children of alcohol abusing women exhibit FAS. There may be genetic factors that program vulnerability, as indicated by twin studies.[73] Maternal age is another contributing factor, because of increased tolerance to alcohol, deterioration of liver function due to many years of alcohol abuse, and increase in body fat/water ratio with older age, leading to higher peaks of alcohol in maternal and fetal blood.[72]

However, when symptoms are present in a lesser degree, the condition is described as Fetal Alcohol Effects (FAE). Heavy drinking, but not mild or moderate exposure, is associated with a 5 to 7 points decrease in IQ score, hyperactive behavior, attentional problems and abnormalities in executive functioning.[74-76] Attention deficit disorder, hyperkinetic behavior and autistic disorder have also been reported.[69]

A topic of debate is the existence of a threshold above which alcohol may have detrimental effects in the fetus. Some researchers found alcohol effects in young children starting from 0.5 absolute alcohol ounces per day,[77] while others did not find evidence for a threshold. Reviews on the effects of low and moderate prenatal alcohol exposure and on fetal exposure to binge-drinking did not find convincing evidence of alcohol induced fetal effects, neither conclude that it might be safe, due to weaknesses in methodology of reviewed studies.[78,79]

3.2 Smoking

Maternal smoking during pregnancy has been associated with intra-uterine growth restriction (IUGR), changes in behavior and neurocognitive development in the child. The most important mechanism is the interference with normal placental function by reducing blood flow to the uterus leading to

deprivation of nutrients and oxygen.[68] Moreover, nicotine, carbon monoxide and other ingredients in tobacco tar can directly affect the fetal brain and the developing central nervous system.[68] Prenatal exposure to nicotine may also result in hypoactive cholinergic neurotransmission, which may account for learning and memory deficits.[68] Finally, fetal exposure to nicotine may be responsible for dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis, which is linked to psychopathology.[68] In the neonate, hypertonicity, heightened excitability, tremors, startles and signs of stress and abstinence were reported,[80,81] even after controlling for prematurity and other birth outcome related factors.[81] In childhood and adolescence, attention deficit hyperactivity disorder (ADHD) and externalizing (e.g., oppositional and aggressive) behavior were found to be increased.[82-87] Some studies suggest a dose-response relationship in which externalizing behavior, criminality and psychiatric inpatient treatment for substance abuse disorder were more frequent with higher levels of tobacco exposure during pregnancy.[88,89] However, Milberger et al. found that ADHD families more commonly smoke than non-ADHD families, which might suggest a common genetic vulnerability for both ADHD and smoking.[90] This can explain part of the variation in behavioral outcome of the child after in utero exposure to tobacco. Neurocognitive changes such as lower IQ scores in 6-17 year-olds,[91] lower academic achievements in 14-year-olds,[92] deficits in verbal learning memory, problem solving, and eye-hand coordination in 10-year-olds,[93] deficits in auditory processing and visual perceptual processing in 6-11 year-olds,[94] and problems with sustained attention, response inhibition and memory in 6-year-olds have also been reported.[95,96] It is not clear whether these cognitive deficits can be explained by a syndrome like ADHD.

3.3 Maternal stress

Pregnancy and suffering from cancer are challenging life events that may cause prenatal maternal stress. In healthy women, maternal stress and anxiety during pregnancy have been associated with adverse birth outcomes, developmental and cognitive impairments and psychopathology in the offspring. Studies have found an increased risk of spontaneous abortion, preterm labor, malformations, growth restriction and low birth weight.[97,98] Huizink et al. reported lower mental and motor developmental scores at 8 months after high levels of stress during pregnancy.[99] Henrichs et al. found prenatal stress to be related to low word comprehension and poorer nonverbal cognitive development at 18 months, as measured by parent report.[100] Some studies also reported cognitive dysfunctions. Van den Bergh et al. found increased impulsivity on a computerized attention task and lower scores on two intelligence subtasks measured in 14- and 15-year-olds, specifically Vocabulary and Block Design, which are highly correlated to Full Scale IQ.[101] Mennes et al. reported lower scores on tasks requiring integration and control of different task parameters in 17-year-olds, but no impairment in working memory, response inhibition or visual orienting of attention.[102] Moreover, a

link with psychopathology has been described. Loomans et al. studied antenatal maternal state-anxiety in a large community based cohort by parent and teacher report and noticed more overall problem behavior, emotional symptoms, peer relationship problems, conduct problems and less pro-social behavior.[103] Stronger evidence for overall problem behavior was found for boys. Antenatal anxiety was also related to hyperactivity and inattention problems in boys, but not in girls. Van den Bergh et al. found an association between antenatal exposure to maternal anxiety and high, flattened cortisol day-time profiles in 14- to 15-year-old offspring, which was related to depressive symptoms for female adolescents only.[104] However, Huizink et al. conclude in a review on fetal outcome after antenatal stress exposure that prenatal stress enhances susceptibility for psychopathology, rather than exerting a direct effect on specific disorders, based on the underlying mechanisms found in animal models.[105]

The role of maternal stress hormones during pregnancy has been described as the main mechanism explaining the impact of maternal stress on fetal development. Gitau et al. found a linear relationship between maternal and fetal cortisol levels in plasma.[106,107] Two pathways are hypothesized.[108] First, increased maternal stress hormone levels, especially glucocorticoids, may cross the placenta and thereby increase fetal stress hormone levels. Second, maternal stress may result in impaired uterine artery blood flow and therefore cause oxygen restriction leading to direct stress for the fetus. Increased prenatal fetal cortisol levels may lead to disturbances in HPA-axis regulation.[104] This may contribute to regulation problems at the cognitive, behavioral and emotional level of children.[108] Moreover, the developmental processes that take place in different brain areas, such as the prefrontal cortex and the limbic system, may be altered by antenatal maternal stress hormone release.[108] Genetic susceptibility and other pre- and postnatal environmental factors, such as smoking during pregnancy or postnatal stress, may also play a role in the outcome for the child.[108] More research is needed to determine the impact of maternal stress and anxiety due to cancer disease and treatment on fetal development.

3.4 Prematurity

The length of a normal pregnancy is 37 to 42 weeks. Babies born at 37 weeks of gestation or later are born at term, while birth before 37 weeks is defined as preterm birth. Distinctions can be made according to the timing of prematurity: extremely preterm (<28 weeks), very preterm (28 to <32 weeks), moderately preterm (32 to <34 weeks) and late preterm birth (34 to <37 weeks).

Over the past decades, there has been a general increase in survival rates of preterm born babies, but this has not been accompanied by a decrease in long-term physical and cognitive disability.[109] Prematurity represents the main determinant of early neonatal morbidities and later neurodevelopmental impairment: the more immature the infant, the higher the risk of postnatal complications and impaired long-term outcome. Late preterm infants are the most represented

premature infants in pregnancies complicated by cancer, but an increased risk of adverse early neonatal outcomes (temperature instability, respiratory distress syndrome, excessive weight loss and dehydration, sepsis, hypoglycemia, jaundice and neurologic morbidities) has been well demonstrated also in this low-risk preterm population.[110]

Furthermore, prematurity has been related to long-term neurocognitive dysfunction. This is not surprising as the last weeks of gestation represent a critical period of brain development, including rapid increases in brain weight, and cortical, grey, and white matter volumes.[111] The cognitive development of very preterm born children has been widely studied, with a high reported incidence of developmental delay which increases with decreasing gestational age. For example, Bhutta et al. found lower general cognitive ability scores in preterm versus term born children at school age in their meta-analysis, including 15 studies.[112] Others have investigated the impact on specific neurocognitive functions, such as executive functions. Sun et al. found that very preterm infants performed worse than term born infants on measures of working memory, inhibitory control and planning at the corrected age of 8 months.[113] Discrepancies between very preterm and term born children in executive functions may persist into young adulthood. In the study of Nosarti et al., very preterm born children performed worse on cognitive flexibility and inhibitory control tasks at the age of 20 to 25 years.[114] Less research has focused on the cognitive outcome of late preterm born children, although these children represent the great majority of preterm births. Nonetheless, some studies also found more subtle cognitive sequelae in this low-risk preterm population. For example, Brumbaugh et al. compared executive functioning in late preterm and term born children at the age of 4 years and found that preterm children performed worse on verbal inhibitory control and short-term verbal memory tasks, even when controlling for verbal intelligence. However, there were no group differences in non-verbal inhibitory control, spatial memory tasks and parent-reported behavior problems.[115] Two studies found an increased risk of special educational needs in moderate and late preterm born children at school age.[116,117] Behavior problems, especially internalizing problems and attention problems, have also been reported in the late preterm cohort.[117] Few studies have followed the development of late preterm born children into adulthood. For example, Heinonen et al. compared measures of intelligence, attention, memory and executive functioning between late preterm born adults (34-36 weeks) and term born adults (37-41 weeks) at a mean age of 25 years.[118] Late preterm born adults scored 3 points lower on Full Scale and Verbal IQ compared to term born adults after adjustment for age and sex, but the difference was no longer significant after adjustment for parental education. Also, no between-group differences in memory, attention and executive functioning skills were found and the authors suggest that 'higher level' cognitive functioning may resist the impact of late preterm birth.

3.5 Small for gestational age birth

Small for gestational age (SGA) birth is defined as a birth weight below the 10th percentile of gender and gestational age matched children and refers to the inability of the fetus to achieve its growth potential. Growth restricted fetuses have a substantial risk of perinatal morbidity and mortality. Preterm birth, neonatal hypothermia, hypoglycemia, morbidities, and even perinatal mortality can occur in the acute setting, and cardiovascular and metabolic diseases, such as diabetes and arterial hypertension, have been observed in the long-term follow-up of these children.[119,120]

Inconsistent findings have been reported about the effects of SGA birth on neurocognitive development, which may be related to the use of different definitions of SGA, heterogeneous causes, and the difficulty to control for psychosocial confounding factors. Often, a distinction is made between preterm and term SGA birth, compared to preterm and term appropriate for gestational age born children (AGA, 10th < X < 90th birth weight percentile).

Several studies found no or only small effects of term SGA birth on cognitive development. Theodore et al. found no differences in intelligence at the age of 7 years between term born SGA and AGA children.[121] O'Keeffe et al. investigated the independent effects of term SGA birth on learning, cognition and attention in adolescence.[122] SGA adolescents were more likely to experience learning difficulties than appropriately grown peers. Very low birth weight girls (≤ 3rd percentile) more frequently experienced attention problems and had lower reading scores. However, IQ scores were not different between SGA and AGA adolescents. Paz et al. reported only slightly lower intelligence scores at the age of 17 years in term born SGA versus AGA children, but question the clinical importance.[123]

The evidence for an impact of preterm SGA birth on cognitive development is also inconclusive. Nögel et al. investigated the cognitive development at the age of 2 years, using the Mental Scale of the Bayley Scales of Infant Development, of very low birth weight SGA children born before 35 weeks of gestation, compared to AGA children.[124] Cognitive development was positively related to gestational age, but being born preterm and SGA was not additionally associated with worse outcomes. On the other hand, Heinonen et al. found that being born late preterm and SGA increased the risk for neurocognitive deficits in young adulthood, compared to being born late preterm alone.[118] Guellec et al. found that SGA children born between 29 and 32 weeks gestational age had a higher risk for mortality, minor cognitive difficulties, inattention-hyperactivity symptoms, and school difficulties at the age of 5 years, compared with AGA children.[125] Hutton et al. also found that SGA was associated with intelligence scores, reading comprehension and motor abilities in children born before 33 weeks of gestation and followed-up at the age of 8 to 9 years.[126] Jensen et al. suggest that catch-up growth after birth may be a moderating factor in the association between SGA and cognitive outcome.[127]

4. 'CHEMO BRAIN' AND RADIOTHERAPY-INDUCED NEUROTOXICITY

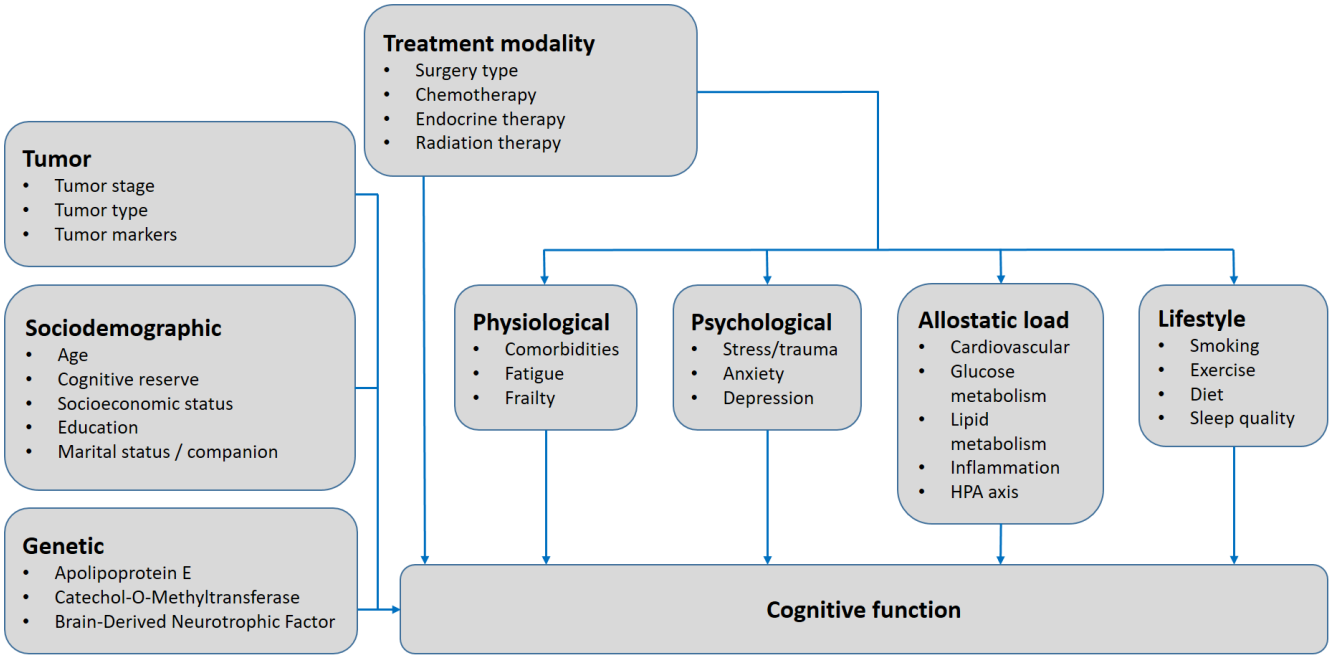
In this section, the effects of chemotherapy and radiotherapy on cognition of children and adults with cancer will be discussed.

Studies have shown that chemotherapy during child- and adulthood may cause cognitive dysfunction, a condition referred to as 'chemo brain'. Studies in adults who have been treated with chemotherapy have described an array of potentially long-lasting disturbances in cognitive functions such as concentration, memory, word finding, reaction time, information processing, multitasking, judgment, and planning.[128-132] Similarly, survivors of childhood acute lymphoblastic leukemia have been reported to exhibit variations in cognitive functions such as information processing speed, Verbal, Performance and Full Scale Intelligence, attention, and verbal and visual memory.[133-135]

Radiotherapy-induced cognitive effects are mainly found in patients treated with cranial irradiation. Armstrong et al. reviewed the clinical effects of therapeutic irradiation damage to the brain.[136] In general, low doses of whole-brain irradiation were related to less cognitive sequelae than high doses on specific brain regions. Adults mainly exhibited problems with memory, attentional control and problem-solving, while intelligence scores were generally not affected. Young children are at higher risk of cognitive dysfunctions, which can be a consequence of the brain tumor itself, but also low doses of cranial irradiation may lead to long-term cognitive problems in this group. In children, decreases in intelligence scores are common and learning, memory, novel problem-solving, planning, attention and reaction times are often affected by cranial irradiation. The effects are larger in younger than in older children. Data on the outcome of children prenatally exposed to irradiation mainly comes from studies on atomic bomb survivors. Otake et al. reported that exposure in the most sensitive period, between 8 and 15 weeks of gestation, may lead to an increased risk of severe mental retardation or a diminution in IQ score and school performance.[137] Less pronounced effects were also found in children exposed in the 16th until 25th week of gestation. A linear dose-response model fitted adequately to the data.

Investigating the real impact of chemotherapy- and radiotherapy-induced cognitive dysfunctions is difficult, due to the many confounding factors (Figure 3).[138] Treatment modalities (surgery, chemotherapy, radiotherapy, hormonal therapy) are often combined, which makes it hard to unravel the independent effect of chemotherapy or radiotherapy on cognition. Moreover, psychological factors (stress, anxiety, depression), physiological factors (comorbidities, fatigue, frailty), dysregulation across multiple biological systems and lifestyle factors (smoking, exercise, diet, sleep), may contribute to post-treatment cognitive decline. Interindividual differences in cognitive decline may also be related to tumor characteristics, genetic factors and sociodemographic factors, such as age, education level, cognitive reserve, socioeconomic status and marital or relational status.

Figure 3. Conceptual model of predictors of cognitive change in cancer survivors, according to Ahles and Root (2018)



The mechanisms through which cancer and chemotherapy may induce cognitive changes are largely unknown. However, several potential mechanisms have been proposed. First, there might be shared genetic factors for the development of cancer and cognitive problems, such as deficits in DNA-repair mechanisms that lead to greater DNA damage.[139] Neuronal DNA damage may occur as a consequence of oxidative stress caused by chemotherapy exposure.[140] Moreover, chemotherapy may have direct effects on the brain structure and function, leading to grey and white matter volume loss, reduced white matter integrity and altered brain activation.[141-143] Chemotherapy may also lead to hormonal changes, causing dysregulation of the HPA-axis, which plays an important role in brain development.[144] Furthermore, peripheral immune responses are activated by tissue damage, which may cause neuroinflammation.[145]

5. PEDIATRIC OUTCOME AFTER PRENATAL EXPOSURE TO CANCER TREATMENT: AN OVERVIEW OF THE LITERATURE

In this section, we will give an overview of the available literature on the effects of cancer treatment during pregnancy on the fetus (e.g., congenital malformations and growth restriction), on the neonate (e.g., preterm birth and neonatal morbidities) and on the long-term child development (e.g., health problems, cardiotoxicity, ototoxicity, dental problems, neurocognitive development and school performance, and behavior problems).

5.1 Effects on the fetus

In this subsection, the possible effects of systemic therapy on the development of congenital malformations and growth restriction will be discussed.

During the first trimester, when the fetus is extremely susceptible, chemotherapy increases the risk of congenital malformations to 8-25%, compared with 4% in the general population.[146-149] However, in a long-term follow-up study of 54 children born after chemotherapy exposure during the first trimester, no congenital abnormalities were detected.[150] Although the investigators concluded that chemotherapy given in the first trimester is safe, data that allow the estimation of teratogenic risks (the developmental stage at exposure, the dose, the duration, and the frequency of drug administration) are absent.[151] If chemotherapy is administered after this critical period, the risk of congenital malformations is not increased (about 3 % for major malformations and 8% for minor malformations).[12]

Contradictory results have been published on the effects of chemotherapy on fetal growth. Although some studies recorded normal birth weight and length according to gestational age, most studies revealed an increased prevalence of small for gestational age (SGA) babies after chemotherapy exposure.[11,12,15,33,152,153] Incidences of SGA range between 7 and 17%, depending on the type of cancer and treatment.[15] In a study by Cardonick et al., including 231 pregnant women diagnosed with cancer, a significant difference was seen in birth weight in babies born to women who had chemotherapy (mean 2647g (SD 713)) and those who did not (mean 2873g (SD 788)).[154] In the study of de Haan et al., 21% (167/796) of children prenatally exposed to maternal cancer (with or without treatment during pregnancy) were born SGA.[155]

Growth restriction can be attributed to fetal, maternal, or placental causes. Direct effects (toxicity of the chemotherapeutic agents to the trophoblasts), indirect effects (inflammation), or the maternal illness itself (with effects such as malnutrition and anemia), along with high concentrations of stress hormones, might contribute to the increased occurrence of SGA in babies born to women with cancer during pregnancy.[156,157] In a study of nearly 4 million singleton births in Swedish national registries, a diagnosis of cancer during pregnancy was associated with an increased risk of stillbirths, mainly of fetuses small for gestational age, and also with preterm SGA births. However, this association declined over the study period (1973-2012), suggesting an improvement in obstetric and oncologic care.[158] Fortunately, although SGA birth seems to be more frequent in women who had cancer during pregnancy, especially those who received chemotherapy, postnatal growth seems to be unaffected. In a study that followed growth curves until 3 years of age, most children born SGA caught up on their growth curves within the follow-up period.[35]

5.2 Neonatal outcomes

The use of chemotherapeutic agents during pregnancy also affects the risk of preterm delivery and neonatal morbidities.

In the study by Amant et al., 67% of children prenatally exposed to cancer treatment were born preterm, in contrast with a general population percentage of preterm births of 6.8-8.0% in the participating countries.[11] Although the neurodevelopment of these children was normal at a median age of 22 months, there was a negative impact of prematurity on the cognitive outcome.

Prematurity, and in particular late preterm birth (34^{+0} to 36^{+6} weeks gestation), is indeed the most commonly reported neonatal outcome: a mean gestational age at birth of 35.8 ± 2.8 weeks was reported by Cardonick et al. on 157 chemotherapy-exposed neonates born to mothers enrolled in the USA International Cancer and Pregnancy Registry between 1995 and 2008.[154] Similar findings were described in the majority of published studies and case series on infants born to pregnant mothers with cancer.[11,12,153,159-161] In case of pregnancy complicated by cancer, preterm birth is mainly due to iatrogenic preterm delivery based on the need to initiate maternal treatment or due to deterioration of maternal health status.

Recently, Lu et al. reported about the risk of stillbirth and infant mortality associated with maternal cancer during pregnancy based on nationwide health registers in Sweden.[158] Both neonatal mortality and preterm birth were positively associated with maternal cancer diagnosed during pregnancy and the association with preterm birth was due to iatrogenic instead of spontaneous preterm birth. Moreover, 89% of the association of maternal cancer during pregnancy with neonatal morbidity was explained by preterm birth. In the study of Van Calsteren et al., 51.2% of 172 children born after cancer diagnosed during pregnancy were admitted to a neonatal intensive care unit and prematurity was the main indication for admission (85.2% of cases).[12]

The incidence of preterm labor in the general population is 4%. In comparison, Van Calsteren et al. observed an incidence of preterm labor of 12.9%.[12] A high rate of spontaneous preterm birth or preterm premature rupture of membranes (30%) was observed in ten women treated with dose-dense chemotherapy (every two weeks). With conventional chemotherapy this event was not more likely to occur (17%, N=99).[161] Chemotherapeutic agents may cause an increase of preterm contractions, but up till now, no clear evidence on the underlying pathophysiology is known.[12] Therefore, close monitoring, including gynecologic examination and cervicometry, is advised.

Maternal hematological malignancies carry the highest risk of obstetric and perinatal complications, such as premature birth and intrauterine growth restriction. Impairments in nutrient exchange, blood flow, and oxygen delivery in the intervillous placental spaces due to leukemia cells have been suggested as potential pathogenetic mechanisms.[12]

Most of the short-term neonatal morbidities reported in babies born to pregnant mothers with cancer are likely to be related to the premature birth, in particular respiratory distress syndrome.[160,162] In the observational study by Loibl et al. on treatment of breast cancer during pregnancy, adverse neonatal events (sepsis, jaundice, SGA, hypercalciuria, necrotising enterocolitis, patent foramen ovale, cerebral bleeding, respiratory distress syndrome, malformations, pulmonary artery stenosis, aspiration pneumoniae, increased muscle tension, high serum concentration of N-terminal pro B-type natriuretic peptide (proBNP), neutropenia, anemia) appeared to be more common in neonates in utero exposed to chemotherapy (15%) compared to those not exposed (4%) and in preterm compared to term infants, but differences were not clinically significant.[33] A tendency, towards a higher incidence of high-grade respiratory distress syndrome was documented by Fischer et al. in a retrospective analysis on 19 preterm and three term infants born to mothers with oncologic diseases, compared to controls born to healthy mothers and matched for gestational age.[159]

Transient hematotoxicity is a potentially serious neonatal side effect of antenatal chemotherapy but this is a rare event when a 3-week interval is maintained between the mother's last course of chemotherapy and delivery. Few cases of leukopenia/pancytopenia, requiring hematological growth factors, have been reported when an unplanned delivery occurred within a few days after chemotherapy administration (leukopenia and pancytopenia in two babies born ten weeks after administration of a multiple agents regimen for acute lymphatic leukemia; neutropenia in one child born just 19 days after treatment with docetaxel and anemia requiring transfusion in one child exposed to cyclophosphamide, doxorubicin, vincristine and prednisone five days before spontaneous preterm delivery).[12,154] However, anemia was reported by Chang et al. as the most common side effect of treatment of acute myeloid leukemia during pregnancy and Fischer et al. described a case of pancytopenia (treated with substitution of packed red cells, platelets and erythropoietin) in a child whose mother suffered from the same malignancy.[159,163]

5.3 Long-term outcomes of the child

Prenatal exposure to cancer treatment, especially chemotherapy, can have long-term effects on general health, cardiac function, auditory function, dental health, neurocognitive development, school performance, and behavior of the child. These topics will be addressed in the next subsections.

5.3.1 General health

Several studies have documented general health status of children born to mothers treated for cancer during pregnancy. Some of them only used parent-report questionnaires,[13,162] while others also performed a clinical examination,[11,150,152,164] and only few included a control group.[14,35] After in utero exposure to chemotherapy and/or radiotherapy, no major health problems were reported and the

incidence of medical problems was in general comparable between study and control group or to the general population. However, Murthy et al. reported an increased incidence of allergies and/or eczema (18/50, 36%) in the study group at a median age of 7 years, as compared to 11-22% in the general population.[13]

5.3.2 Cardiotoxicity

Anthracyclines, as being important agents in the treatment of breast cancer and hematological malignancies, are frequently administered during pregnancy. Nonetheless these agents are cardiotoxic, in the acute as well as chronic setting.[17] Acute cardiotoxicity may occur within the first two weeks after treatment, is usually reversible and is characterized by an acute and mild depression of the contractile function. Chronic cardiotoxicity can occur within the first year (early onset) or many years after chemotherapy treatment (late onset) and can lead to ventricular dysfunction, heart failure, cardiomyopathy and death. Anthracyclines are widely used in the treatment of childhood leukemia, with a four-fold increase of cardiovascular death.[165] However, cardiotoxicity seems to manifest itself after longer intervals and has a different pattern of development compared to adults (restrictive versus dilated cardiomyopathy).[18] Adverse cardiac fetal outcomes have been described after exposure to anthracyclines in utero, despite low transplacental passage.[9,11,166] Because of the different properties of the fetal myocardium as compared to the adult myocardium (single nucleus, fewer sarcomeres per mass unit, immature sarcoplasmic reticulum, lower number of mitochondria, underdeveloped anti-oxidant pathways), the fetal heart may be more vulnerable to anthracyclines.[167,168] Aviles et al. reported the first study on the cardiac outcome after prenatal exposure to anthracyclines with normal echocardiographic findings for all children.[169] In the acute phase, there is no significant effect of maternal anthracycline exposure on both the maternal and fetal cardiac functions.[170] In 2012, Amant et al. evaluated the global heart function of 65 children prenatally exposed to chemotherapy and compared the results to controls.[11] Statistically significant small differences in the ejection fraction, fractional shortening, and some of the diastolic parameters (isovolumic relaxation time and mitral A-duration) were noticed, but there were no clinically relevant differences. Comparable results were found in a subgroup analysis on 50 children exposed to anthracyclines compared to healthy controls. These small differences as well as the knowledge that anthracycline-related cardiotoxicity may only become apparent after many years indicate that long-term follow-up is warranted.

5.3.3 Ototoxicity

Studies on children and adults with cancer treated with cisplatin have found an increased incidence of ototoxicity, especially hearing loss.[171,172] Adverse effects on hearing have also been reported after prenatal exposure to cisplatin. Amant et al. reported results of 21 children prenatally exposed to

chemotherapy, aged 5.0 to 17.6 years, who were assessed by means of an audiometry.[11] Eighteen children (85.7%) had normal outcome, including three children exposed to cisplatin in utero. One child, who was exposed to cisplatin during pregnancy, was diagnosed with hearing loss in the high regions at the age of 6 years. However, computed tomography showed a perforated eardrum, which may be a consequence of multiple middle ear infections. Minor right-side hearing loss in the low regions was found in a twin exposed to idarubicin and cytosine arabinoside in utero, diagnosed at 6 and 9 years of age. Pre-existing neurodevelopmental problems may confound the results in this twin. A single case report of a boy with severe bilateral perceptive hearing loss after prenatal exposure to cisplatin (5 cycles of 70mg/m²), diagnosed shortly after birth, was previously described.[173] These adverse effects described may be a consequence of in utero exposure to chemotherapy. Nevertheless, it is hard to determine the direct effect of chemotherapy on hearing loss at older age, because of the existence of many confounding factors such as ear infections and exposure to loud noise. Given the observation that platin-based therapy may cross the placenta in substantial amounts (up to 57% for carboplatin)[10] and the anecdotal hearing loss, cisplatin should only be administered after careful consideration. In many cases, carboplatin can replace cisplatin with the same oncologic efficacy, though with less toxicity and no neurotoxicity.[8]

5.3.4 Dental problems

Survivors of childhood cancer treated with chemotherapy may experience damage to the developing teeth and are more prone to dental caries.[174] Since primary teeth start to develop around 11 to 14 weeks of gestation and tooth formation is completed postnatally, dental problems may be a possible adverse effect of second and/or third trimester exposure to chemotherapy. One study reported sound teeth in two children at the age of 18 months and 3 years after exposure to adriamycin and cytoxan in the third trimester of pregnancy.[175] However, dental examinations have not yet been included in large cohort studies.

5.3.5 Neurocognitive development and school performance

When chemotherapy is administered during pregnancy, there might be a long-term impact on neurocognitive functioning, as the development of the central nervous system starts around the fifth week of pregnancy and continues throughout pregnancy. Aviles and Neri were the first to report on the neurocognitive outcome of 84 children aged 6 to 29 years born to mothers treated with chemotherapy during pregnancy for hematological malignancies.[152] Neurological and psychological evaluations were performed by a physician and schools were asked to provide information on educational performance. No abnormalities in learning were observed, children exhibited a normal educational performance and neurological examinations were normal. However, the methodology of

this study is not well specified and no intelligence or other neuropsychological tests were performed. In 2012, the same group reported on the outcome of 54 children and adults, aged 3.8 to 32.0 years, exposed to chemotherapy in the first trimester of pregnancy.[150] Verbal, Performance and Full Scale Intelligence were within the normal range as compared to a group of control children. Also, educational performance was normal, taking social and economic factors into account. A study by Hahn et al. reported on the outcome of 40 children, assessed between 2 months and 13 years, who were in utero exposed to fluorouracil-adriamycin-cyclophosphamide (FAC) chemotherapy for maternal breast cancer.[162] Parent or guardian surveys were sent out. Two out of 18 children at school-age required special attention in school: one for ADHD and one for Down's syndrome. All other children were thought to develop normally. In 2012, Amant et al. published the first prospective multicenter evaluation of 70 children, aged 1.5 to 18 years (median 22 months), in utero exposed to chemotherapy.[11] Mental development, intelligence, attention and memory tests were performed at predefined ages and compared to the norms of the respective tests. The results of all tests were considered normal. However, both children of a twin pregnancy were found to have a severe cognitive delay. Moreover, prematurity was related to a worse cognitive outcome. Another study was recently published by Cardonick et al., comparing cognitive outcome and school performance of 35 chemotherapy-exposed children to 22 non-exposed children born to mothers diagnosed with cancer during pregnancy.[14] Mental development, intelligence, and school performance were assessed between 1.5 and 10.4 years and were mostly within the normal range. However, a score below the normal range was found for three children (one chemotherapy-exposed and two non-exposed children). The number of abnormal results was not significantly different between the study and control group. Also, school performances were comparable between the two groups (normal results for chemotherapy-exposed versus non-exposed children: 75% versus 67% for mathematics and 75% versus 83% for reading). As the median follow-up duration in most studies that have been published up to now is restricted to infancy, toddlerhood or early childhood and given the knowledge that neurocognitive problems may become more apparent at school-age, long-term follow-up studies including detailed assessment of neurocognitive functions such as intelligence, attention, memory and executive functions are highly needed.

5.3.6 Behavior problems

Amant et al. reported on the behavioral outcome of 21 children aged 5.0 to 15.9 years and exposed to chemotherapy in utero, assessed by means of the Child Behavior Checklist (CBCL), a questionnaire on behavior problems to be filled out by the parents.[176] Twenty-nine percent of the children had an increased score for internalizing problems (e.g., symptoms of depression, anxiety, withdrawn behavior), externalizing problems (e.g., rule-breaking, delinquent or aggressive behavior) or the total

problems scale (a combination of internalizing and externalizing problems together with social problems and thought problems). Cardonick et al. compared parent-reported behavior problems, assessed by means of the CBCL, between 35 chemotherapy-exposed children and 22 non-exposed controls, aged 1.5 to 10.4 years, all born to women who were diagnosed with cancer while pregnant.[14] There were no significant between-group differences for internalizing, externalizing or total problem behavior. However, 23% (8/35) of the chemotherapy-exposed group and 18% (4/22) of the non-exposed controls demonstrated behavior problems in the borderline or clinical range. The incidence of internalizing behavior problems was significantly higher in older than in younger children. Behavior problems were not significantly affected by maternal survival, mother's health status at the time of evaluation, child sex or age.

6. RESEARCH QUESTIONS AND HYPOTHESES

In the previous sections, we reviewed the literature with regard to the outcome of children prenatally exposed to maternal cancer and its treatment. Data on the long-term outcome of these children are scarce. Although previous studies found in general reassuring outcomes, most of these studies did not investigate cognitive development in depth (by using a comprehensive neuropsychological test battery), pooled data of children examined in a wide age range and did not compare the results to those of a control group of children. Therefore, we formulated the following exploratory research questions and hypotheses for part 1 of this PhD project.

6.1 Research questions according to the timing of follow-up and developmental domains

Research question 1:

What is the impact of prenatal exposure to cancer and its treatment (especially chemotherapy) on the cognitive development in **infancy and early toddlerhood (1.5 and 3 years) (Chapter 3)**?

Research question 2:

What is the impact of prenatal exposure to cancer and its treatment (especially chemotherapy) on the cognitive development and behavior in **early childhood (6 years) (Chapter 4)**?

Primary outcome: What is the impact on Full Scale Intelligence?

Secondary outcomes:

a. What is the impact on Verbal and Performance Intelligence and Processing Speed?
b. What is the impact on verbal and non-verbal memory?

c. What is the impact on alertness, selective attention, divided attention and response inhibition?
d. What is the impact on the incidence of behavior problems?

Research question 3:

What is the impact of prenatal exposure to cancer and its treatment (especially chemotherapy) on the cognitive development and behavior in **middle childhood (9 years) (Chapter 5)**?

Primary outcome: What is the impact on Full Scale Intelligence?

Secondary outcomes:

a. What is the impact on Verbal and Performance Intelligence and Processing Speed?
b. What is the impact on verbal and non-verbal memory?
c. What is the impact on alertness, sustained attention, selective attention, divided attention, attentional control and response inhibition?
d. What is the impact on the incidence of behavior problems?
e. Are the results found at 6 years confirmed or rejected in the cohort of 9-year-old children?

Hypotheses:

Data on the long-term outcome of children prenatally exposed to maternal cancer and its treatment are scarce. Therefore, the studies in this PhD project can be considered as exploratory studies.

A cancer diagnosis during pregnancy can be considered as a stressful life-event for pregnant women. Prenatal exposure to maternal stress has been related to cognitive and behavior problems in the children.[99-104] Therefore, we expect that a cancer diagnosis during pregnancy may have short- and/or long-term effects on the cognitive and behavioral development of the children.

Cancer during pregnancy is not only associated with maternal stress, but is in many cases also supplemented with diagnostic imaging, surgery (including anesthesia), supportive drugs, chemotherapy and/or radiotherapy. Studies in children and adults with cancer have found that chemotherapy and/or radiotherapy may have transient or long-term effects on the cognitive outcome.[128-136] In our study population, the placenta acts as a protective barrier to shield the fetus (in part) from noxious substances.[9,10] The first publications on the outcome of children prenatally exposed to chemotherapy document cognitive outcomes within the normal range.[11,152,162] According to these publications and the fact that the placenta may act as a protective barrier, the effects of prenatal exposure to chemotherapy, if any, are expected to be small. In the studies of this PhD project, the cognitive outcome will be investigated in depth by using a comprehensive neuropsychological

assessment and comparing the results to those of a control group, which enables to reveal more subtle cognitive sequelae, if any.

6.2 Research questions to investigate throughout all age cohorts

Research question 4:

Is the type of chemotherapy (anthracyclines, taxanes, platin-based treatment) related to the cognitive outcome?

Hypothesis:

Previous research has shown that the transplacental passage of chemotherapy varies according to the type of chemotherapeutic agent. As the transplacental passage of platin-based treatments (up to 57% for carboplatin)[10] is much higher than the transplacental passage of anthracyclines (4% for epirubicin and 8% for doxorubicin)[9] and taxanes (1% for paclitaxel and not detectable for docetaxel)[10], we hypothesize to find differential effects on cognitive development according to treatment type, with larger effects on cognitive development in children exposed to platin-based treatments and smaller effects in children exposed to anthracyclines and taxanes.

Research question 5:

Is the number of chemotherapy cycles during pregnancy related to the cognitive outcome?

Hypothesis:

Comparable to the use of some other mediations in pregnancy (e.g., valproate for the treatment of epilepsy),[177] the effects of chemotherapy on the cognitive outcome may be dose-dependent. Due to the heterogeneity and combinations of chemotherapeutic schemes used in the treatment of cancer during pregnancy, it is difficult to examine the relationship between the dose of a specific chemotherapeutic agent and the cognitive outcome. Hence, we hypothesize to find a linear relationship between the number of chemotherapy cycles administered during pregnancy and the cognitive outcome.

Research question 6:

Is the estimated fetal dose of radiation related to the cognitive outcome?

Hypothesis:

Data on the outcome of children prenatally exposed to radiotherapy are scarce. However, studies on atomic bomb survivors have suggested a linear relationship between the dose of prenatal radiation exposure and the cognitive outcome (especially IQ).[137] Therefore, we hypothesize that the effects of prenatal exposure to radiotherapy on cognition are dose-dependent and expect to find a linear relationship between the estimated fetal dose of radiation and the cognitive outcome. Possibly, an interaction between the dose and timing of exposure may be present, as the most sensitive period of radiation exposure to the developing brain is between 8 and 15 weeks of gestation.

Research question 7:

Is prematurity related to the cognitive outcome?

Hypothesis:

The incidence of preterm birth is high in our study population. Previous studies already highlighted the possible long-term impact of prematurity on cognitive development, with an increased risk of developmental delay with decreasing gestational age.[178-180] Hence, we hypothesize the existence of a linear relationship between gestational age at birth and cognitive outcomes, as found in our pilot study.[11]

Chapter 3

Effects of maternal cancer diagnosis and treatment during pregnancy on cognitive development in infancy and early toddlerhood (1.5 and 3 years)

An extended version of this manuscript has been published:

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ABSTRACT

Background

Data on the long-term outcome of children who are exposed to maternal cancer with or without treatment during pregnancy are lacking.

Methods

In this multicenter cohort study, we compared children whose mothers received a diagnosis of cancer during pregnancy with matched children of women without a cancer diagnosis. All children were prospectively assessed by means of the Bayley Scales of Infant Development (second or third edition) at 18 months, 36 months, or both.

Results

A total of 129 children (median age, 22 months; range, 12 to 42) were included in the group whose mother had cancer (prenatal-exposure group) with a matching number in the control group. During pregnancy, 96 children (74.4%) were exposed to chemotherapy (alone or in combination with other treatments), 11 (8.5%) to radiotherapy (alone or in combination), 13 (10.1%) to surgery alone, 2 (1.6%) to other drug treatments, and 14 (10.9%) to no treatment. Birth weight was below the 10^{th} percentile in 28 of 127 children (22.0%) in the prenatal-exposure group and in 19 of 125 children (15.2%) in the control group (P=0.16). There was no significant between-group difference in cognitive development on the basis of the Bayley score (P=0.08) or in subgroup analyses according to treatment type. The gestational age at birth was correlated with the cognitive outcome in the prenatal-exposure and control group.

Conclusions

Prenatal exposure to maternal cancer with or without treatment did not impair the cognitive development of children in infancy and early toddlerhood. Prematurity was correlated with a worse cognitive outcome, but this effect was independent of cancer treatment.

The study is registered as ClinicalTrials.gov, NCT00330447.

INTRODUCTION

Fetal development is a complex process. At different stages of development, different aspects can be influenced by external factors (e.g., teratogenic drugs, alcohol, smoking, maternal stress, and altered nutrition). Among women in whom cancer is diagnosed during pregnancy, factors such as maternal illness, diagnostic tests, cancer treatment, and increased levels of maternal stress can negatively influence fetal development. Cancer treatment during pregnancy exposes the fetus to potentially toxic substances that influence cell division. Chemotherapeutic drugs can cross the placenta in varying amounts.[9,10] Data on fetal effects of maternal cancer treatment are based mainly on retrospective cohort studies.[13,152,162,169] From our 10-year experience, it appears that the limited availability of safety data can influence therapeutic decision making, which results in a high threshold for initiating chemotherapy and a low threshold for terminating pregnancy. It can also delay maternal treatment and result in preterm induction of labor. Limited data are also available on prenatal exposure to radiotherapy.[181]

Our group published combined prospective and retrospective data from a multicenter study involving children who had prenatal exposure to chemotherapy. Our initial data seemed to suggest that fetal exposure to maternal cancer treatment was not associated with cognitive or cardiac abnormalities.[11] The combined retrospective and prospective design limited the interpretation of the results, since the findings from different tests at different ages (16.8 months to 17.6 years of age) were pooled. Therefore, we enlarged the prospective cohort to include only those in infancy and early toddlerhood (12 to 42 months) and evaluated the general health status, growth, cognitive development, and cardiac structure and function and compared the results with those for children in a matched control group. Here we highlight the cognitive development.

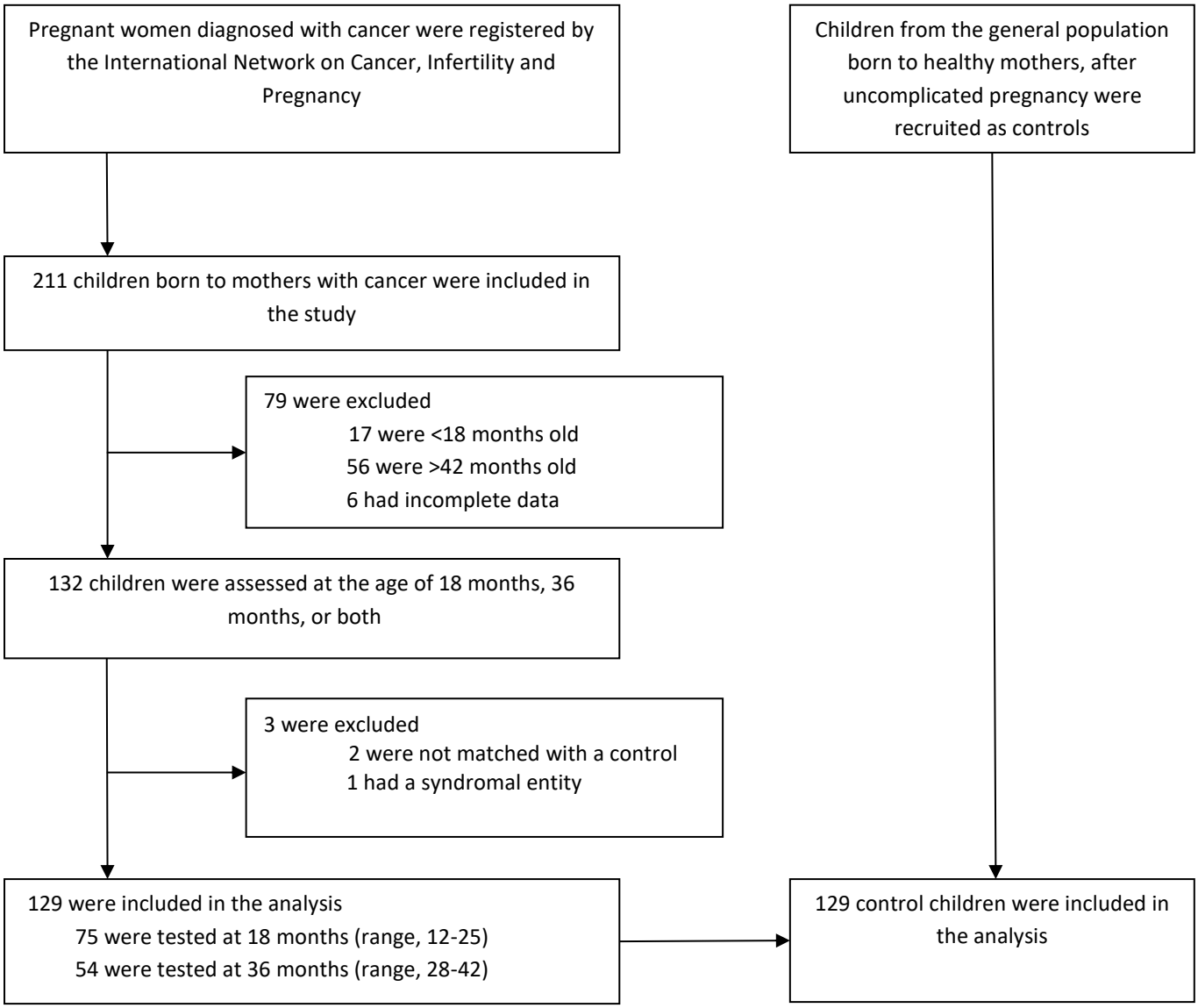
METHODS

Study participants

This study is based on a collaboration between national referral centers in Belgium, the Netherlands, Italy, and the Czech Republic, all members of the International Network on Cancer, Infertility, and Pregnancy. Children in the prenatal-exposure group had mothers in whom cancer was diagnosed during pregnancy with or without treatment during pregnancy. Controls were children born to healthy mothers after uncomplicated pregnancies. The study design and recruitment are summarized in Figure 1. The study protocol is available with the full text of the article at NEJM.org. For the cognitive developmental examinations, control children were recruited in Belgium (for Belgium and the Netherlands), Italy, and the Czech Republic and were matched in a 1:1 ratio with respect to gestational

age and age at testing with the children in the prenatal-exposure group in that particular country. Details regarding recruitment are provided in the Methods section in the Supplementary Appendix. Ethical approval was obtained by each center. Written parental informed consent was provided for each child.

Figure 1. Study design and recruitment



Note: The 129 children in the prenatal-exposure group who were evaluated in the final analysis included 98 children who underwent new testing by means of the Bayley Scales of Infant Development and 31 children for whom results were published previously.

Study testing

We collected obstetric, perinatal (including congenital malformations), and oncologic data for each mother-child pair. We calculated birth weight percentiles, considering the gestational age at birth, sex, race or ethnic group, parity, and maternal height and weight when available. The fetal radiation dose was calculated according to the dose program Peridose developed by van der Giessen.[182] From 2005 through 2011, we invited the children in the fetal-exposure group and the control group to participate in follow-up at the age of 18 months. From 2012 through 2015, children in the two groups were invited to participate at both 18 months and 36 months. For children who were tested at both 18 months and 36 months, we included only one test result (the one for which a matched control was available) in the analysis.

We assessed the cognitive development of the children in the two groups using the Bayley Scales of Infant Development.[183,184] Standard scores on this test range from 50 to 150, with higher scores indicating more advanced development; the mean (± SD) score is 100 ± 15, and a score of less than 85 indicates a developmental delay. The third edition (cognitive scale) was used in Italy, whereas the second edition (mental scale) was used in Belgium, the Netherlands, and the Czech Republic, according to the availability of the most recent edition at the start of inclusion. Bayley III cognitive scores were found to be significantly higher than Bayley II mental developmental index scores among both children who were born at term and those who were born preterm.[185] We handled this finding in our study by means of a 1:1 matched comparison of the prenatal-exposure group and the control group as assessed in the same country with the same Bayley edition and by calculating correlations and regression models only on Bayley II scores.

Statistical analysis

We used descriptive statistics to describe maternal oncologic data. We compared between-group background variables (child and maternal age, gestational age, sex, birth weight, race or ethnic background, maternal height and weight, parity, and parental education levels) using the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical data, depending on distribution characteristics, sample size, and number of categories.

Raw cognitive scores were converted to standardized cognitive scores (not corrected for prematurity) according to normative data for each country in the Bayley manual. Univariate and multivariate linear regression models were used to look at the relationship between gestational age and cognitive outcome. Pearson correlations were used to investigate the relationship between cognitive outcome and parental education levels or the number of chemotherapy cycles. The relationship between

cognitive outcome and the estimated fetal dose of radiation was investigated by means of Spearman's rank-correlation coefficient (rho). We used the Wilcoxon signed-rank test to compare cognitive scores and analysis of variance to adjust for covariates.

A two-sided P value of less than 0.05 was considered to indicate statistical significance for all analyses.

RESULTS

Treatment characteristics

A total of 129 children (including four pairs of twins) were included in the prenatal-exposure group: 103 from Belgium, 8 from the Netherlands, 10 from Italy, and 8 from the Czech Republic. These children were matched with 129 control children: 111 from Belgium, 10 from Italy, and 8 from the Czech Republic. Children in the two groups were examined at a median age of 22 months (range, 12 to 42 months; P=0.15) and were equally distributed according to sex (P=0.32) (Table 1). Of the 129 children, data were included for 75 children and matching controls who were tested at the age of 18 months and for 54 children and matching controls who were tested at the age of 36 months; a total of 48 children were tested at both time points.

At the time of cancer diagnosis, the median maternal age was 33.4 years (range, 19.6 to 43.5), and the median gestational age was 17.7 weeks (range 1.0 to 37.5). During pregnancy, 96 children (74.4%) were exposed to chemotherapy (alone or in combination with other treatments), 11 (8.5%) to radiotherapy (alone or in combination), 13 (10.1%) to surgery alone, 2 (1.6%) to other drug treatments, and 14 (10.9%) to no treatment (Table 2). A total of 391 cycles of chemotherapy were administered to 93 women (including 3 carrying twins). Additional details regarding the maternal cancer type and specific treatments are provided in Tables S1 to S4 in the Supplementary Appendix.

Perinatal characteristics

Children in the prenatal-exposure group were born at a median gestational age of 36 weeks (range, 27 to 41). A total of 79 children (61.2%) were born preterm, as compared with a general percentage of preterm births of 6.8 to 8.0% in the participating countries.[186] (Gestational age was not specified for the control group, since children in the prenatal-exposure group were matched with controls according to gestational age at birth.) Eleven children were born between 27.0 and 31.9 weeks (very preterm), 16 between 32.0 and 33.9 weeks (moderately preterm), 52 between 34.0 and 36.9 weeks (late preterm), and 50 at 37 weeks or later (full term). The number and type of congenital malformations were similar to those in the general population and the results of the neonatal neurologic examinations

Table 1. Demographic characteristics of the children

Characteristic	**Prenatal-Exposure group (N=129)**		**Control group (N=129)**		**P value**
Median age (range) - months	22 (12-42)		22 (12-42)		0.15
Median gestational age (range) - weeks	36 (27-41)		36 (27-41)		1.00
Median birth weight (range) - g	2705 (720-4690)		2755 (1100-4905)		0.50
Median maternal age at birth of this child (range) **-** years	33.4 (19.6-43.5)		31.0 (20.6-40.2)		0.001
Sex – number (%)					0.32
Male	60 (46.5%)		68 (52.7%)		
Female	69 (53.5%)		61 (47.3%)		
Race – number (%)*					0.12
White	108 (85.7%)		106 (91.4%)		
Black	11 (8.7%)		3 (2.6%)		
Other	7 (5.4%)		7 (6.0%)		
Unknown	3		13		
Highest level of education of parents – number (%)†	Mother	Father	Mother	Father	Mother: <0.001
No education	0	1 (0.8%)	0	0	
Primary school	3 (2.4%)	3 (2.5%)	0	0	Father:
Secondary school	50 (40.7%)	52 (42.6%)	18 (17.0%)	29 (27.6%)	0.02
Bachelor	29 (23.6%)	30 (24.6%)	29 (27.4%)	25 (23.8%)	
Master's degree or higher	41 (33.3%)	36 (29.5%)	59 (55.7%)	51 (48.6%)	
Unknown	6	7	23	24	

Note: *Race was self-reported by the parents.

†The highest level of education is presented according to the European educational system. A bachelor's degree is earned at both traditional universities and nonuniversity institutions of higher education and requires between three and four years of full-time study. A master's degree is earned at university and requires one to two years of full-time study after a bachelor's degree.

were normal. Among 127 children for whom data on birth weight were available, the median birth weight was 2705g (range, 720 to 4690). A birth weight below the 10th percentile (i.e., the definition of small for gestational age) was reported in 28 of 127 children in the prenatal-exposure group and in 19 of 125 children in the control group (22.0% and 15.2%, respectively; P=0.16). More specifically, status as small for gestational age was reported in 24 of 95 children (25.0%) who were exposed to chemotherapy and for whom data were available and in 4 of 11 children (36%) who were exposed to radiotherapy (Table 2).

Table 2. Cancer treatment during pregnancy for all children and those categorized as small for gestational age

Cancer treatment	**All children (N=129)** Number (%)	**Small for gestational age (N=28)*** Number (% of children with treatment)
Surgery	13 (10.1)†	2 (15.4)
Chemotherapy	41 (31.8)	11 (27.5)
Radiotherapy	1 (0.8)	0
Surgery and chemotherapy	48 (37.2)†	10 (20.8)
Surgery and radiotherapy	3 (2.3)	1 (33.3)
Chemotherapy and radiotherapy	3 (2.3)†	2 (66.7)
Surgery, chemotherapy, and radiotherapy	4 (3.1)	1 (25.0)
Trastuzumab	1 (0.8)	0
Interferon-β	1 (0.8)	1 (100.0)
No treatment	14 (10.9)	0

Note: *Data regarding birth weight were available for 127 children in the prenatal-exposure group; no data were available for 1 child in the chemotherapy subgroup and for 1 child in the no-treatment subgroup. Shown are the percentages of children who were small for their gestational age as compared with all children who were exposed to each cancer treatment. †One pair of twins was exposed to surgery alone, two pairs of twins to surgery and chemotherapy, and one pair of twins to chemotherapy and radiotherapy.

Demographic characteristics

We compared the children in the two groups for several background variables with respect to cognitive development (Table 1). There were no significant between-group differences in gestational age, test

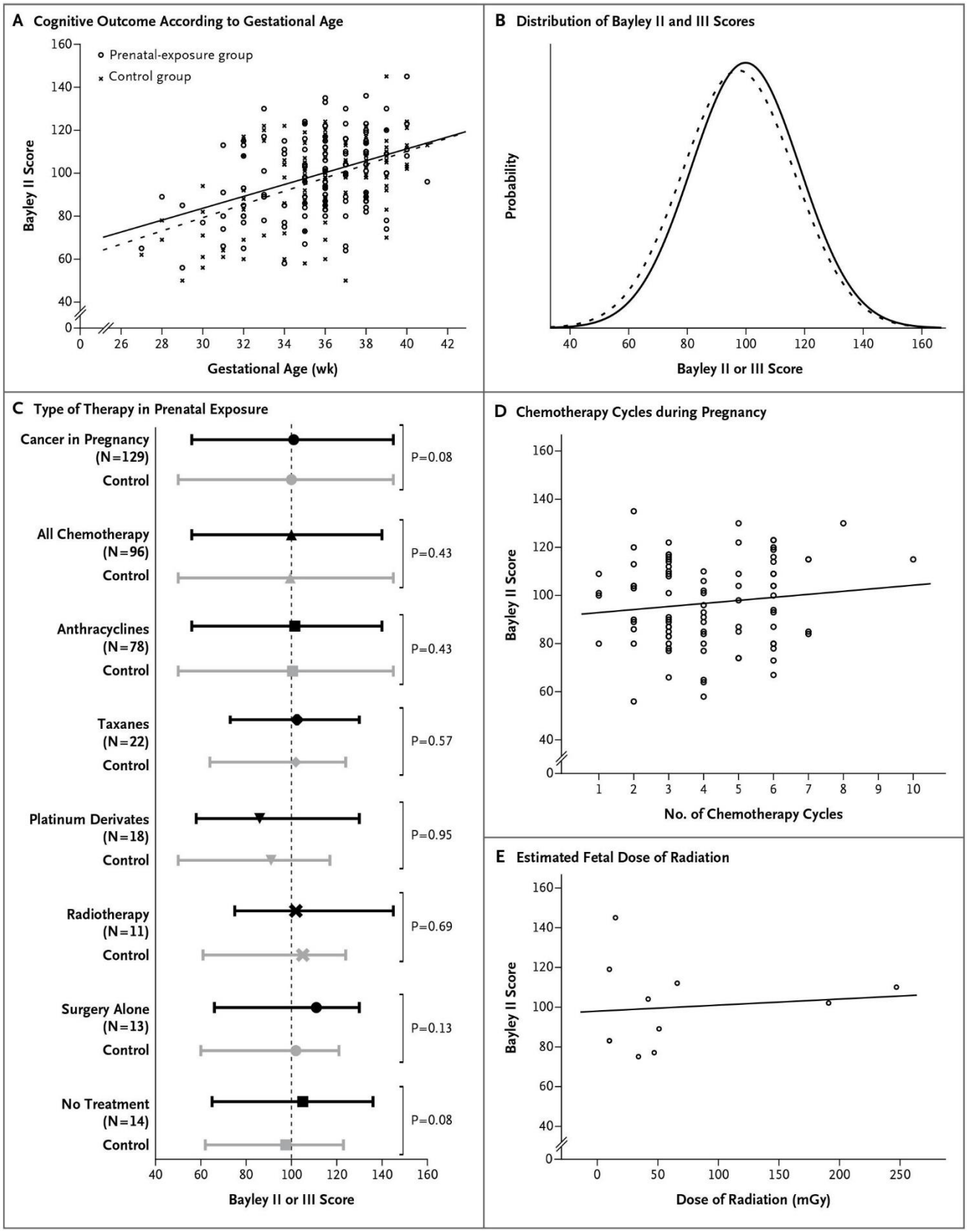
age, sex, or race. A significant difference was found for parent's level of education, since the parents of children in the control group were on average more highly educated than those of children in the prenatal-exposure group (P<0.001 for mothers and P=0.02 for fathers or female coparents). Maternal and paternal education levels were related to the cognitive outcome on the Bayley II (r=0.30, P=0.001 for mothers and r=0.21, P=0.03 for fathers) in the prenatal-exposure group but not in the control group (r=0.02, P=0.84 and r=0.01, P=0.93 respectively). In further analyses, parental education levels were included as a covariate.

Cognitive development

Sex differences in cognitive outcome were found on the Bayley II and III scales. A total of 130 girls for whom data were available had a median score of 104 (range, 58 to 145), which was significantly higher than that for 128 boys (median score, 97.5; range, 50 to 145; P=0.001), even after adjustment for study group. Gestational age was related to the cognitive score in the two groups (Figure 2A). A univariate linear regression model showed that for all 238 children who were assessed by means of the Bayley II scale, the average cognitive score tended to increase by 2.9 points for each additional week in gestational age at birth (95% confidence interval [CI], 2.2 to 3.7; P<0.001), as calculated from an increase of 2.8 points (95% CI, 1.6 to 3.9) in the prenatal-exposure group and of 3.1 points (95% CI, 2.0 to 4.1) in the control group (P<0.001 for both comparisons). In a regression model with gestational age, group, and the interaction between gestational age and group as predictors of cognitive outcome, the interaction term was not significant (P=0.68) (P=0.05 for gestational age and P=0.62 for group). After adjustment for sex, test age, country, parental education level, and race, there was an average increase of 2.2 points (95% CI, 1.5 to 3.0; P<0.001) for each additional week of gestational age. However, sex and gestational age were not included as covariates in later analyses because they were equally distributed in the two groups.

Most of the children in the two groups had normal cognitive development (Figure 2B), with no significant between-group differences (P=0.08). Cognitive outcome was not significantly different between children who were exposed to chemotherapy and children in the control group (P=0.43) (Figure 2C and Supplementary Appendix Table S5). Even after adjustment for parental education levels, the between-group difference was not significant (P=0.52). As compared with matched controls in subanalyses, there were no significant differences in cognitive outcome for children who were exposed to radiotherapy, surgery alone, or no treatment during pregnancy and no differences according to the type of chemotherapy (anthracyclines, taxanes, and platinum derivates) (Figure 2C). Cognitive outcome on the Bayley II scale was not related to the number of chemotherapy cycles that were

Figure 2. Cognitive outcome



Note: **Panel A** shows the scores for the cognitive outcome on the Bayley Scales of Infant Development, second edition (Bayley II), according to gestational age at birth for 119 children in the prenatal-exposure group and a matching number of children in the control group. (A total of 10 children with Bayley III scores are not included

in this analysis, since pooling of the data that were scored with the two versions was inappropriate because of differences in scoring method.) Standard scores on the Bayley II range from 50 to 150, with higher scores indicating more advanced development; the mean (± SD) score is 100 ± 15, and a score of less than 85 indicates a developmental delay. Mean values (as calculated by linear regression) are indicated by a solid line for the prenatal-exposure group and a dashed line for the control group. **Panel B** shows the distribution of the results of the last performed Bayley Scales (II or III) for 129 children in the prenatal-exposure group and a matching number of children in the control group. Scores in the prenatal-exposure group are represented by a solid line, and scores in the control group by a dashed line. By definition, the area under the curve of a probability density function sums to 1. **Panel C** shows cognitive outcome (as reported as the median Bayley II or III score) for subgroups of children according to the cancer treatment received by their mothers. The horizontal bars indicate the simple range of scores. Each child in the prenatal-exposure group is matched with a child in the control group according to gestational age at birth and test age. Some children had prenatal exposure to a combination of treatment options (e.g., taxanes plus platinum derivates) and therefore are included in more than one group. **Panel D** shows Bayley II scores for 87 children in the prenatal-exposure group in relation to the number of chemotherapy cycles administered during pregnancy. **Panel E** shows Bayley II scores for 11 children in relation to the estimated fetal dose of radiation exposure (expressed in milligrays) during pregnancy. Two children (twins) had the same score, which appears as one data point.

administered during pregnancy (r=0.13, P=0.24) (Figure 2D) or to the estimated fetal dose of radiation (r=0.11, P=0.75) (Figure 2E). The inclusion of the single case with a syndromal entity in the analysis instead of another child in the prenatal-exposure group with the same gestational age, test age, sex, country, and maternal disease did not change the results with respect to cognitive development (data not shown).

DISCUSSION

In this multicenter, prospective cohort study involving 129 children and their matched controls, we documented the effects of prenatal exposure to maternal cancer and cancer treatment on general health, prenatal and postnatal growth, cognitive development, and cardiac structure and function. Although the incidence of preterm delivery in the prenatal-exposure group was high (61.2%), the cognitive development of these children at a median age of 22 months was normal for their gestational age at birth. In subgroup analyses, the cognitive development of 96 children who were exposed to chemotherapy and of the 11 children who were exposed to radiotherapy did not differ significantly from that of children in the control group.

Cognitive outcomes were similar in the prenatal-exposure group and the control group, a finding that is consistent with the results of previous studies.[11,14,152,162] Cognitive outcomes seemed to have no correlation with the number of chemotherapy cycles. Also, the negative prognostic effect of prematurity on cognitive development was confirmed, and the effect was similar in the two groups.

Children who were small for their gestational age were more frequently born to mothers with cancer during pregnancy than were children in the control group (22.0% vs. 15.2%); however, the difference was not significant. Earlier studies have highlighted the finding that the proportion of children who are small for their gestational age is increased in pregnancies complicated by maternal cancer.[12] Such children are at increased risk for perinatal complications and death.[187] Among these children, factors associated with a small size at birth include a compromised placental supply of nutrients and oxygen to the fetus (in 80 to 90% of all cases), altered metabolic adaptations of pregnancy, and chronic inflammation.[120,188-190] It has been hypothesized that several of these factors are present in a pregnancy complicated by cancer.

The reassuring outcome may be explained by the timing of chemotherapy administration and the role of the placenta. All cycles of chemotherapy in this series were administered after the first trimester of pregnancy. The period before a gestational age of 10 weeks is the most vulnerable, since organogenesis is occurring during this period. Administration of chemotherapy after the first trimester does not result in an increased rate or additional types of congenital malformations.[12,14,33] Both the placental brush border and the basolateral membrane contain active drug transporters that influence fetal drug exposure. Apart from the drug-transporter affinity, transplacental passage depends on lipid solubility, molecular weight, binding capacity to plasma proteins, and placental metabolism of the agents. These regulatory mechanisms result in fetal plasma levels that are lower in the fetus than in the mother, although variation in transplacental passage ranges from 0% for taxanes to 57% for carboplatin.[9,10,191,192]

Our study has some limitations. Our results cannot be extrapolated to all chemotherapeutic drugs, especially new targeted drugs. In addition, the follow-up period was too short to document long-term neurocognitive problems that may become more apparent later in life.

In conclusion, children who had prenatal exposure to cancer and the associated stress, imaging studies, and treatments had normal development during testing at 18 months, 36 months, or both. In particular, chemotherapy had no clear adverse effects on cognitive development. Our data suggest that the diagnosis of cancer during pregnancy is not necessarily an indication to terminate the pregnancy. Although caution is always indicated, treatment of the maternal cancer in the second trimester or later may not be harmful to the fetus. Pregnant women may be informed that the

likelihood of prematurity is higher than that in the general population, but among preterm babies, the child is unlikely to have unique problems more serious than those of preterm babies born of women without cancer during pregnancy.

SUPPLEMENTARY APPENDIX

1. Methods

1.1 Recruitment of study and control children

All women diagnosed with cancer during pregnancy and referred to one of the participating centers in Belgium (University Hospitals Leuven), The Netherlands (VU University Medical Center and Academic Medical Center Amsterdam, University Medical Center Utrecht, Erasmus Medical Center Rotterdam, University Medical Center Groningen and Radboud University Medical Center Nijmegen), the Czech Republic (Faculty Hospital Motol, Charles University Prague) and Italy (Istituto Europeo di Oncologia Milan) were prospectively or retrospectively invited to take part in the study. Children who were not able to perform the age-specific cognitive tests due to severe intellectual disability were excluded. Parents signed the informed consent at the moment of inclusion. Denial of participation or drop-out were mainly due to the distance to the hospital, difficulties to reach the patient after moving out or death of the mother and fear of overload for the child due to the supplementary examinations. Participants were offered to be assessed by means of the Bayley test at home if the distance to the hospital was the main reason for drop-out.

Control children were recruited in Belgium, the Czech Republic and Italy. Preterm born children were recruited through the screening of birth lists from the participating hospitals. Children born full term were recruited by distributing information letters in nurseries and by advertising on the webpage of the hospital. All parents who were willing to let their child participate in the study first filled out a questionnaire on general health and prenatal history, in order to check if they met the inclusion criteria. Exclusion was based on all pregnancy-related (e.g., hypertension, preeclampsia, gestational diabetes with medical treatment, liver problems, epilepsy …) or neonatal problems (e.g., admission to a neonatal ward because of infections, long-term need of oxygen, malformations, brain lesions …) that may impact on development. Immediate postnatal oxygen administration (CPAP) was not considered an exclusion criterion. Parents whose child met all the inclusion criteria signed the informed consent consecutively. Reasons for denial of participation or drop-out were the same as for the study children.

2. Results

2.1 Maternal tumor types treated during pregnancy (125 mothers, 129 children) and the incidence of small for gestational age (SGA) children (Table S1)

Maternal malignancy	N mothers	% mothers	N SGA*	% SGA
Breast cancer	69 (2 twin pregnancies)	55.2	9	12.7
Hematological Malignancy	20	16.0	8	40.0
- Acute Lymphoid Leukemia	1	0.8	1	100.0
- Acute Myeloid Leukemia	4	3.2	1	25.0
- Chronic Myeloid Leukemia	1	0.8	1	100.0
- Hodgkin's Disease	8	6.4	3	37.5
- Non-Hodgkin's Disease	6	4.8	2	33.3
Cervical cancer	10 (1 twin pregnancy)	8.0	2	18.2
Ovarian cancer	9	7.2	2	22.2
Brain tumor	3	2.4	1	33.3
Colon cancer	3	2.4	1	33.3
Gastric cancer	2	1.6	1	50.0
Renal cell cancer	1	0.8	0	0.0
Tongue cancer	2 (1 twin pregnancy)	1.6	3	100.0
Lung cancer	1	0.8	0	0.0
Thyroid cancer	2	1.6	1	50.0
Melanoma	1	0.8	0	0.0
Ewing sarcoma	1	0.8	0	0.0
Soft tissue sarcoma	1	0.8	0	0.0
TOTAL	125	100.0	28	22.0

*Birth weight was available for 127 of 129 children.

2.2 Chemotherapy regimens applied during pregnancy in 93 women (including 3 twin pregnancies) (Table S2)

Chemotherapy scheme	N cycles	N patients	% patients	N SGA***	% SGA***	GA (median (range))
(F)AC/(F)E(C)†**	195	58	53.7	8	13.8	32.0 (18.5-34.8)
ABVD†	41	7	6.5	2	28.6	27.8 (22.7-33.0)
(R) - CHOP†	34	7	6.5	3	42.9	27.7 (22.6-34.1)
Cisplatin (± Epirubicin)†	27	6	5.6	2	33.3	22.7 (17.3-28.3)
Carboplatin (± 5-Fluorouracil)**	3	1	0.9	2**	100.0	17.7 (14.7-20.7)
Paclitaxel-Cis/Carboplatin**	36	9	8.3	4	44.4	24.9 (20.0-33.5)
Paclitaxel/Docetaxel	38	14	13.0	3	21.4	31.0 (24.9-34.9)
Hovon 37†	2	1	0.9	1	100.0	23.7 (21.0-26.3)
Temozolomide	5	1	0.9	0	0.0	26.0 (18.0-33.9)
Idarubicin-AraC†	4	1	0.9	1	100.0	22.0 (15.0-29.0)
Daunorubicin-AraC†	2	1	0.9	0	0.0	22.4 (19.9-24.9)
5-Fluorouracil	3	1	0.9	1	100.0	31.2 (29.1-33.3)
VIM (without MTX)	1	1	0.9	0	0.0	29.1
TOTAL	391	108*	100	24††	25.3	26.6 (20.5-32.5)

Abbreviations: SGA, small for gestational age; GA, gestational age; (F)AC, 5-fluorouracil, doxorubicin, cyclophosphamide; (F)E(C), 5-fluorouracil, epirubicin, cyclophosphamide; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; (R)-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; Hovon 37, cycle 1 prednisolone, vincristine, daunorubicin, L-asparaginase, MTX, and cycle 2 cytarabine, mitoxantrone, intrathecal MTX; AraC, cytarabine; MTX, methotrexate; VIM, ifosfamide, etoposide, MTX

*15 patients received 2 different schemes; † including anthracyclines; ** including 1 twin-pregnancy

††Two SGA children were exposed to both FEC and docetaxel and 1 SGA child to both AC and docetaxel. Therefore they are mentioned double in the table. In total, 24 chemotherapy-exposed children were born SGA.

***Birth weight was available for 95 of 96 chemotherapy-exposed children, 1 unknown in the paclitaxel-carboplatin group.

2.3 Overview of registered dosages received per drug (Table S3)

Anti-cancer agent	N patients	Cumulative dosage *mg/m²: median (range)
Doxorubicin	25	150 (50-350)
Epirubicin	27	300 (100-600)
Daunorubicin	2	142.5 (45-240)
Idarubicin	1	84
Cyclophosphamide	44	1500 (150-3750)
5-FU	30	1500 (150-3000)
Docetaxel	7	300 (16-400)
Paclitaxel	9	560 (175-1050)
Cisplatin	7	450 (60-525)
Carboplatin	4	1600 (1200-2000)
Vincristine	5	6 (3-9.8)
Bleomycine	4	50 (20-80)
Dacarbazine	4	1875 (320-3000)
Vinblastine	4	30 (12-48)
Cytarabine	3	2800 (2100-6000)
Prednisolone	3	200 (120-360)
Rituximab	2	2250 (1875-2625)
L-Asparaginase	1	5000 IU/m²
MTX	1	15
Mitoxantrone	1	10
Temozolomide	1	3750

Abbreviations: 5-FU, 5-fluorouracil; MTX, methotrexate; IU, international units

*Dosages expressed in mg/m² unless otherwise specified.

2.4 Overview of radiation exposure in 10 patients (including 1 twin pregnancy) and the gestational period of exposure (Table S4)

Patient	Cancer type	Radiation Field	GA (w)	Maternal Dose (Gy)	Estimated Fetal Dose (mGy)
1	Breast	thoracic wall	15-21	50	247
2	Tongue	head and neck	17-21	60	10
3	Breast	breast	16-20	65	51
4	Thyroid	head and neck	11-17	46	66
5	NHL	head	28	33	34
6	Brain	head	16-19	54	42
7	AML	left eye	20-22	20	15
8 (twin)	Tongue	head and neck	15-17	60	10
9	Breast	breast	10-15	60	191
10	Breast	mediastinum	13-15	39	47

Abbreviations: GA, gestational age; w, weeks; Gy, Gray; mGy, milliGray; NHL, Non-Hodgkin's disease; AML, acute myeloid leukemia

2.5 Cognitive development of study and control children (Table S5)

Group	N study group	MDI / Cognitive scale study group		MDI / Cognitive scale control group		P value
		Median	Range	Median	Range	
Cancer in pregnancy (= total group)	129	101	56-145	100	50-145	0.08
Chemotherapy	96	100	56-140	99.5	50-145	0.43
Anthracyclines	78	101.5	56-140	100.5	50-145	0.43
Taxanes	22	102.5	73-130	102	64-124	0.57
Platinum derivates	18	86	58-130	91	50-117	0.95
Radiotherapy	11	102	75-145	105	61-124	0.69
Chemotherapy and/or radiotherapy	100	100	56-145	100	50-145	0.42
Surgery alone	13	111	66-130	102	60-121	0.13
No treatment during pregnancy	14	105	65-136	97.5	62-123	0.08

Abbreviations: MDI, Mental Developmental Index

Chapter 4

Effects of maternal cancer diagnosis and treatment during pregnancy on cognitive development and behavior in early childhood (6 years)

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ABSTRACT

Background

Data on the long-term effects of prenatal exposure to maternal cancer and its treatment on child development are scarce.

Methods

In a multicenter cohort study, the outcome of 6-year-old children born to women diagnosed with cancer during pregnancy (study group) was compared to the outcome of children born to healthy women after an uncomplicated pregnancy (control group). Children were prospectively examined by means of a comprehensive neuropsychological test battery, including intelligence, attention and memory tests and a behavior questionnaire.

Results

In total, 132 study children and 132 matched controls (median age 6.1 years) were included. In the study group, 97 children (73.5%) were prenatally exposed to chemotherapy (alone or in combination with other treatments), 14 (10.6%) to radiotherapy (alone or in combination), 1 (0.8%) to trastuzumab, 12 (9.1%) to surgery alone and 16 (12.1%) had no cancer treatment exposure. Although within the normal range, Full Scale and Verbal IQ were significantly lower in the study versus control group (M=97.0 vs M=102.1, P=0.006; M=99.6 vs M=107.1, P<0.001; respectively) and in a subgroup of chemotherapy-exposed versus control children (M=97.4 vs M=102.7, P=0.02; M=101.0 vs M=108.9, P<0.001; respectively). No significant differences were found in Performance IQ, Processing Speed, memory and attention skills.

Conclusion

Children prenatally exposed to maternal cancer and its treatment show normal Performance IQ, Processing Speed, memory and attention skills at the age of 6 years. The encountered 5-points difference in Full Scale IQ and 8-points difference in Verbal IQ between the study and control group underscore the need for longer-term follow-up.

The study is registered as ClinicalTrials.gov, NCT00330447.

INTRODUCTION

Cancer during pregnancy is a medical challenge, as the lives of both mother and fetus have to be considered in therapeutic decision making. Over the past 20 years, clinical management of pregnant cancer patients has evolved into a higher number of patients starting cancer treatment during pregnancy, less terminations of pregnancy and less medically induced preterm deliveries.[155] However, evidence on the short- and long-term fetal risks and safety are indispensable for therapeutic decision making in this patient group, given that cancer treatment may have acute and/or chronic side effects, including neurotoxicity and cardiotoxicity, and the knowledge that chemotherapy may cross the placenta in varying amounts.[9,10] Additionally, cancer may be accompanied by maternal stress, diagnostic imaging, surgical anesthesia and supportive drugs, potentially influencing fetal development.

Our group has previously published two studies, documenting reassuring health status, cognitive and cardiac outcome at a median age of 22 months after maternal cancer diagnosis and treatment during pregnancy.[11,35] However, cognitive problems may become more apparent at school-age and can be more accurately examined at older ages. At the age of 6 years, children from the participating countries start to attend primary school where tasks become more complex and demanding for their general cognitive abilities, attention and memory skills and executive functions. Moreover, cardiac problems may develop many years after chemotherapy exposure. Therefore, follow-up of the infant and toddler cohort is highly important. This study aims to investigate the health status, cognitive development and cardiac outcome of 6-year-old children prenatally exposed to maternal cancer and the associated stress, imaging studies and treatments and in particular to chemotherapy. In this chapter, we highlight the cognitive development and behavior.

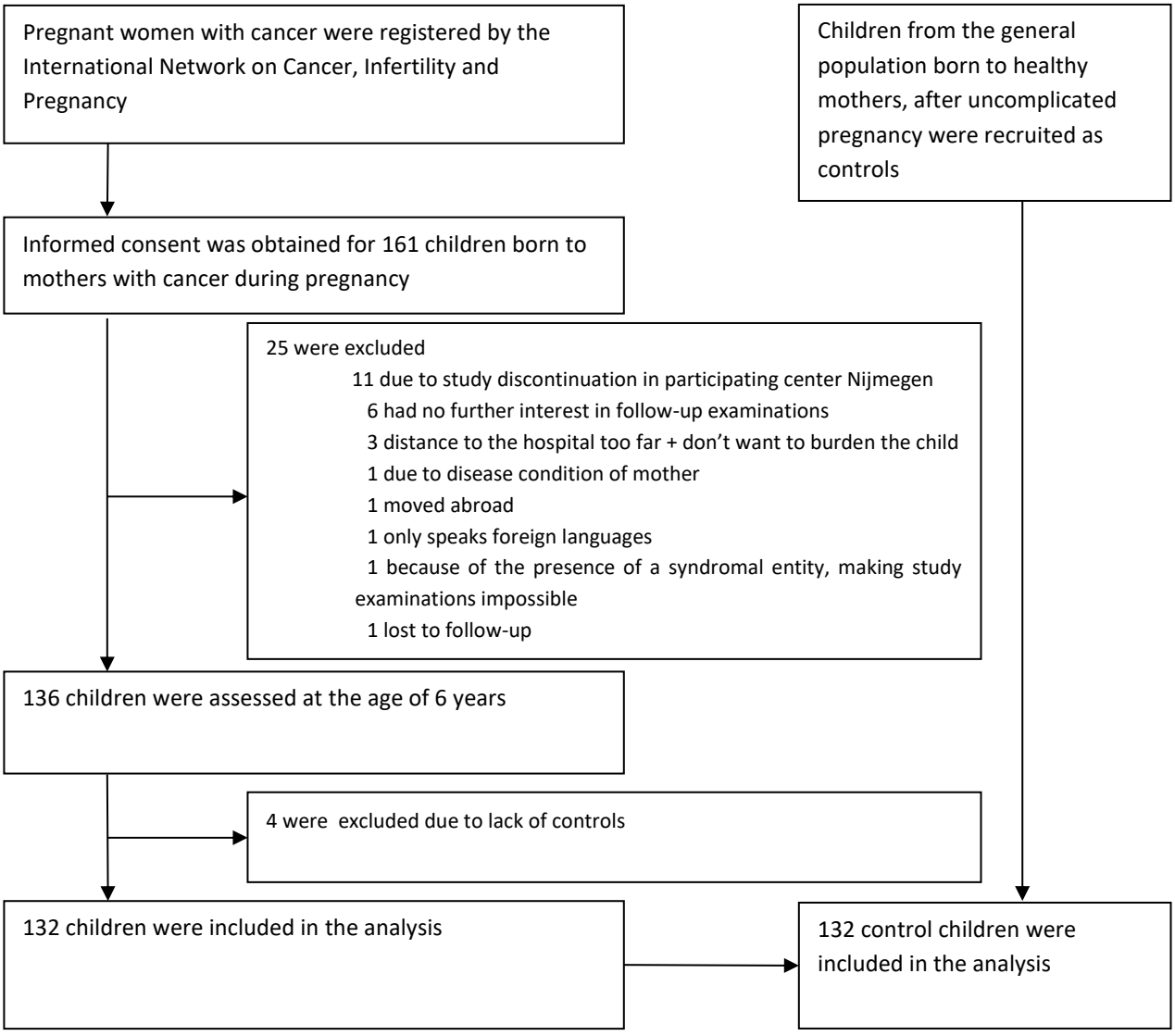
METHODS

Study participants

This is a multicenter cohort study in which children born to women diagnosed with cancer during pregnancy (with or without treatment during pregnancy) (study group) are followed from birth until the age of 18 years. At predefined ages (1.5, 3, 6, 9, 12, 15 and 18 years), the children are invited for follow-up examinations. In this study, we compare the outcome of 6-year-old children from the study group with children born to healthy women after an uncomplicated pregnancy (control group). Children were identified and enrolled prospectively (during pregnancy) or retrospectively (between birth and 6 years) and all children were prospectively examined at 6 national referral centers in Belgium, the Netherlands, the Czech Republic and Italy, all members of the International Network on

Cancer, Infertility and Pregnancy (INCIP). The study design and recruitment are summarized in Figure 1. For the neurocognitive tests, the study and control children were one-to-one matched for country, gender, age, gestational age at birth and language of the tests. Details on the recruitment and exclusion criteria are provided in the Methods section in the Supplementary Appendix. Ethical approval was obtained by each institution and the parents of each child provided written informed consent to participate. The study is registered as ClinicalTrials.gov, NCT00330447.

Figure 1. Study design and recruitment



Note: This cohort of 132 children evaluated at the age of 6 years includes 83 children who underwent cognitive evaluation in our previously published 1.5-3 years cohort study.[35] The results of 12 children at the age of 6 years were previously published,[11] whereas 120 children underwent new testing.

Oncological, obstetrical and neonatal data were collected for each mother-child pair. Cognitive development was examined using a comprehensive neuropsychological test battery to assess intelligence, memory, attention and behavior problems. In 75.5% of children, the Wechsler Preschool and Primary Scale of Intelligence – third edition (WPPSI-III)[39] was used to measure intelligence. In the remaining children, other Wechsler tests/editions or the Snijders-Oomen Nonverbal Intelligence test (SON-R $2^{1/2}$-7)[193] were used. The same intelligence test was used for each pair of matched study and control children. More information about the intelligence tests is provided in the Methods section in the Supplementary Appendix. The primary cognitive outcome was Full Scale Intelligence Quotient (IQ), as this is a measure of general cognitive abilities. Secondary cognitive outcomes included Verbal and Performance IQ and Processing Speed. Higher scores indicate more advanced development. The average test result is set to 100 and scores between 90 and 110 are considered average. Memory was assessed using subtests of the Children's Memory Scale (CMS).[194] Verbal and visuospatial memory span, visuospatial short- and long-term memory, verbal working memory and short- and long-term memory for faces were considered as secondary cognitive outcomes. Higher scores indicate more advanced memory skills. Attention was measured using subtasks of the Amsterdam Neuropsychological Tasks (ANT).[195] Secondary outcomes included alertness, divided attention, selective attention and response inhibition. Lower reaction times and lower percentage of errors indicate better performance. The parents filled out the Child Behavior Checklist (CBCL),[176] which was used to measure internalizing and externalizing behavior problems and the total amount of behavior problems as secondary outcomes. Higher scores indicate more behavior problems. Further details on the test protocol are provided in the Methods section in the Supplementary Appendix.

Statistical analysis

Descriptive statistics were used to describe maternal oncologic data and demographic characteristics of both groups (gender, child and maternal age, gestational age and weight at birth, ethnic background, parental education levels, use of reproductive medicine to achieve the pregnancy, smoking and alcohol use during pregnancy and bilingual education).

We converted raw scores into standardized scores for the intelligence tests and behavior questionnaires, according to normative data for each country provided by the test. For the memory tests, raw total scores for each outcome parameter were used. Raw reaction times and percentage of errors were used for the attention tasks. We also calculated composite scores in order to obtain measures of the increase of memory load and distraction on reaction time and accuracy, according to other studies using these tests.[196,197] Details on the calculation of these parameters are provided in the

Methods section in the Supplementary Appendix. Univariate analyses of covariance (ANCOVA) were used to investigate between-group differences in cognitive outcome with small for gestational age birth (SGA) and education level of parents as covariates. A subgroup analysis was performed in chemotherapy-exposed children versus matched controls. The associations between cognitive outcome and gestational age or the number of chemotherapy cycles were investigated using Pearson correlations. The Spearman's rank-correlation coefficient was used to investigate the relationship between cognitive outcome and the estimated fetal dose of radiation.

Given that most cognitive variables had more than 5% of missing data (range 1.9-30.1%), the aforementioned analyses were repeated using 50 multiply imputed datasets and analyzed using a linear mixed model analysis of (co)variance. The alpha level for the primary outcome was set to 0.05. For the ANCOVA's with the secondary outcomes, alpha was adjusted using Bonferroni's correction for multiple testing. As 51 comparisons were made with regard to the cognitive outcomes, a two-sided P value of less than 0.001 (0.05/5) was considered to indicate statistical significance.

RESULTS

Treatment characteristics

In total, 132 children (including 5 pairs of twins) born to mothers diagnosed with cancer during pregnancy were included, of whom 88 from Belgium, 25 from the Netherlands, 12 from Italy and 7 from the Czech Republic.

During pregnancy, 97 children (73.5%) were exposed to chemotherapy (alone or in combination with other treatments), 14 (10.6%) to radiotherapy (alone or in combination), 1 (0.8%) to trastuzumab, 12 (9.1%) to surgery alone and 16 children (12.1%) were born to mothers not treated during pregnancy (Table 1). In total, 390 chemotherapy cycles were administered to 93 pregnant women (including 4 women carrying twins). Twenty-five mothers (19.7%) died before the child was 6 years old. Additional information about the maternal cancer types and specific treatments is provided in Tables S1-S4 in the Supplementary Appendix.

Perinatal characteristics

In the cancer in pregnancy group, median gestational age at birth was 36.1 weeks (range, 27.4-40.7) and median birth weight was 2705g (range, 720-4200). Eighty children (60.6%) were born preterm, of whom 8 (6.1%) very preterm (27.0-31.9 weeks gestational age), 16 (12.1%) moderately preterm (32.0-33.9 weeks) and 56 (42.4%) late preterm (34.0-36.9 weeks), and 52 children (39.4%) were born at term

(37.0 weeks or later). The incidence of preterm birth in the general population is estimated at 6.8 to 8.0% in the participating countries.[186] In the study group, 22/132 children (16.7%) were born small for gestational age (SGA), which is defined as a birth weight below the tenth percentile of gender and gestational age matched children. The incidence of SGA was 17/132 (12.9%) in the control group.

Table 1. Cancer treatment during pregnancy for all children and those categorized as small for gestational age

Cancer treatment	**All children (N=132)** Number (%)	**Small for gestational age (N=22)** Number (% of children with treatment)
Surgery	12 (9.1)*	2 (16.7)†
Chemotherapy	38 (28.8)	10 (26.3)
Radiotherapy	1 (0.8)	0 (0.0)
Surgery and chemotherapy	51 (38.6)*	5 (9.8)
Surgery and radiotherapy	5 (3.8)	2 (40.0)
Surgery, chemotherapy, and radiotherapy	8 (6.1)*	2 (25.0)‡
Trastuzumab	1 (0.8)	0 (0.0)
No treatment	16 (12.1)	1 (6.3)

Note: *One pair of twins was exposed to surgery alone, three pairs of twins to surgery and chemotherapy, and one pair of twins to surgery, chemotherapy and radiotherapy.

†One child of a twin pregnancy was born small for gestational age.

‡Both children of a twin pregnancy were born small for gestational age.

Demographic characteristics

The median age at cognitive evaluation was 6.1 years in both study and control group (range study group: 4.8-7.9, controls: 4.7-7.6). Children from the study and control group were compared for several background variables, which are important for cognitive development (Table 2 and Supplementary Appendix Tables S5-S8). The groups were matched for country, gender, age, gestational age at birth and language of the tests. Furthermore, the groups were comparable with respect to birth weight, maternal age at birth, ethnicity, the use of reproductive medicine to achieve the pregnancy, smoking and alcohol use during pregnancy and the number of children who were raised bilingual. However, parents of control children were on average more highly educated than parents of study children. In

Table 2. Demographic characteristics of the children

Characteristic	**Cancer in pregnancy group (N=132)**		**Control group (N=132)**	
Median age (range) - years	6.1 (4.8-7.9)		6.1 (4.7-7.6)	
Median gestational age (range) - weeks	36.1 (27.4-40.7)		36.1 (28.6-41.0)	
Median birth weight (range) - grams	2705 (720-4200)		2700 (1025-4075)	
Median maternal age at birth of this child (range) - years	33 (19-44)		31 (20-46)	
Sex – number (%)				
Male	71 (53.8%)		71 (53.8%)	
Female	61 (46.2%)		61 (46.2%)	
Race – number (%)*				
White	115 (87.1%)		119 (90.2%)	
Black	11 (8.3%)		5 (3.8%)	
Other	6 (4.5%)		8 (6.1%)	
Highest level of education of parents – number (%)†	Mother	Father	Mother	Father
Primary school	5 (3.8%)	6 (4.5%)	2 (1.5%)	4 (3.0%)
Secondary school	50 (37.9%)	57 (43.2%)	21 (15.9%)	37 (28.0%)
Bachelor	41 (31.1%)	31 (23.5%)	46 (34.8%)	31 (23.5%)
Master's degree or higher	33 (25.0%)	32 (24.2%)	49 (37.1%)	43 (32.6%)
Unknown	3 (2.3%)	6 (4.5%)	14 (10.6%)	17 (12.9%)

Note: *Race was self-reported by the parents. †The highest level of education is presented according to the European educational system. A bachelor's degree is earned at both traditional universities and nonuniversity institutions of higher education and requires between three and four years of full-time study. A master's degree is earned at university and requires one to two years of full-time study after a bachelor's degree.

further analyses, education level of parents and SGA status were included as covariates, because of the differences between the two groups and their possible impact on cognitive development.

Cognitive development

Intelligence

The primary outcome Full Scale IQ was significantly lower in the study group (M=97.0, 95% CI 90.6 to 103.5) compared to the control group (M=102.1, 95% CI 95.6 to 108.5) (P=0.006) (Figure 2 and Supplementary Appendix Table S9), although the means of both groups were situated around the mean of 100 set by the test. In a subgroup analysis, chemotherapy-exposed children also scored significantly lower on Full Scale IQ, compared to their matched controls (M=97.4, 95% CI 88.9 to 105.9 versus M=102.7, 95% CI 94.0 to 111.4, P=0.02) (Supplementary Appendix Table S10). Full Scale IQ was not related to gestational age in the chemotherapy-exposed group (r=-0.04, P=0.74) and the control group (r=-0.06, P=0.59) (Figure 3), to the number of chemotherapy cycles administered during pregnancy (r=0.04, P=0.07) (Figure 4) or to the estimated fetal dose of radiation (r=0.19, P=0.52) (Supplementary Appendix Figure S1). The size of the between-group differences in Full Scale IQ was comparable for children exposed to anthracyclines, taxanes or platin-based treatments compared to their matched controls (Supplementary Appendix Table S11). Full Scale IQ was not significantly different in children born SGA compared to non-SGA children, controlling for group (study or control) (Supplementary Appendix Table S12).

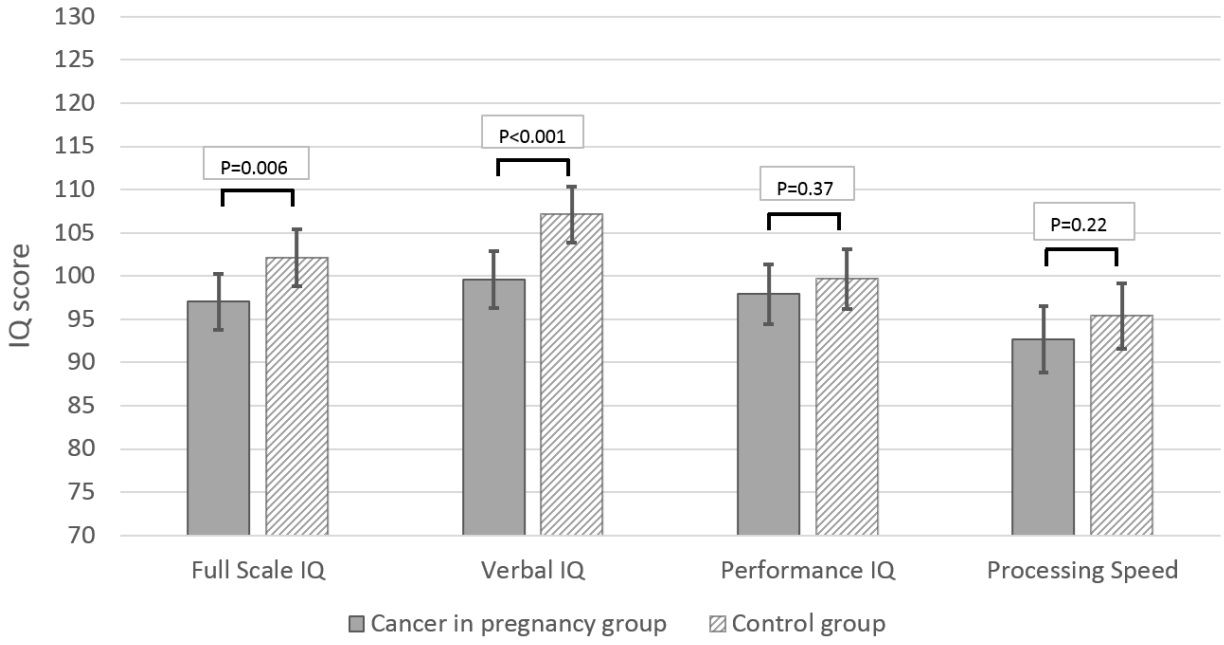
With regard to the secondary outcomes, Verbal IQ was significantly lower in the study group (M=99.6, 95% CI 93.2 to 106.0) compared to the control group (M=107.1, 95% CI 100.7 to 113.6) (P<0.001) and in chemotherapy-exposed children (M=101.0, 95% CI 92.8 to 109.2) compared to their matched controls (M=108.9, 95% CI 100.5 to 117.3) (P<0.001). There were no statistically significant between-group differences in Performance IQ or Processing Speed (Figure 2 and Supplementary Appendix Tables S9-S10).

Memory

With regard to memory, children from the total study group and chemotherapy-exposed children scored slightly lower on the subtests measuring visuospatial short- and long-term memory and children from the total study group also had slightly lower scores for the verbal memory span compared to controls, although not statistically significant after Bonferroni's correction. No statistically significant differences between the total study and control group and between

chemotherapy-exposed and control children were found in visuospatial memory span, verbal working memory and short- and long-term memory for faces (Figure 5 and Supplementary Appendix Tables S13-S14).

Figure 2. Comparison of the mean Full Scale IQ, Verbal IQ, Performance IQ and Processing Speed between the cancer in pregnancy group and the control group



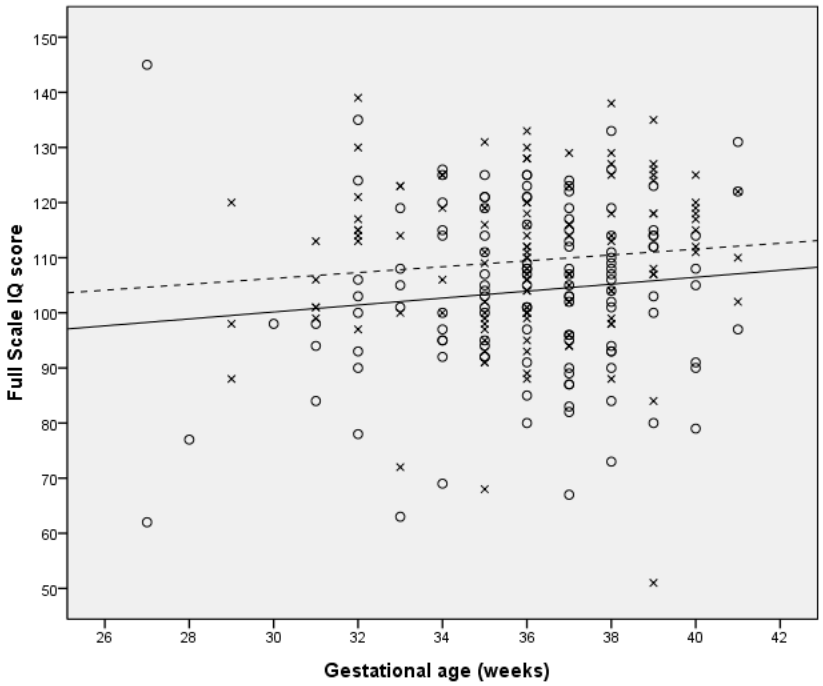
Note: The figure shows estimated marginal means with standard errors of the means for each group and variable. Raw P values are presented.

The mean of standardized IQ-scores is 100 with a standard deviation of 15 and scores between 90 and 110 are considered average. Higher scores indicate more advanced development.

Attention

On the attention tests, the study and control group and the chemotherapy and control group did not differ significantly on any of the subtasks measuring alertness, response inhibition, selective attention and divided attention (Supplementary Appendix Tables S15-S16). There were no statistically significant between-group differences in reaction times or percentage of errors on the tasks. Neither did we find significant differences in the effect of memory load or distraction on speed and accuracy of responses.

Figure 3. The relation between Full Scale IQ and gestational age at birth (in weeks) for the cancer in pregnancy and control group



Note: Values of children from the cancer in pregnancy group are represented by circles, those of children from the control group are represented by crosses. Mean values (as calculated by linear regression) are indicated by a solid line for the cancer in pregnancy group and a dashed line for the control group.

Figure 4. The relation between Full Scale IQ and the number of chemotherapy cycles administered during pregnancy

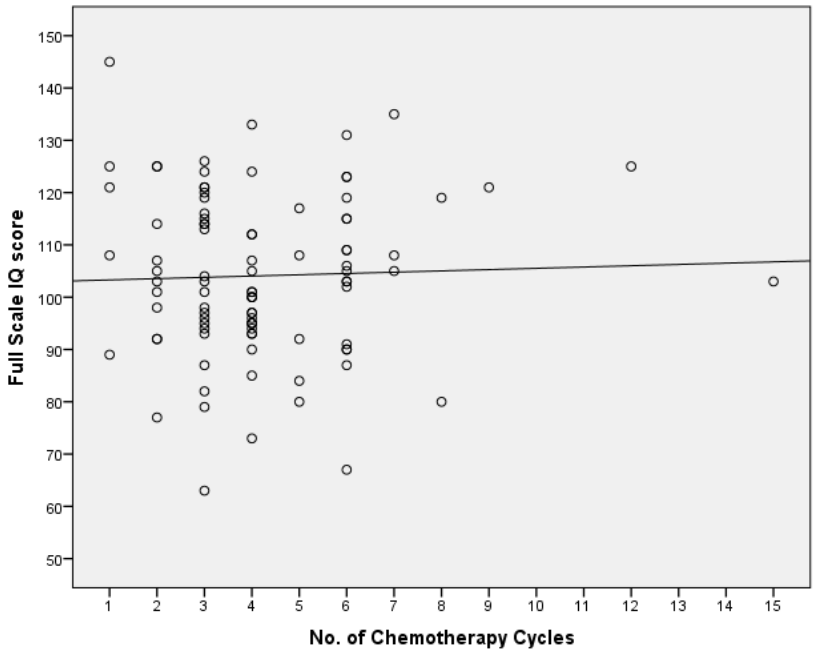
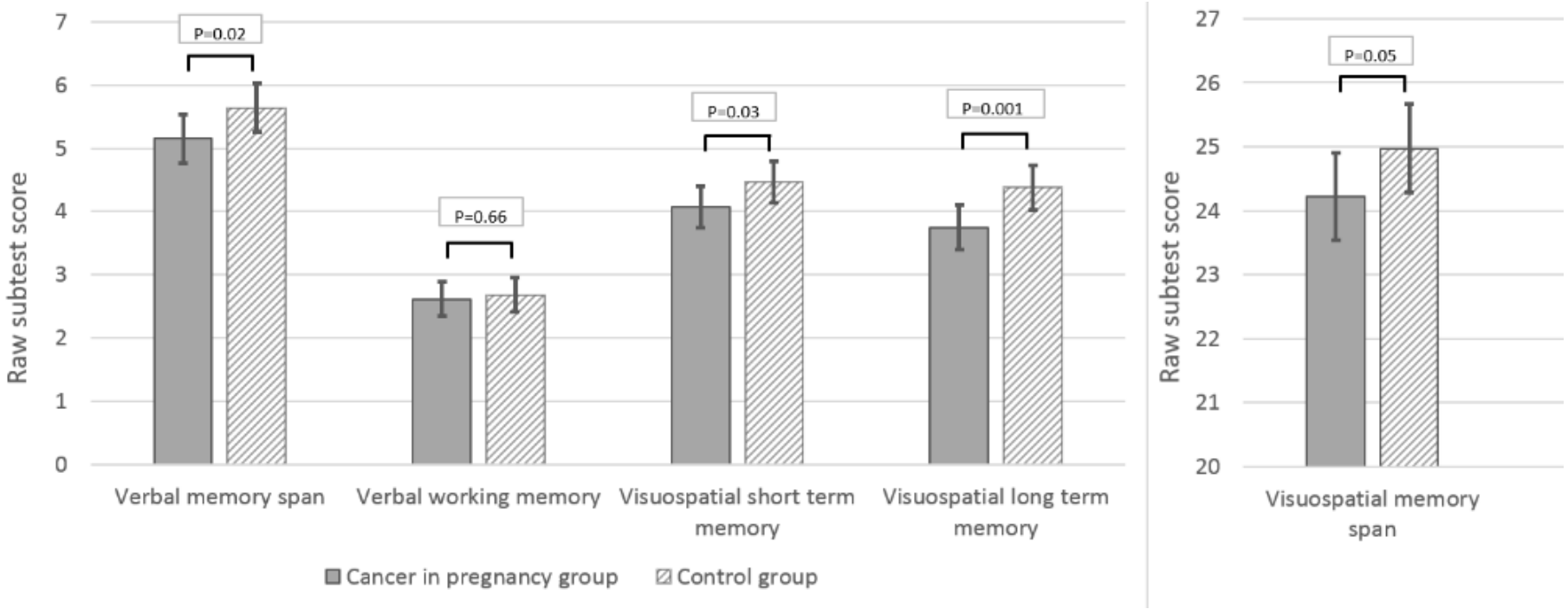


Figure 5. Comparison of the raw memory scores from the subtests of the Children's Memory Scale between the cancer in pregnancy group and the control group



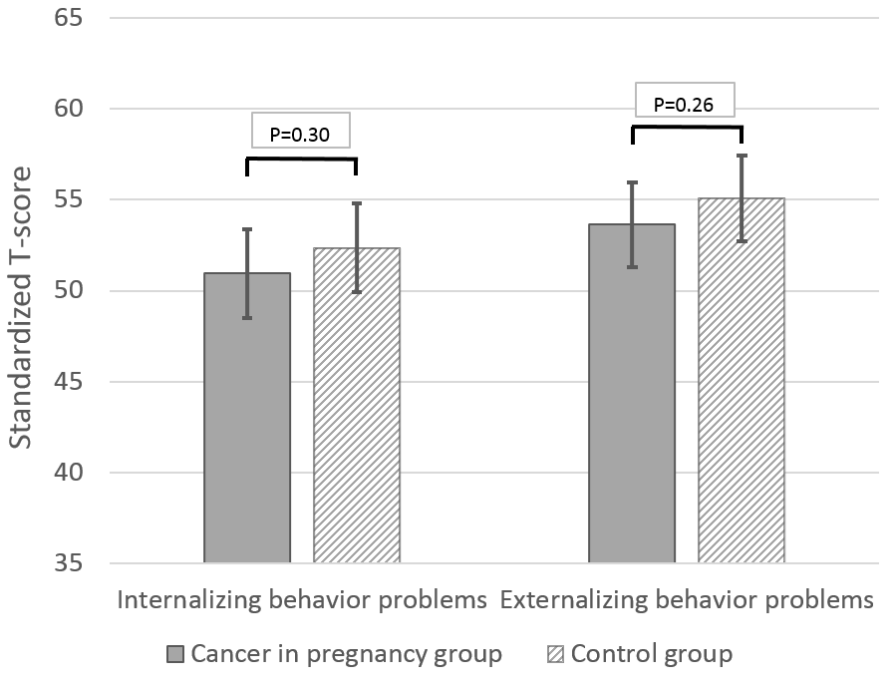
Note: The figure shows estimated marginal means with standard errors of the means for each group and variable. Raw P values are presented.

Verbal memory was measured using the subtest Numbers (range of scores between 0-14 for Numbers Forward (verbal memory span) and 0-12 for Numbers Backward (verbal working memory)). Visuospatial short- and long-term memory were measured using the subtest Dot Locations (range 0-6). Visuospatial memory span was measured using the subtest Picture Locations (range 0-30). Higher scores indicate more advanced memory skills.

Behavior problems

Additionally, there were no significant differences between the total study and control group and between chemotherapy-exposed and control children in internalizing or externalizing behavior problems (Figure 6 and Supplementary Appendix Tables S17-S18). The scores for internalizing and externalizing behavior problems did also not significantly differ between study children whose mothers died and those with surviving mothers (Supplementary Appendix Table S19).

Figure 6. Comparison of the standardized T-scores for internalizing and externalizing behavior problems on the Child Behavior Checklist between the cancer in pregnancy group and the control group



Note: The figure shows estimated marginal means with standard errors of the means for each group and variable. Raw P values are presented.

The mean of standardized T-scores is 50 with a standard deviation of 15. Higher scores indicate more behavior problems.

Results of mixed model ANCOVA with multiply imputed data were comparable to the ANCOVA without imputations for all outcome parameters, indicating minimal bias due to missing data (results not shown).

DISCUSSION

In this multicenter prospective cohort study, the incidence of medical problems, prenatal and postnatal growth and cognitive development were compared between 132 children born to mothers diagnosed with cancer during pregnancy and their matched controls and between a subgroup of 97 chemotherapy-exposed children and matched controls. The cardiac structure and function were also evaluated in 78 chemotherapy-exposed children and controls. Although premature and SGA birth were more frequent (60.6 and 16.7% respectively) and children from the study group had lower Full Scale and Verbal IQ scores than their matched controls, the overall development of these children was normal at a median age of 6.1 years. Fortunately, most SGA born children caught-up on their growth curves at the age of 6 years.

The cognitive outcomes on most tests were not different between the study and control group and between the chemotherapy-exposed subgroup and controls. However, children from the study group and children exposed to chemotherapy scored significantly lower on Full Scale IQ (5 points difference) and Verbal IQ (8 points) than their matched controls. A difference of 6 to 8 IQ points has also been demonstrated in a meta-analysis of children treated with chemotherapy-only for acute lymphoblastic leukemia compared to healthy controls.[198] Although not completely comparable to our study population, the results indicate that chemotherapy exposure may be related to worse intellectual outcomes. The difference in Full Scale IQ in our sample can be attributed to the difference in Verbal IQ. Verbal intelligence relies on specific acquired knowledge with regard to vocabulary and general information, which is a product of educational and cultural experience in interaction with inherent capacities to reason and solve novel problems.[199] Therefore, postnatal environmental factors, such as education and socio-cultural environment, also play an important role in cognitive development, especially with regard to verbal intelligence. Given that parents from the control group were on average more highly educated, group differences in other aspects that were not measured may exist, for example in socio-economic status or parenting style, which may contribute to the group differences in verbal intelligence. In the case of cancer during pregnancy, death of the mother is also a major life event that may influence child development. Despite the group differences in Full Scale and Verbal IQ, the scores of the study children were within normal ranges. Therefore, the possible clinical relevance of the encountered group differences may be questionable. Furthermore, Full Scale IQ was not related to the number of chemotherapy cycles administered during pregnancy or to the estimated fetal dose of radiation. No significant between-group differences were found in Performance IQ, Processing Speed, memory and attention skills or behavior problems. Overall, no major cognitive developmental problems were encountered at the age of 6 years, which is consistent with our previous findings in the 1.5-3 years cohort and other studies.[11,14,35] In contrast, prematurity was associated with a worse

cognitive outcome in the 1.5-3 years cohort.[35] This relationship was no longer present at the age of 6 years with regard to Full Scale intelligence. Inconsistent findings have been reported on the long-term effects of premature birth on cognition, especially for late preterm born children, who are the most represented preterm born children in our study.[112,116,200,201] Nevertheless, more subtle cognitive sequelae in memory or attention skills may be present in premature and SGA born children, but this was not the scope of this study. The encountered between-group differences in Full Scale and Verbal intelligence underscore the need for longer-term follow-up in larger samples of children prenatally exposed to maternal cancer and its treatment, as cognitive difficulties may become more apparent when cognitive and school demands increase with older age.

Our study has some limitations. The results cannot be extrapolated to all types of chemotherapeutic agents and to all trimesters of pregnancy, as most children were exposed to chemotherapy in the second and third trimester of pregnancy. First-trimester chemotherapy-exposure is related to an increased risk of congenital malformations and therefore contraindicated.[148,149] Moreover, the rarity of cancer diagnosis during pregnancy, the heterogeneity of cancer types, the combination of different cancer treatments during pregnancy and the possible confounding impact of postnatal environmental factors challenge the research on the long-term effects of prenatal exposure to cancer and its treatment on child development. Finally, follow-up until adult ages is needed to investigate the impact on fertility and cancer development in the children and to evaluate the evolution of the encountered group differences in Full Scale and Verbal IQ.

In conclusion, our data suggest that cancer treatment during pregnancy is possible without major long-term developmental problems in the child, although caution is always needed. This observation may influence therapeutic decision making, as newly diagnosed patients can be better informed about their treatment options and about the possible risks and safety of these treatments for their child. This will help them to make a well-informed decision about the continuation of pregnancy and the treatment options.

SUPPLEMENTARY APPENDIX

1. Methods

1.1 Recruitment of study and control children

Between 2005 and 2018, women diagnosed with cancer during pregnancy and referred to one of the participating centers in Belgium (University Hospitals Leuven), The Netherlands (VU University Medical Center and Academic Medical Center Amsterdam, University Medical Center Utrecht, Erasmus Medical Center Rotterdam, University Medical Center Groningen and Radboud University Medical Center Nijmegen), the Czech Republic (Faculty Hospital Motol, Charles University Prague) and Italy (Istituto Europeo di Oncologia Milan, Ospedale San Gerardo Monza) were prospectively (during pregnancy) or retrospectively (after delivery but before the child was 6 years old) invited to take part in the study. All children were prospectively examined. Children who were not able to perform the age-specific cognitive tests due to severe intellectual disability were excluded. Parents signed the informed consent at the moment of inclusion. Denial of participation or drop-out were mainly due to the distance to the hospital, difficulties to reach the patient after moving out or death of the mother and fear of overload for the child due to the supplementary examinations. Participants were offered to do (part of) the neuropsychological assessment at home if the distance to the hospital was the main reason for drop-out.

Control children were recruited in Belgium, the Netherlands, the Czech Republic and Italy. Preterm born children were recruited through the screening of birth lists from the participating hospitals. Children born full term were recruited by distributing information letters in schools and by advertising on the webpage of the hospital. All parents who were willing to let their child participate in the study first filled out a questionnaire on general health and prenatal history, in order to check if they met the inclusion criteria. Exclusion was based on all pregnancy-related (e.g., hypertension, severe preeclampsia, gestational diabetes with medical treatment, liver problems, epilepsy …) or neonatal problems (e.g., admission to a neonatal ward because of infections, long-term need of oxygen, malformations, brain lesions …) that may impact on child development. Immediate postnatal oxygen administration (CPAP) was not considered an exclusion criterion. Parents whose child met all the inclusion criteria signed the informed consent consecutively. Reasons for denial of participation or drop-out were the same as for the study children.

1.2 Description of the neuropsychological assessment protocol

The neuropsychological assessment consisted of two parts: an intelligence test of about 1 to 1,5 hour and several attention and memory tests of about 1 hour altogether.

Part 1: intelligence test

The following intelligence tests were used in our study:
Wechsler Preschool and Primary Scale of Intelligence – revised edition (WPPSI-R)[202] (N = 19)
Wechsler Preschool and Primary Scale of Intelligence – third edition (WPPSI-III)[39] (N = 194)
Wechsler Preschool and Primary Scale of Intelligence – fourth edition (WPPSI-IV)[203] (N = 2)
Wechsler Intelligence Scale for Children – third edition (WISC-III)[204] (N = 29)
Wechsler Intelligence Scale for Children – fourth edition (WISC-IV)[205] (N = 6)
Snijders-Oomen Nonverbal Intelligence Test (SON-R 2.5-7 years)[193] (N = 7)

Different intelligence tests were used due to several reasons:

1. Intelligence tests are regularly revised in order to provide test materials that are adapted to the daily life of today's children and in order to update the norms to correct for the Flynn effect (i.e., the increase of intelligence scores in many parts of the world over the 20th century). The long-term nature of our study therefore implies that tests are revised during the duration of the project.

2. The Wechsler intelligence tests are developed in the United States of America and further translated, adapted and validated in other countries and languages. This implies that certain editions or revisions are not (yet) available in all languages (Dutch, French, Italian, Czech) and countries. As our study is a multicenter international study, the currently used edition of the Wechsler test is not always the same in all participating countries.

For WPPSI-III and WISC-III, Full Scale Intelligence Quotient (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ) and Processing Speed (PS) were calculated. For WPPSI-R, only FSIQ, VIQ and PIQ were calculated, as this test does not provide a score for Processing Speed. For WPPSI-IV and WISC-IV, only FSIQ and PS were used, as these tests do not provide scores for VIQ and PIQ. For SON-R, the SON-IQ score was calculated and we used this value as the 'Full Scale IQ' score.

All IQ-tests used in this study have a mean score of 100 with a standard deviation of 15. Higher scores indicate more advanced development. Scores between 90 and 110 are considered average.

Correlations between Wechsler intelligence tests and editions are high. For example, *r* = 0.80 for Full Scale Intelligence (FSIQ) measured by means of the Dutch edition of WPPSI-III and WISC-III.[206] Correlations for Verbal Intelligence (VIQ), Performance Intelligence (PIQ) and Processing Speed are also high between the two tests (VIQ: *r* = 0.81, PIQ: *r* = 0.70, PS: *r* = 0.73).

Part 2: attention and memory tests

Four subtasks from the **Amsterdam Neuropsychological Tasks (ANT)** were used to evaluate different aspects of attention.[195] ANT is a computerized program which enables to measure not only the accuracy of responses but also the reaction times. Prior to each task, the subjects were given verbal instructions and were shown the stimulus material. Next, they received a practice trial before the test of each task.

1. 'Baseline Speed'

   This task assesses **alertness** by measuring simple reaction time to 32 visual stimuli expressed in milliseconds. Subjects have to press a key as soon as a rectangle appears on the screen. The interval between two stimuli is variable in order to induce uncertainty about the timing of the appearance of the next stimulus. Mean reaction time and standard deviation of the reaction time were obtained for the dominant and non-dominant hand.

2. 'GoNoGo'

   This task is a measure of **response inhibition** and inattention. A key has to be pressed when a 'go'-signal (a complete square) is presented. When a 'no-go'-signal (an incomplete square) is presented, this prepotent response has to be inhibited. We used a balanced design with 24 'go'-signals and 24 'no-go'-signals, randomly presented. Mean reaction time of the hits, number of missed targets and number of false alarms were obtained. Response inhibition was measured as the percentage of false alarms.

3. 'Memory Search Objects 2 keys'

   This **divided attention** task measures **speed and accuracy of memory search processes**. An image of a house with four animals in the windows and the door is presented. Subjects have to press the yes-key when the house contains an animal from the memory set, and to press a no-key when this is not the case. The animals change positions in each trial. The task consists of two parts and memory load is increased with target set size rising from one animal in part one to two animals in part two. Divided attention is needed because all four stimuli are relevant and the subject has to divide the attention over the field of stimuli in order to search for animals from the target set. The reaction time for hits (RT hits) and for correct rejections

(RT CR) were measured separately in part 1 and part 2, together with the number and percentage of missed targets (P-MI) and of false alarms on non-targets (P-FA). Also, the total percentage of errors was calculated as ($P\text{-}MI_{part1}$ + $P\text{-}FA_{part1}$ + $P\text{-}MI_{part2}$ + $P\text{-}FA_{part2}$)/4. The speed and accuracy of memory search processes were measured by calculating the increase in reaction time and error rate during higher memory load. A new variable Load[RT] was constructed as an index of the memory search rate, by calculating ((RT hits + RT CR)$_{part2}$ – (RT hits + RT CR)$_{part1}$)/2. Similarly, a new variable Load[Acc] was constructed as an index of the effect of increasing memory load on accuracy, calculated as ((P-MI + P-FA)$_{part2}$ – (P-MI + P-FA)$_{part1}$)/2.

4. <u>'Focused Attention Objects 2 keys'</u>

   This task is a measure of **selective attention**. Four pieces of fruit are presented in a fruit basket, of which two pieces are located at the vertical axis (top and bottom) and two pieces at the horizontal axis (left and right). Subjects have to press the yes-key if the target fruit is presented at one of the two relevant locations, i.e. the left or right location of the horizontal axis. A no-response is required if the target fruit is shown at an irrelevant location (at the top or the bottom of the vertical axis) or if the target fruit is absent altogether. The three signal types (28 targets, 14 irrelevant targets, 14 non-targets) were presented in a random order. The reaction times for hits (RT hits), correct rejection of irrelevant targets (RT CR [irrelevant target]) and correct rejection of non-targets (RT CR [non-target]) were obtained, together with the number and percentage of missed targets (P-MI), false alarms on irrelevant targets (P-FA [irrelevant target]) and false alarms on non-targets (P-FA [non-target]). Focused attention is studied by examining the reaction time to targets presented on the irrelevant axis, since an attention shift to these targets illustrates a disruption of focused attention. The difference between the mean RT CR [irrelevant target] and RT CR [non-target] can be interpreted as a measure of the size of the distraction effect on reaction time. The difference between P-FA [irrelevant target] and P-FA [non-target] can be interpreted as a measure of the size of the distraction effect on accuracy. The accuracy of task performance is measured as the percentage of total errors, calculated as (2 x P-MI + P-FA [irrelevant target] + P-FA [non-target])/4. The mean reaction time gives an indication of overall processing speed.

Four subtasks from the **Children's Memory Scale (CMS)** were used to evaluate different aspects of memory.[194]

1. 'Numbers'

   This task is a measure of the **verbal memory span** (repeating numbers forward) and **verbal working memory** (repeating numbers backward). Raw scores range from 0 to 16 (numbers forward) and from 0 to 14 (numbers backward), with higher scores indicating better performance.

2. 'Picture Locations'

   The **visuospatial memory span** is measured as the proportion of correctly recalled picture locations. The number of picture locations is gradually increased during the task, ranging from one to five pictures. Raw scores range from 0 to 30, with higher scores indicating better performance.

3. 'Dot Locations'

   This task is a measure of **visuospatial learning, short- and long-term visuospatial memory**. Subjects have to learn and recall the location of six blue dots. Three learning trials are offered. Next, subjects have to learn and recall a new pattern with six red dots in one trial. Immediate recall is measured as the proportion of correctly recalled blue dot locations after the interference of the red dots. Delayed recall is measured after 20 minutes of attention tasks of the ANT. Raw scores range from 0 to 6 for both the immediate and delayed recall phase, with higher scores indicating better performance.

4. 'Faces'

   This task is a measure of **short- and long-term memory for faces**. In the learning phase, subjects are presented 12 target faces. Next, 36 target and non-target faces are presented in a random order and the subject has to decide whether the face is a target or a non-target. The proportion of correctly recalled faces is a measure of immediate recall. After 20 minutes of attention tasks of the ANT (delayed recall), subjects are shown another series of 36 target and non-target faces presented in a random order and the subject has to decide again whether the face is a target or a non-target. Raw scores range from 0 to 36 for both the immediate and delayed recall phase, with higher scores indicating better performance.

Behavior questionnaire

The parents were asked to fill out a questionnaire on the incidence of **behavior problems** (Child Behavior Checklist, CBCL).[176] The items measure a range of emotional and behavioral problems on a three point Likert scale (0 = 'not true', 1 = 'somewhat or sometimes true', or 2 = 'very true or often

true'). The questionnaire consists of two empirically derived broadband scales (internalizing and externalizing problems) and several subscales. The total score of all problems results in the overall scale 'total problems'. Raw scores are converted into standardized T-scores (mean 50, standard deviation 10), using computerized software provided by the developers of the questionnaire, which enables to control for gender, age and country.

1.3 Additional information on the statistical analysis

Partial eta squared is used as a measure of effect size in ANCOVA. Partial eta squared looks at the proportion of variance that a variable explains that is not explained by other variables in the analysis. A partial eta squared value of 0.01 can be interpreted as a small effect, 0.09 as a medium effect and 0.25 as a large effect.

2. Results

2.1 Maternal tumor types treated during pregnancy (127 mothers, 132 children) and the incidence of small for gestational age (SGA) children (Table S1)

Maternal malignancy	N mothers	% mothers	N mothers deceased	% mothers deceased	N SGA*	% SGA
Breast cancer	69 (3 twin pregnancies)	54.3	12 (1 twin)	17.4	5	6.9
Hematological Malignancy	20	15.7	3	15.0	5	25.0
- Acute Lymphoid Leukemia	2	1.6	0	0.0	1	50.0
- Acute Myeloid Leukemia	5	3.9	0	0.0	1	20.0
- Chronic Myeloid Leukemia	2	1.6	2	100.0	1	50.0
- Hodgkin's Disease	5	3.9	0	0.0	1	20.0
- Non-Hodgkin's Disease	6	4.7	1	16.7	1	16.7
Cervical cancer	10 (1 twin pregnancy)	7.9	3	30.0	4	36.4
Ovarian cancer	10	7.9	1	10.0	2	20.0
Brain tumor	4	3.1	1	25.0	1	25.0
Oral cavity and oropharyngeal cavity cancer	4 (1 twin pregnancy)	3.1	0	0.0	2	40.0
Nasopharynx tumor	1	0.8	0	0.0	0	0.0
Gastric cancer	2	1.6	2	100.0	1	50.0
Colon cancer	1	0.8	1	100.0	0	0.0
Melanoma	2	1.6	0	0.0	0	0.0
Thyroid cancer	1	0.8	0	0.0	1	100.0
Soft tissue sarcoma	1	0.8	1	100.0	1	100.0
Kidney carcinoma	1	0.8	0	0.0	0	0.0
Lung cancer	1	0.8	1	100.0	0	0.0
TOTAL	127	100.0	25	19.7	22	16.7

2.2 Chemotherapy regimens applied during pregnancy in 93 women (including 4 twin pregnancies) (Table S2)

Chemotherapy scheme	N cycles	N patients	% patients	N SGA	% SGA	GA (median (range))
(F)AC†	75	22**	23.7	1	4.3	27.0 (14.4-37.3)
(F)E(C)†	156	36**	38.7	3	8.1	26.0 (9.3-35.4)
ABVD†	15	5	5.4	1	20.0	29.6 (15.4-38.0)
(R) - CHOP†	18	5	5.4	1	20.0	30.6 (18.7-35.7)
Cisplatin (± Epirubicin)†	45	9**	9.7	3	30.0	24.1 (16.9-35.3)
Carboplatin (± 5-Fluorouracil) / Cisplatin (± 5-Fluorouracil)	6	3**	3.2	3**	75.0	25.4 (14.7-33.4)
Paclitaxel-Cis/Carboplatin	31	7	7.5	4	57.1	26.3 (16.9-32.0)
Paclitaxel/Docetaxel	27	12	12.9	2	16.7	30.7 (18.3-36.0)
Hovon 37 / 70 / 42A†	4	2	2.2	1	50.0	25.5 (21.0-32.3)
Temozolomide	4	1	1.1	0	0.0	27.9 (18.0-33.9)
Idarubicin-AraC†	5	2	2.2	1	50.0	20.4 (14.1-26.6)
5-Fluorouracil	3	1	1.1	0	0.0	31.1 (29.1-33.1)
CMF	1	1	1.1	0	0.0	31.6
TOTAL	390	106*		16††	16.5	

Abbreviations: SGA, small for gestational age; GA, gestational age; (F)AC, 5-fluorouracil, doxorubicin, cyclophosphamide; (F)E(C), 5-fluorouracil, epirubicin, cyclophosphamide; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; (R)-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; Hovon 37, cycle 1 prednisolone, vincristine, daunorubicin, L-asparaginase, methotrexate, and cycle 2 cytarabine, mitoxantrone, intrathecal methotrexate; Hovon 70, cycle 1 prenisolone, vincristine, daunorubicin, cyclophosphamide, and cycle 2 methotrexate, 6-thioguanine, cytarabine, cyclophosphamide; Hovon 42A (only induction phase during pregnancy), amsacrine, cytarabine; AraC, cytarabine; CMF, cyclophosphamide, methotrexate, 5-fluorouracil

*13 patients received 2 different schemes; † including anthracyclines; ** including 1 twin-pregnancy

†† One SGA child was exposed to Paclitaxel-Cisplatin and Paclitaxel only, one SGA child to both FEC and docetaxel and one SGA child to Paclitaxel-Carboplatin and Carboplatin only. Therefore they are mentioned double in the table. In total, 16 chemotherapy-exposed children were born SGA.

2.3 Overview of registered dosages received per drug (Table S3)

Anti-cancer agent	N patients*	Cumulative dosage (mg/m²): median (range)
Doxorubicin	28/32	180 (50-360)
Epirubicin	34/37	300 (70-600)
Daunorubicin	2/2	45
Idarubicin	2/2	30 (24-36)
Cyclophosphamide	49/56	1800 (600-4500)
5-Fluorouracil	30/34	1500 (600-3000)
Docetaxel	9/10	300 (100-400)
Paclitaxel	7/9	350 (140-1050)
Cisplatin	10/13	300 (60-450)
Carboplatin	4/5	1235 (210-2000)
Vincristine	5/7	4 (1-9)
Bleomycine	5/5	50 (40-80)
Dacarbazine	5/5	1850 (800-3000)
Vinblastine	5/5	30 (24-48)
Cytarabine	3/4	200 (3-300)
Rituximab	1/2	1500
Methotrexate	2/3	27.5 (15-40)
Mitoxantrone	1/1	10
6-Thioguanine	1/1	120
Amsacrin	0/1	Not reported
Temozolomide	1/1	3000

*Number of patients with registered dosages / Total number of patients receiving this type of anti-cancer agent.

2.4 Overview of radiation exposure in 13 patients (including 1 twin pregnancy) and the gestational period of exposure (Table S4)

Patient	Cancer type	Radiation Field	GA (w)	Maternal Dose (Gy)	Estimated Fetal Dose (mGy)
1	Tongue	Head and neck	17-21	60	10
2	Thyroid	Head and neck	11-17	46	66
3	NHL	Head	28	33	34
4	Brain	Head	16-19	54	42
5	AML	Left eye	20-22	20	15
6 (twin)	Tongue	Head and neck	15-17	60	10
7	Breast	Breast	10-15	60	191
8	Breast	Thoracic wall	19-23	46	131.7
9	Soft tissue liposarcoma (tigh)	Left tigh	19	50 (brachytherapy)	2.5
10	Tongue	Head and neck	27-34	66	46
11	Breast	Breast	14-21	70	153
12	Breast	Chest wall	21-27	66	52
13	Tongue	Neck	7-14	66	100

Abbreviations: GA, gestational age; w, weeks; Gy, Gray; mGy, milliGray; NHL, Non-Hodgkin's disease; AML, acute myeloid leukemia

The dose program "Peridose" developed by van der Giessen was used to estimate the fetal radiation dose.[182]

2.5 Smoking during pregnancy for study and control children (Table S5)

	N of mothers smoked during pregnancy (%)	Median number of cigarettes per week (range)
Cancer in pregnancy group	6 (5.4 %)	15 (5-60)
Control group	9 (7.3 %)	7 (1-15)

Information on smoking during pregnancy was available for 112/132 study children and 123/132 control children.

2.6 Alcohol use during pregnancy for study and control children (Table S6)

	N of mothers drinking alcohol during pregnancy (%)	Reported number of consumptions during pregnancy
Cancer in pregnancy group	3 (2.7 %)	1-2 consumptions per week (N=3)
Control group	10 (8.2 %)	Less than one per month (N=1) Less than one per week (N=6) 1-2 consumptions per week (N=3)

Information on alcohol use during pregnancy was available for 112/132 study children and 122/132 control children.

2.7 Fertility treatment to achieve this pregnancy for study and control children (Table S7)

	N of mothers pregnant through fertility treatment (%)	Type of fertility treatment
Cancer in pregnancy group	14 (11.5 %)	Hormonal stimulation (N=4) IUI (N=1) IUI with donor sperm (N=1) IVF (N=4) ICSI (N=3) Unknown (N=1)
Control group	12 (10.1 %)	Hormonal stimulation (N=1) IUI (N=3) IVF (N=4) ICSI (N=3) Unknown (N=1)

Information on the need of fertility treatment to achieve this pregnancy was available for 122/127 mothers of study children (including 5 twin pregnancies) and 119/126 mothers of control children (including 6 twin pregnancies).

Abbreviations: IUI = intra-uterine insemination, IVF = in vitro fertilization, ICSI = intracytoplasmatic sperm injection

2.8 Bilingual education from birth to 6 years for study and control children (Table S8)

	N of children raised bilingual
Cancer in pregnancy group	30 (23.8%)
Control group	27 (21.6%)

Children were considered to be raised bilingual if they were equally exposed to two languages at home or if at least half of the classes at school were taught in another language than the child's mother tongue.

Information on bilingual education was available for 126/132 study children and 125/132 control children.

2.9 Intelligence outcomes in children from the cancer in pregnancy group compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S9)

Measurement	No.	Cancer in pregnancy group (N=132)				Control group (N=132)				Type 3 test of fixed effects		
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
				Lower	Upper			Lower	Upper			
Full Scale IQ	234	**97.0**	3.3	90.6	103.5	**102.1**	3.3	95.6	108.5	7.77	0.006	0.034
Verbal IQ	222	**99.6**	3.2	93.2	106.0	**107.1**	3.3	100.7	113.6	17.26	<0.001	0.075
Performance IQ	222	**97.9**	3.4	91.2	104.7	**99.6**	3,4	92.9	106.4	0.82	0.37	0.004
Processing Speed	193	**92.7**	3.9	85.1	100.3	**95.4**	3.8	87.8	102.9	1.50	0.22	0.008

Abbreviations: CI, confidence interval; S.E., standard error of the mean

Results are expressed as standardized IQ-scores (M=100, SD=15). Higher numbers indicate better performance.

Raw P values are presented.

2.10 Intelligence outcomes in chemotherapy-exposed children compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S10)

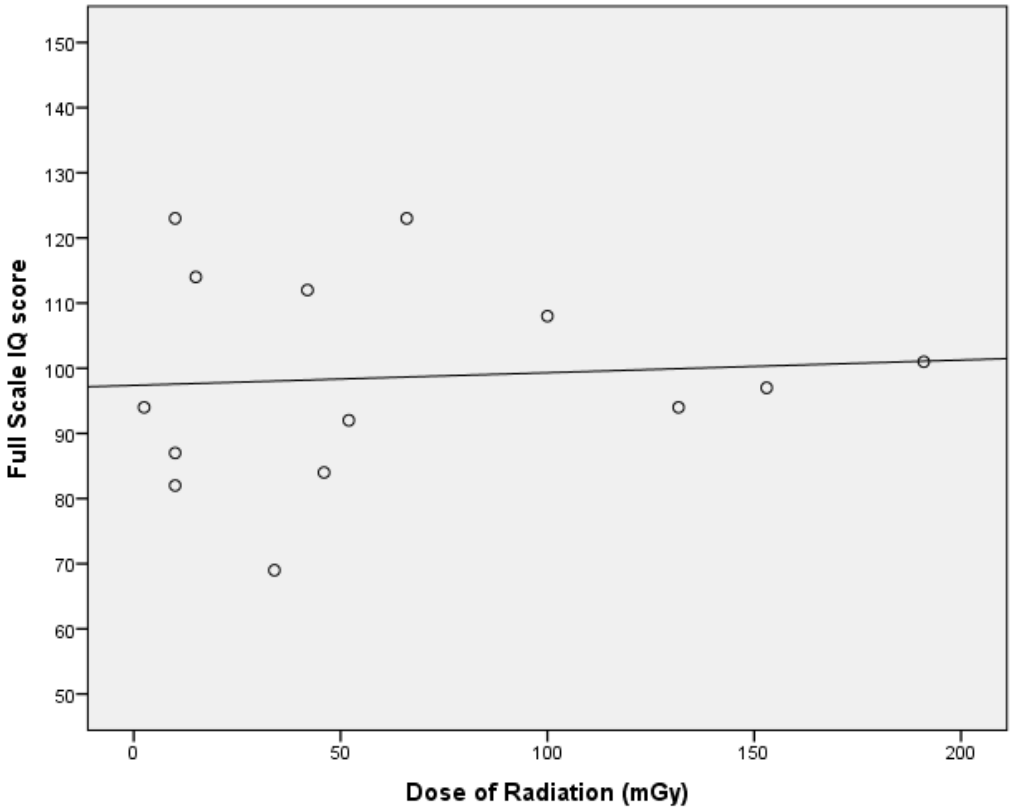
Measurement	No.	Chemotherapy group (N=97)				Control group (N=97)				Type 3 test of fixed effects		
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
				Lower	Upper			Lower	Upper			
Full Scale IQ	159	**97.4**	4.3	88.9	105.9	**102.7**	4.4	94.0	111.4	5.71	0.02	0.035
Verbal IQ	147	**101.0**	4.2	92.8	109.2	**108.9**	4.2	100.5	117.3	13.13	<0.001	0.082
Performance IQ	147	**96.7**	4.5	87.8	105.5	**98.5**	4.6	89.4	107.5	0.58	0.45	0.004
Processing Speed	123	**94.7**	5.1	84.6	104.8	**97.2**	5.1	87.0	107.4	0.84	0.36	0.007

Abbreviations: CI, confidence interval; S.E., standard error of the mean

Results are expressed as standardized IQ-scores (M=100, SD=15). Higher numbers indicate better performance.

Raw P values are presented.

2.11 Full Scale IQ in relation to the estimated fetal dose of radiation (expressed in milligrays) for 14 children exposed to radiotherapy during pregnancy (Figure S1)



The dose program "Peridose" developed by van der Giessen was used to estimate the fetal radiation dose.[182]

2.12 Full Scale and Verbal IQ in children exposed to anthracyclines, taxanes or platin-based treatments compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S11)

Measurement	No.	Children exposed to anthracyclines (N=75)*				Control group (N=75)				
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		Between-group difference of the means
				Lower	Upper			Lower	Upper	
Full Scale IQ	132	**97.5**	4.6	88.5	106.5	**102.9**	4.6	93.7	112.0	-5.4
Verbal IQ	124	**101.1**	4.5	92.2	110.0	**108.8**	4.5	99.9	117.8	-7.7

Measurement	No.	Children exposed to taxanes (N=17)*				Control group (N=17)				
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		Between-group difference of the means
				Lower	Upper			Lower	Upper	
Full Scale IQ	31	**107.9**	7.0	93.3	122.5	**111.1**	6.6	97.5	124.7	-3.2
Verbal IQ	31	**103.6**	6.4	90.4	116.8	**113.6**	6.0	101.3	125.9	-10

Measurement	No.	Children exposed to platin-based treatments (N=20)*				Control group (N=20)				
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		Between-group difference of the means
				Lower	Upper			Lower	Upper	
Full Scale IQ	33	**104.3**	3.8	96.4	112.2	**109.5**	5.4	98.3	120.7	-5.2
Verbal IQ	31	**105.5**	3.9	97.3	113.6	**114.9**	5.6	103.4	126.5	-9.4

Abbreviations: CI, confidence interval; S.E., standard error of the mean.

Note continues on the next page.

Results are expressed as standardized IQ-scores (M=100, SD=15). Higher numbers indicate better performance. Raw P values are presented.

*Some children had prenatal exposure to a combination of treatment options (e.g., anthracyclines followed by taxanes or taxanes plus platin-based treatment) and therefore are included in more than one group.

We cannot directly compare the results of children exposed to anthracyclines with those of children exposed to taxanes or to platin-based treatments, as the groups may differ with respect to the distribution of gender, gestational age, test age, country and language and some children are included in more than one group. The results of one group should be compared to their matched controls. Although the groups of children exposed to taxanes and platin-based treatments are small, we can have a look at the size of the between-group differences for the different types of chemotherapy to see whether the between-group differences are larger for one type of chemotherapy compared to the others. We can conclude from these tables that the size of the between-group differences seems to be comparable for the different types of chemotherapy (given the small sample sizes), so it does not seem that one type of chemotherapy has a larger effect on Full Scale and Verbal IQ than the others.

2.13 Full Scale IQ in children born small for gestational age compared to non-SGA children using ANCOVA with group (study or control) as covariate (Table S12)

Measurement	No.	Children born SGA (N=39)*				Non-SGA born children (N=224)				Type 3 test of fixed effects		
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
				Lower	Upper			Lower	Upper			
Full Scale IQ	256	**102.5**	2.4	97.8	107.2	**107.3**	1.0	105.4	109.3	3.54	0.06	0.014

Abbreviations: CI, confidence interval; S.E., standard error of the mean

Results are expressed as standardized IQ-scores (M=100, SD=15). Higher numbers indicate better performance.

Raw P values are presented.

2.14 Memory outcomes in children from the cancer in pregnancy group compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S13)

CMS subtask	Measurement	Minimum to maximum raw score	No.	Cancer in pregnancy group (N=132)				Control group (N=132)				Type 3 test of fixed effects		
				Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
						Lower	Upper			Lower	Upper			
Numbers forward	Verbal memory span	0-16	230	**5.15**	0.38	4.40	5.90	**5.64**	0.38	4.89	6.39	5.41	0.02	0.024
Numbers backward	Verbal working memory	0-14	230	**2.62**	0.27	2.09	3.15	**2.68**	0.27	2.15	3.22	0.19	0.66	0.001
Picture Locations	Visuospatial memory span	0-30	232	**24.22**	0.68	22.88	25.57	**24.98**	0.69	23.62	26.33	4.01	0.05	0.018
Dot Locations	Visuospatial short-term memory	0-6	230	**4.08**	0.33	3.43	4.73	**4.47**	0.33	3.82	5.12	4.62	0.03	0.029
Dot Locations	Visuospatial long-term memory	0-6	235	**3.75**	0.35	3.06	4.44	**4.38**	0.35	3.69	5.08	10.71	0.001	0.045
Faces	Short-term memory for faces	0-36	235	**24.36**	0.92	22.56	26.16	**23.79**	0.92	21.97	25.61	1.29	0.26	0.006
Faces	Long-term memory for faces	0-36	233	**25.48**	0.99	23.54	27.43	**25.71**	0.99	23.75	27.67	0.18	0.67	0.001

Abbreviations: CI, confidence interval; S.E., standard error of the mean

Results are expressed as raw subtest scores. Higher numbers indicate better performance.

Raw P values are presented.

2.15 Memory outcomes in chemotherapy-exposed children compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S14)

CMS subtask	Measurement	Minimum to maximum raw score	No.	Chemotherapy group (N=97)				Control group (N=97)				Type 3 test of fixed effects		
				Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
						Lower	Upper			Lower	Upper			
Numbers forward	Verbal memory span	0-16	164	**5.11**	0.49	4.14	6.08	**5.59**	0.50	4.61	6.57	3.63	0.06	0.023
Numbers backward	Verbal working memory	0-14	164	**2.81**	0.36	2.11	3.51	**2.84**	0.36	2.12	3.55	0.02	0.88	0.000
Picture Locations	Visuospatial memory span	0-30	164	**24.32**	0.87	22.61	26.04	**24.78**	0.88	23.04	26.52	1.05	0.31	0.007
Dot Locations	Visuospatial short-term memory	0-6	169	**4.11**	0.42	3.29	4.94	**4.62**	0.42	3.78	5.46	5.57	0.02	0.035
Dot Locations	Visuospatial long-term memory	0-6	166	**3.74**	0.44	2.87	4.61	**4.41**	0.45	3.52	5.29	8.79	0.003	0.052
Faces	Short-term memory for faces	0-36	169	**25.06**	1.14	22.82	27.30	**24.75**	1.16	22.47	27.04	0.27	0.60	0.002
Faces	Long-term memory for faces	0-36	168	**25.63**	1.26	23.15	28.11	**26.64**	1.28	24.12	29.16	2.48	0.12	0.015

Abbreviations: CI, confidence interval; S.E., standard error of the mean

Results are expressed as raw subtest scores. Higher numbers indicate better performance.

Raw P values are presented.

2.16 Attention outcomes in children from the cancer in pregnancy group compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S15)

ANT subtask	Measurement	No.	Cancer in pregnancy group (N=132)				Control group (N=132)				Type 3 test of fixed effects		
			Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
					Lower	Upper			Lower	Upper			
Baseline Speed	**Alertness**												
	Mean RT of dominant and non-dominant hand (ms)	231	**524.0**	31.3	462.3	585.6	**502.4**	31.5	440.3	564.5	1.60	0.21	0.007
Go-NoGo	**Response inhibition**												
	RT hits (ms)	230	**672.9**	27.9	617.9	727.9	**661.0**	28.1	605.7	716.4	0.61	0.44	0.003
	Number of false alarms (%)	230	**15.9**	3.08	9.8	22.0	**13.7**	3.10	7.6	19.8	1.74	0.19	0.008
Memory Search Objects 2 keys	**Divided attention**												
	Total RT (ms)	225	**6076.3**	309.4	5466.4	6686.2	**6047.7**	311.3	5434.0	6661.4	0.03	0.87	0.000
	Total number of errors (%)	225	**9.4**	1.0	7.3	11.4	**9.3**	1.0	7.3	11.4	0.004	0.95	0.000
	Effect of memory load on RT (ms)	225	**469.5**	71.0	329.6	609.5	**431.3**	71.5	290.4	572.1	0.96	0.33	0.004
	Effect of memory load on accuracy	225	**3.79**	1.57	0.70	6.88	**2.97**	1.58	-0.15	6.08	0.91	0.34	0.004
Focused Attention Objects 2 keys	**Selective attention**												
	Total RT (ms)	226	**5100.7**	295.4	4518.5	5682.9	**5139.3**	297.4	4553.1	5725.5	0.06	0.81	0.000
	Total number of errors (%)	228	**8.3**	1.8	4.7	11.9	**7.6**	1.8	3.9	11.2	0.53	0.47	0.002
	Effect of distraction on RT (ms)	228	**74.8**	71.5	-66.1	215.7	**87.9**	71.9	-53.9	226.7	0.11	0.74	0.001
	Effect of distraction on accuracy	228	**0.67**	0.39	-0.11	1.45	**0.51**	0.40	-0.27	1.29	0.54	0.46	0.002

Note and abbreviations: see Table S16.

2.17 Attention outcomes in chemotherapy-exposed children compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S16)

ANT subtask	Measurement	No.	Chemotherapy group (N=97)				Control group (N=97)				Type 3 test of fixed effects		
			Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
					Lower	Upper			Lower	Upper			
Baseline Speed	**Alertness**												
	Mean RT of dominant and non-dominant hand (ms)	157	**513.7**	39.3	436.1	591.2	**504.4**	40.0	425.5	583.4	0.21	0.65	0.001
Go-NoGo	**Response inhibition**												
	RT hits (ms)	157	**668.8**	35.4	598.9	738.7	**678.5**	36.0	607.3	749.7	0.28	0.60	0.002
	Number of false alarms (%)	157	**15.7**	3.9	8.0	23.5	**13.4**	4.0	5.6	21.3	1.3	0.26	0.008
Memory Search Objects 2 keys	**Divided attention**												
	Total RT (ms)	152	**6196.2**	400.4	5405.2	6987.2	**6170.8**	407.3	5366.1	6975.6	0.02	0.90	0.000
	Total number of errors (%)	152	**10.7**	1.3	8.0	13.3	**10.9**	1.4	8.1	13.6	0.07	0.80	0.000
	Effect of memory load on RT (ms)	152	**405.4**	88.0	231.5	579.3	**348.4**	89.6	171.4	525.3	1.54	0.22	0.010
	Effect of memory load on accuracy	152	**3.06**	1.93	-0.75	6.86	**2.16**	1.96	-1.71	6.03	0.79	0.38	0.005
Focused Attention Objects 2 keys	**Selective attention**												
	Total RT (ms)	154	**5184.6**	372.0	4449.7	5919.6	**5237.2**	378.7	4489.1	5985.4	0.07	0.79	0.000
	Total number of errors (%)	155	**9.2**	2.2	4.8	13.6	**8.2**	2.2	3.7	12.6	0.81	0.37	0.005
	Effect of distraction on RT (ms)	155	**70.9**	93.5	-113.7	255.5	**47.2**	95.1	-140.7	235.0	0.24	0.62	0.002
	Effect of distraction on accuracy	155	**0.76**	0.52	-0.27	1.80	**0.69**	0.53	-0.36	1.74	0.08	0.78	0.000

Abbreviations Tables S15 and S16: CI, confidence interval; CR, correct rejections; FA, false alarms; P, percentage; RT, reaction time; S.E., standard error of the mean

Results are expressed as raw subtest scores. Reaction times are expressed in milliseconds (ms), while numbers of errors are expressed in percentages. Higher numbers indicate worse performance. Raw P values are presented.

The effect of memory load on reaction time is calculated as $((\text{RT hits} + \text{RT CR})_{part2} - (\text{RT hits} + \text{RT CR})_{part1})/2$. Higher numbers indicate a larger effect of memory load on reaction time. The effect of memory load on accuracy is calculated as $((\text{P-MI} + \text{P-FA})_{part2} - (\text{P-MI} + \text{P-FA})_{part1})/2$. Higher numbers indicate a larger effect of memory load on accuracy. The effect of distraction on reaction time is calculated as RT CR [irrelevant target] – RT CR [non-target]. Higher numbers indicate a larger effect of distraction on reaction time. The effect of distraction on accuracy is calculated as P-FA[irrelevant target] – P-FA[non-target]. Higher numbers indicate a larger effect of distraction on accuracy.

2.18 Behavior problems in children from the cancer in pregnancy group compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S17)

Measurement	No.	Cancer in pregnancy group (N=132)				Control group (N=132)				Type 3 test of fixed effects		
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
				Lower	Upper			Lower	Upper			
Internalizing problems	230	**51.0**	2.4	46.1	55.8	**52.4**	2.5	47.5	57.2	1.09	0.30	0.005
Externalizing problems	230	**53.6**	2.3	49.0	58.2	**55.1**	2.3	50.5	59.7	1.28	0.26	0.006
Total problems	230	**52.4**	2.5	47.5	57.2	**53.6**	2.5	48.8	58.5	0.86	0.35	0.004

Abbreviations: see Table S18.

2.19 Behavior problems in chemotherapy-exposed children compared to matched controls using ANCOVA with small for gestational age and parental education levels as covariates (Table S18)

Measurement	No.	Chemotherapy group (N=97)				Control group (N=97)				Type 3 test of fixed effects		
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
				Lower	Upper			Lower	Upper			
Internalizing problems	154	**52.9**	3.3	46.5	59.4	**52.2**	3.3	45.7	58.8	0.18	0.68	0.001
Externalizing problems	154	**54.7**	3.1	48.5	60.8	**56.1**	3.1	49.9	62.4	0.88	0.35	0.006
Total problems	154	**53.8**	3.3	47.4	60.2	**54.5**	3.3	48.0	61.0	0.16	0.69	0.001

Abbreviations Tables S17 and S18: CI, confidence interval; S.E., standard error of the mean

Results are expressed as standardized T-scores (M=50, SD=15). Higher number indicate more behavior problems.

Raw P values are presented.

2.20 Behavior problems in children from the cancer in pregnancy group whose mother died compared to those with surviving mothers using independent samples t-test (Table S19)

Measurement	No.	Children whose mother died (N=25)		Children with surviving mothers (N=107)					T-statistic	
		Mean	SD	**Mean**	SD	Mean difference	95% CI		t	P value
							Lower	Upper		
Internalizing problems	117	**48.5**	8.9	**50.1**	10.5	-1.6	-6.4	3.1	-0.68	0.50
Externalizing problems	117	**47.4**	9.5	**49.5**	9.9	-2.0	-6.6	2.5	-0.89	0.37

Abbreviations: CI, confidence interval; SD, standard deviation

Results are expressed as standardized T-scores (M=50, SD=15). Higher numbers indicate more behavior problems.

Raw P values are presented.

Chapter 5

Effects of maternal cancer diagnosis and treatment during pregnancy on cognitive development and behavior in middle childhood (9 years)

Vandenbroucke, T., Schellens, C., Philippe, K., van Gerwen, M., Fruijtier, A., Claes, L., & Amant, F. Child development at 9 years after maternal cancer diagnosed during pregnancy: an interim analysis.

ABSTRACT

Background

It has become clear that for specific cancers and under well-defined circumstances, oncological treatment in pregnancy is possible. Although outcomes in infancy, toddlerhood and early childhood are generally reassuring, long-term follow-up of these children is insufficient.

Methods

In a multicenter cohort study, the cognitive development of 9-year-old children born to women diagnosed with cancer during pregnancy was compared to the development of children born after an uncomplicated pregnancy. Children were prospectively examined using a comprehensive neuropsychological test battery, including intelligence, attention and memory tests and a behavior questionnaire.

Results

Results of an interim analysis of the data are provided. In the study group, 43 children were included (median age, 9.2 years; range, 8.8 to 10.8) together with an equal number of controls who were one-to-one matched to the study group for age, gestational age, gender, country and language of the tests. During pregnancy, 28 children (65.1%) were exposed to chemotherapy (alone or in combination with other treatments), 6 (14.0%) to radiotherapy (alone or in combination), 1 (2.3%) to trastuzumab, 5 (11.6%) to surgery alone and 5 children (11.6%) were born to mothers not treated during pregnancy. No significant between-group differences in intelligence, attention and memory skills were found and the groups did not significantly differ in the number of parent-reported internalizing and externalizing behavior problems.

Conclusion

Children born after a pregnancy complicated by maternal cancer and the associated stress, diagnostic imaging and treatments develop normally at the age of 9 years.

The study is registered as ClinicalTrials.gov, NCT00330447.

INTRODUCTION

Cancer during pregnancy is increasingly prevalent, as many women defer childbearing until the third or fourth decade of life and the incidence of most malignancies rises with increasing age. In therapeutic decision making, the maternal benefit and the fetal risks of oncological treatment during pregnancy need to be well considered. Cancer treatment may have acute and/or chronic side effects on one's health status, including neurotoxicity, cardiotoxicity, ototoxicity and sub- or infertility. In the case of cancer during pregnancy, the placenta may act as a protective barrier, preventing the fetus from noxious substances. Notwithstanding, research has shown that chemotherapy may cross the placenta in varying amounts, possibly leading to acute and/or long-term sequelae in the fetus.[9,10]

It has become clear that for specific cancers and under well-defined circumstances, oncological treatment in pregnancy is possible. Several studies have reported that the cognitive development of these children in infancy, toddlerhood and early childhood is generally reassuring.[11,14,35,152,162] At the age of 1.5 and 3 years, the cognitive development of 129 children prenatally exposed to maternal cancer and the associated stress, imaging and treatments was not significantly different from the development of 129 children born after an uncomplicated pregnancy.[35] In the previous chapter, we discussed the cognitive development of 132 6-year-old children born to mothers diagnosed with cancer during pregnancy and compared the outcomes to those of 132 children born after an uncomplicated pregnancy. We found that the Full Scale and Verbal IQ scores of the study group were significantly lower than those of the control group, although the scores were within the normal range. The groups did not significantly differ in their scores for Performance IQ and Processing Speed, on the subtests measuring different aspects of memory and attention and in the number of parent-reported behavior problems. The encountered group differences together with the fact that cognitive problems may become more manifest with increasing age as school demands become more complex and challenging, underscore the need for longer-term follow-up. Currently, data on the long-term effects of maternal cancer and different types of treatments on child development are scarce. Therefore, this study aims to investigate the cognitive development of 9-year-old children born after a pregnancy complicated by maternal cancer and the associated stress, imaging and treatments.

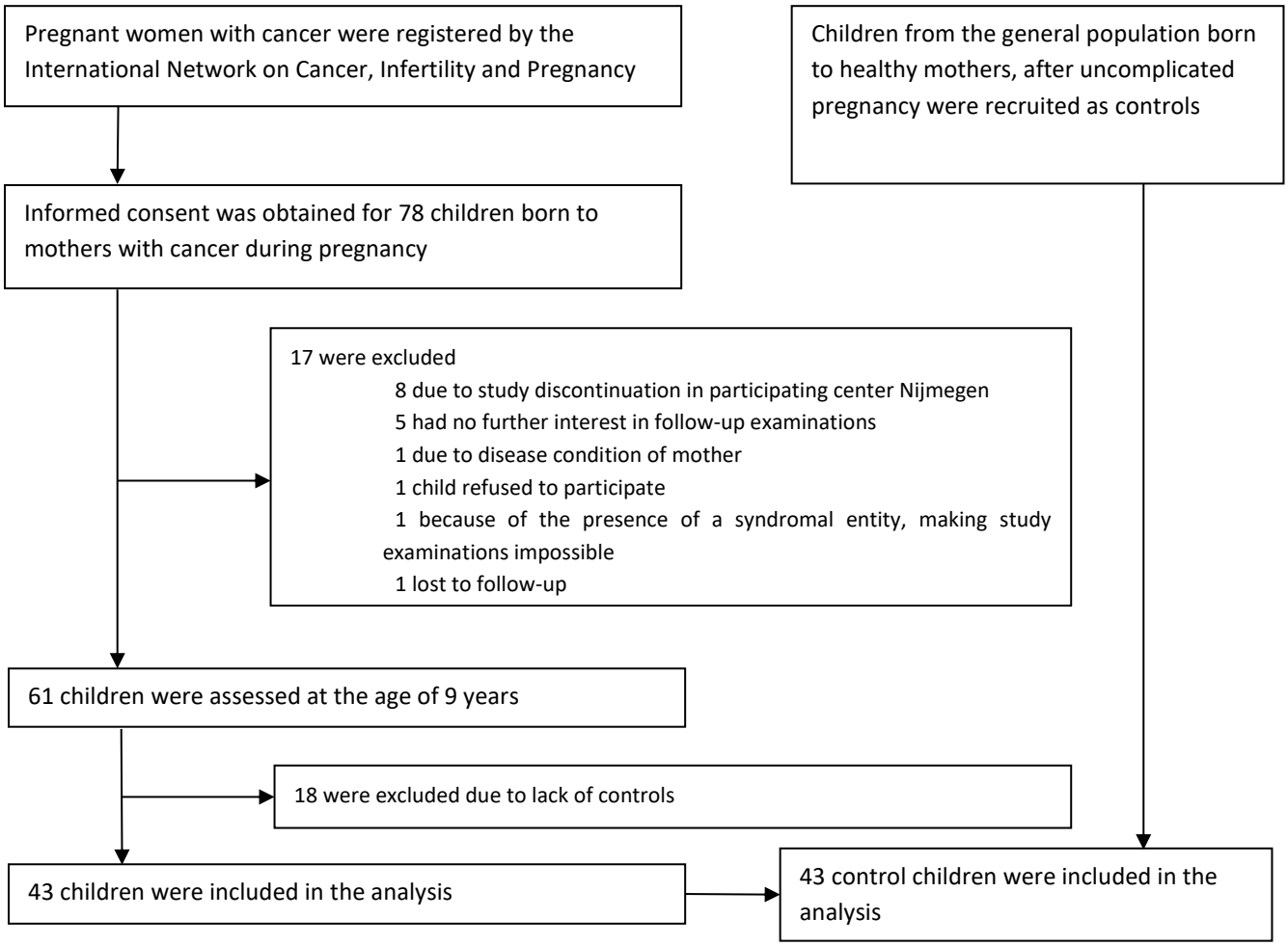
METHODS

Study participants

This is a multicenter cohort study by the International Network on Cancer, Infertility and Pregnancy (INCIP), in which children born after a pregnancy complicated by maternal cancer and its treatment are followed from birth until the age of 18 years (study group). Children are invited for follow-up

examinations at the ages of 1.5, 3, 6, 9, 12, 15 and 18 years. In this study, the outcome of 9-year-old children is cross-sectionally compared to the outcome of children born after an uncomplicated pregnancy (control group). Children were identified and enrolled prospectively (during pregnancy) or retrospectively (between birth and 9 years) and all children were prospectively examined at 3 national referral centers in Belgium and the Netherlands. Children from the control group were one-to-one matched to the study group for age, gestational age at birth, gender, country and language of the tests. Figure 1 summarizes the study design and recruitment and more information on the recruitment and exclusion criteria is provided in the Methods section in the Supplementary Appendix. The study was approved by the ethical committee of each center and written informed consent of the parents was obtained for each child to participate. The study is registered as ClinicalTrials.gov, NCT00330447.

Figure 1. Study design and recruitment



Note: This cohort of 43 children evaluated at the age of 9 years includes 36 children who underwent cognitive evaluation in our 6 years cohort study. The results of 5 children at the age of 9 years were previously published,[11] whereas 38 children underwent new testing.

Study testing and outcomes

For each mother-child pair, we collected oncological, obstetrical and neonatal data through the INCIP registry. Cognitive development was evaluated using a comprehensive neuropsychological test battery, consisting of intelligence, attention and memory tests and a parent-report behavior questionnaire. Intelligence was assessed using the Wechsler Intelligence Scale for Children (WISC), third edition[204] (in 92.9% of children), fourth[205] (in 4.8%) or fifth edition[40] (in 2.4%). The same intelligence test was used for each pair of matched study and control children. Full Scale Intelligence Quotient (IQ) was chosen as the primary outcome of this study, as this measure gives an indication of the global cognitive capacities of the child. Verbal IQ, Performance IQ and Processing Speed were considered as secondary outcomes. The mean of the different tests is set at 100 and scores between 90 and 110 are considered average, according to the manuals provided by the tests. Higher scores indicate better performance. Memory was assessed using the Auditory Verbal Learning Test (AVLT)[207] and subtasks of the Children's Memory Scale (CMS)[194]. Secondary outcomes included verbal and visuospatial memory span, verbal and visuospatial short- and long-term memory, verbal working memory and short- and long-term memory for faces. Higher scores indicate more advanced memory skills. Verbal proactive interference (i.e., an adverse impact of previously learned material on the acquisition or recall of new information) and retroactive interference (i.e., an adverse impact of the acquisition of new material on the recall of previously learned material) were also evaluated. Attention was assessed using the Test of Everyday Attention for Children (TEA-Ch)[51] and subtasks of the Amsterdam Neuropsychological Tasks (ANT)[195]. Measures of sustained attention, selective attention, divided attention, attentional control and response inhibition were included as secondary outcomes. Higher reaction times and higher numbers of errors indicate worse performance on the subtasks. Behavior problems were evaluated using the parent-report form of the Child Behavior Checklist (CBCL)[176]. Secondary outcomes included internalizing problems, externalizing problems and total problem behaviors. Higher scores indicate more behavior problems. More information on the test protocol is provided in the Methods section in the Supplementary Appendix.

Statistical analysis

Maternal oncologic data and demographic characteristics of both groups (gender, child and maternal age, gestational age and weight at birth, ethnic background, parental education levels, use of reproductive medicine to achieve the pregnancy, smoking and alcohol use during pregnancy and bilingual education) were analyzed using descriptive statistics.

For the intelligence tests and the behavior questionnaires, raw scores were converted into standardized scores according to normative data for each country provided by the test. For the CMS memory test, raw total scores of each subtest were used as the outcome parameters. For the AVLT memory test, raw scores were obtained for each learning trial, the total number of words recalled and the number of words recalled during the immediate and delayed recall phase. More information on the calculation of the proactive and retroactive interference scores is available in the Methods section of the Supplementary Appendix. For the attention tests of the TEA-Ch, raw subtest scores or composite scores were calculated according to the test manual. For the ANT attention tests, raw reaction times and percentage of errors were used. Additionally, we calculated composite scores in order to obtain measures for the increase of memory load and distraction on reaction time and accuracy. Details on the calculation of these parameters are provided in the Methods section of the Supplementary Appendix.

Between-group differences in cognitive development were investigated using univariate analyses of covariance (ANCOVA) with parental education levels as covariates. The Spearman's rank-correlation coefficient was used to investigate the relationship between the cognitive outcome and gestational age, the number of chemotherapy cycles administered during pregnancy or the estimated fetal dose of radiation.

The alpha level for the primary outcome Full Scale IQ was set to 0.05. In order to correct for multiple testing, alpha was adjusted using Bonferroni's correction for the secondary cognitive outcomes. As 43 between-group comparisons were made, a two-sided P value of less than 0.001 (0.05/43) was considered to indicate statistical significance.

RESULTS

Treatment characteristics

A total of 43 children (including one pair of twins) born from pregnancies complicated by maternal cancer were included, of whom 36 from Belgium and 7 from the Netherlands. During pregnancy, 28 children (65.1%) were exposed to chemotherapy (alone or in combination with other treatments), 6 (14.0%) to radiotherapy (alone or in combination), 1 (2.3%) to trastuzumab, 5 (11.6%) to surgery alone and 5 children (11.6%) to no treatment (Table 1). In total, 94 chemotherapy cycles were administered to 27 pregnant women (including one woman carrying twins). Six mothers (14.3%) died before the child was 9 years old. More information about the maternal cancer types and specific treatments is provided in the Supplementary Appendix Tables S1-S4.

Table 1. Cancer treatment during pregnancy for all children and those categorized as small for gestational age

Cancer treatment	**All children (N=43)** Number (%)	**Small for gestational age (N=7)** Number (% of children with treatment)
Surgery	5 (11.6)	0 (0.0)
Chemotherapy	13 (30.2)*	5 (38.5)
Radiotherapy	1 (2.3)	0 (0.0)
Surgery and chemotherapy	13 (30.2)	1 (7.7)
Surgery and radiotherapy	3 (7.0)	1 (33.3)
Surgery, chemotherapy, and radiotherapy	2 (4.7)	0 (0.0)
Trastuzumab	1 (2.3)	0 (0.0)
No treatment	5 (11.6)	0 (0.0)

Note: *One pair of twins was exposed to chemotherapy alone.

Perinatal characteristics

For children in the study group, the median gestational age at birth was 35.6 weeks (range, 28.4-40.6) and the median birth weight was 2825g (range, 720-3905). Nineteen children (44.2%) were born at term (37.0 weeks gestational age or later), while 24 children (55.8%) were born preterm, of whom 3 (7.0%) very preterm (27.0-31.9 weeks), 7 (16.3%) moderately preterm (32.0-33.9 weeks) and 14 (32.6%) late preterm (34.0-36.9 weeks). The incidence of preterm birth in the general population was estimated at 8.0% in Belgium and 7.7% in the Netherlands in 2008.[186] Small for gestational age birth (i.e., a birth weight below the tenth percentile of gender and gestational age matched children) was observed in an equal number of children from the study and control group (7/43, 16.3%).

Demographic characteristics

The median age of the children at cognitive evaluation was 9.2 years (range, 8.8-10.8) in the study group and 9.4 years (range, 8.2-10.7) in the control group. Demographic characteristics of the study and control children were comparable with respect to maternal age, gestational age and weight at birth, gender and ethnic background (Table 2). Additionally, the use of reproductive medicine to achieve the pregnancy and smoking and alcohol use during pregnancy were comparable between the

groups (Supplementary Appendix Tables S5-S7). In the study group, 10 children (23.3%) were raised bilingual as opposed to none in the control group (Supplementary Appendix Table S8). The highest level of education was on average higher for parents of children from the control group compared to the study group (Table 2). In further analyses, maternal and paternal education levels were included as covariates.

Table 2. Demographic characteristics of the children

Characteristic	**Cancer in pregnancy group (N=43)**		**Control group (N=43)**	
Median age (range) - years	9.2 (8.8 – 10.8)		9.4 (8.2 – 10.7)	
Median gestational age (range) - weeks	35.6 (28.4 – 40.6)		36.0 (28.3 – 40.0)	
Median birth weight (range) - grams	2825 (720 – 3905)		2715 (940 – 4450)	
Median maternal age at birth of this child (range) - years	32 (21 – 45)		30 (26 – 38)	
Sex – number (%)				
Male	24 (55.8%)		24 (55.8%)	
Female	19 (44.2%)		19 (44.2%)	
Race – number (%)*				
White	40 (93.0%)		41 (95.3%)	
Other	3 (7.0%)		2 (4.7%)	
Highest level of education of parents – number (%)†	Mother	Father	Mother	Father
Primary school	2 (4.7%)	2 (4.7%)	0 (0.0%)	0 (0.0%)
Secondary school	21 (48.8%)	22 (51.2%)	8 (18.6%)	14 (32.6%)
Bachelor	8 (18.6%)	6 (14.0%)	17 (39.5%)	12 (27.9%)
Master's degree or higher	12 (27.9%)	11 (25.6%)	18 (41.9%)	17 (39.5%)
Unknown	0 (0.0%)	2 (4.7%)	0 (0.0%)	0 (0.0%)

Note: *Race was self-reported by the parents.

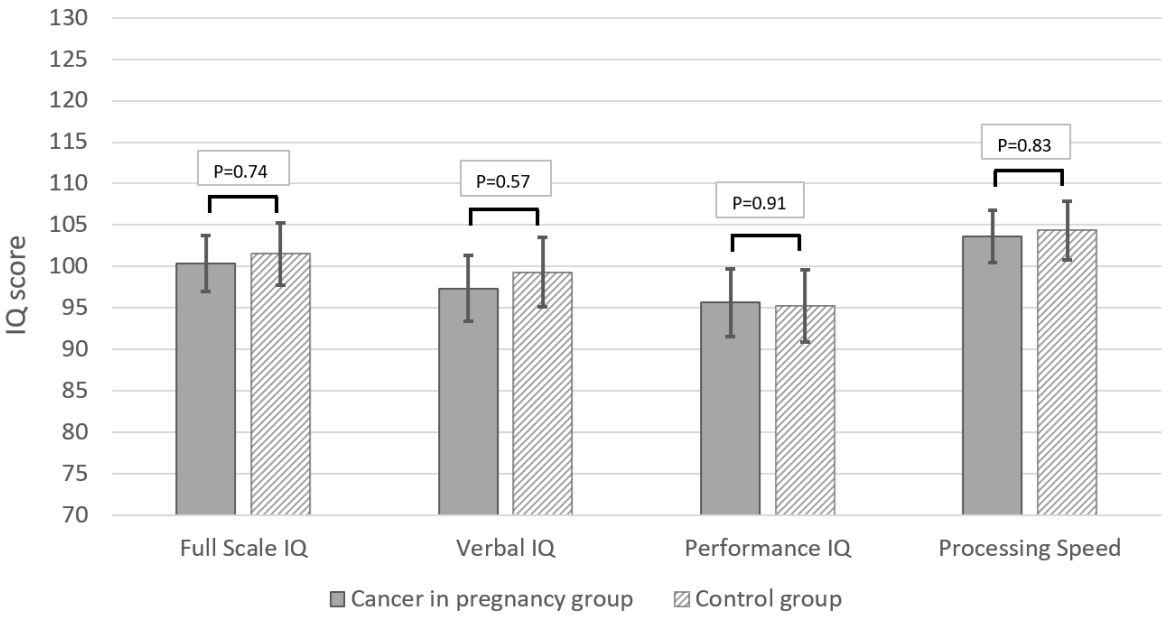
†The highest level of education is presented according to the European educational system. A bachelor's degree is earned at both traditional universities and nonuniversity institutions of higher education and requires between three and four years of full-time study. A master's degree is earned at university and requires one to two years of full-time study after a bachelor's degree.

Cognitive development

Intelligence

The primary outcome Full Scale IQ was not significantly different between the study group (M=100.4, 95% CI 93.6 to 107.2) and control group (M=101.5, 95% CI 94.0 to 109.0) (P=0.74) (Figure 2 and Supplementary Appendix Table S9). Gestational age at birth was moderately correlated to the Full Scale IQ score in the study group (r=0.36, P=0.02) and control group (r=0.30, P=0.05) (Figure 3). Full Scale IQ was not related to the number of chemotherapy cycles (r=0.28, P=0.17) (Figure 4) or to the estimated fetal dose of radiation (r=0.14, P=0.79) (Supplementary Appendix Figure S1). Considering the secondary outcomes, no significant between-group differences were found in Verbal IQ, Performance IQ or Processing Speed (Figure 2 and Supplementary Appendix Table S9).

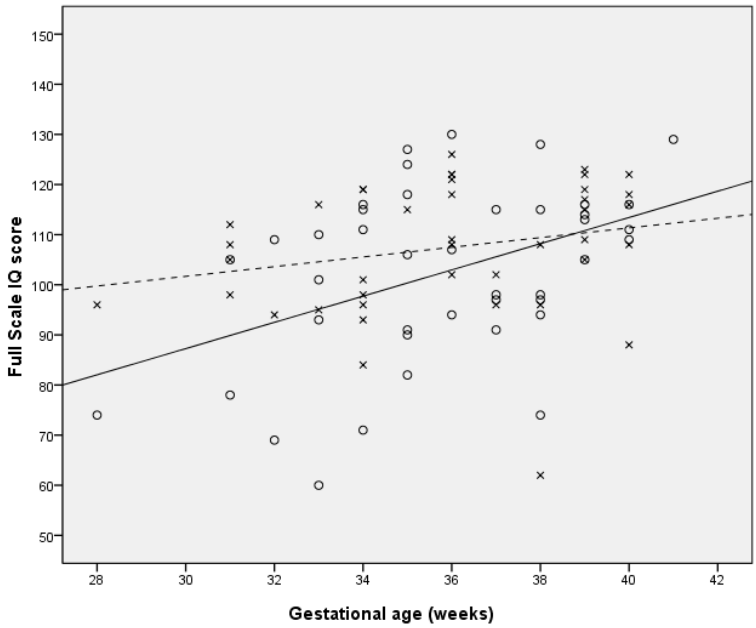
Figure 2. Comparison of the mean Full Scale IQ, Verbal IQ, Performance IQ and Processing Speed between the cancer in pregnancy group and the control group



Note: The figure shows estimated means with standard errors of the means for each group and variable. Raw P values are presented.

The mean of IQ-tests is set at 100 with a standard deviation of 15 and scores between 90 and 110 are considered average. Higher scores indicate more advanced development.

Figure 3. The relation between Full Scale IQ and gestational age at birth (in weeks) for the cancer in pregnancy and control group



Note: Values of children from the cancer in pregnancy group are represented by circles, those of children from the control group are represented by crosses. Mean values (as calculated by linear regression) are indicated by a solid line for the study group and a dashed line for the control group.

Figure 4. The relation between Full Scale IQ and the number of chemotherapy cycles administered during pregnancy

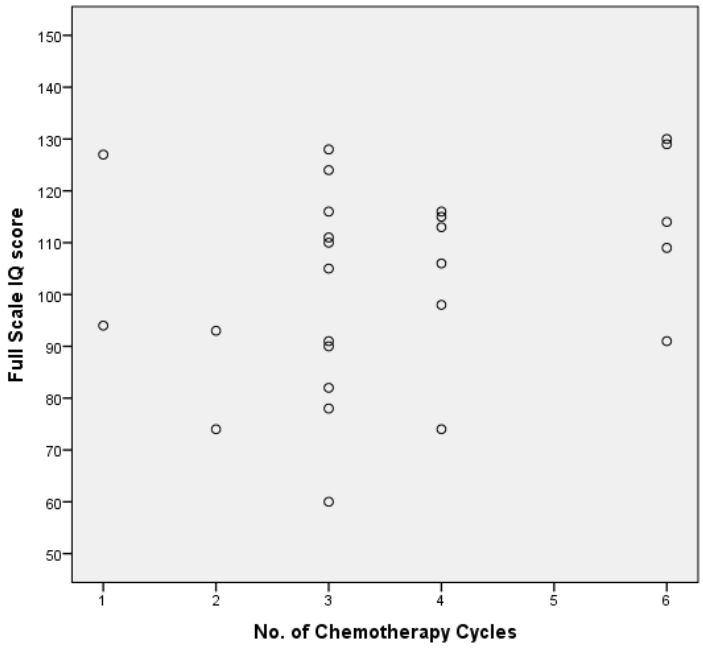
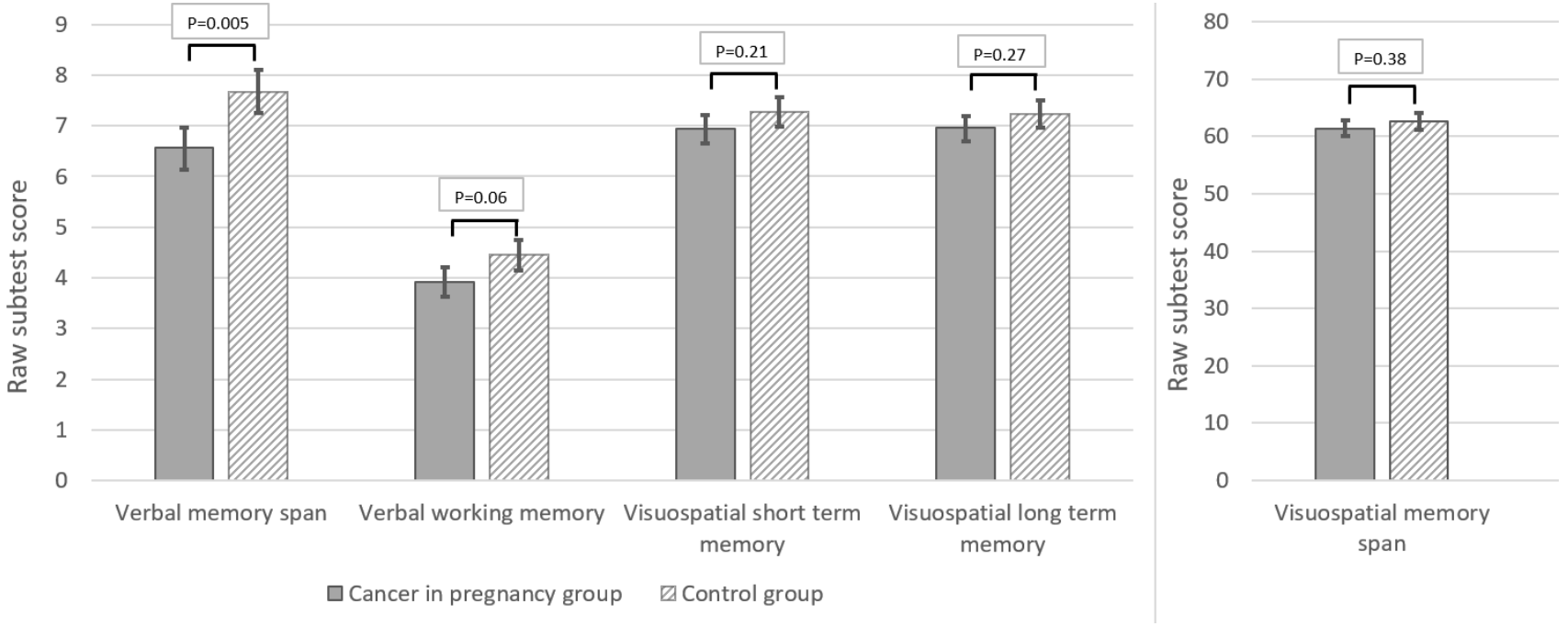


Figure 5. Comparison of the raw memory scores from the subtests of the Children's Memory Scale between the cancer in pregnancy group and the control group



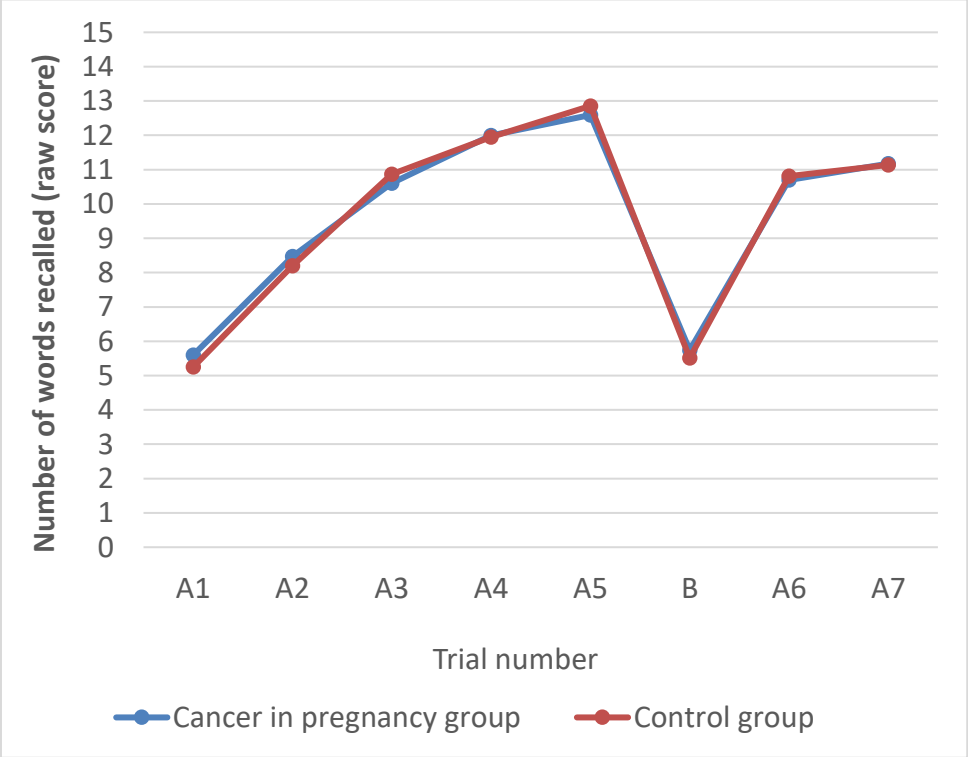
Note: The figure shows estimated marginal means with standard errors of the means for each group and variable. Raw P values are presented.

Verbal memory was measured using the subtest Numbers (range of scores between 0-14 for Numbers Forward (verbal memory span) and 0-12 for Numbers Backward (verbal working memory)). Visuospatial short- and long-term memory were measured using the subtest Dot Locations (range 0-8). Visuospatial memory span was measured using the subtest Picture Locations (range 0-72). Higher scores indicate more advanced memory skills.

Memory

On the subtests of the CMS, children from the study group scored slightly lower on verbal memory span and slightly higher on short-term memory for faces, compared to the control group, although not statistically significant after Bonferroni's correction. The raw scores of children from the study group were not significantly different to those of children from the control group for the measures of visuospatial memory span, verbal working memory, short- and long-term memory for visuospatial information and long-term memory for faces (Figure 5 and Supplementary Appendix Table S10). Additionally, no significant between-group differences were found on the AVLT with regard to the verbal memory span, the learning curve, the total number of words learned, short- and long-term verbal memory and scores for proactive and retroactive interference (Figure 6 and Supplementary Appendix Table S11).

Figure 6. Comparison of the raw memory scores on the Auditory Verbal Learning Test between the cancer in pregnancy group and the control group

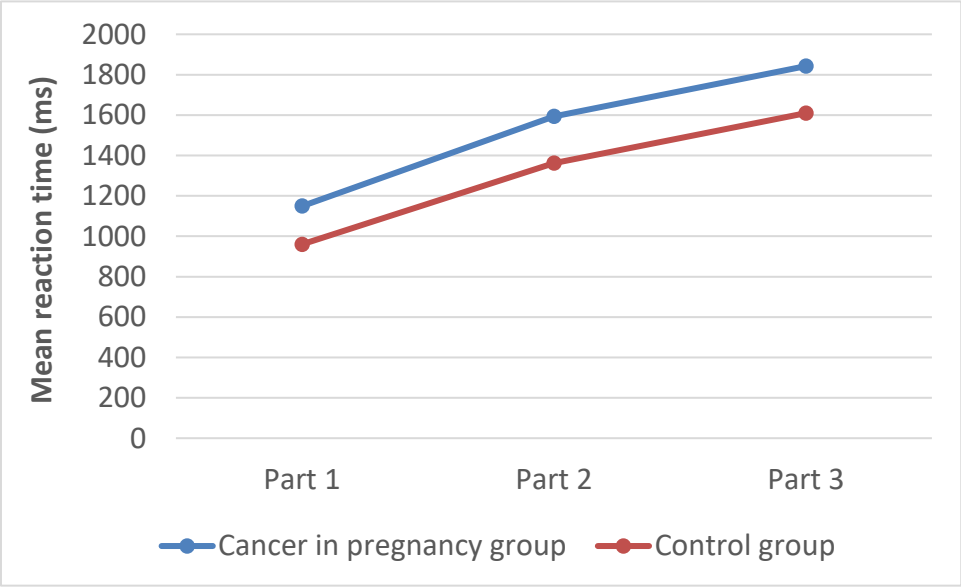


Note: A1 to A7 represent the number of words recalled during the learning trials (A1-A5), the immediate recall (A6) and the delayed recall (A7) phase of word list A. B represents the number of words recalled from the interference word list B. Estimated marginal means are presented.

Attention

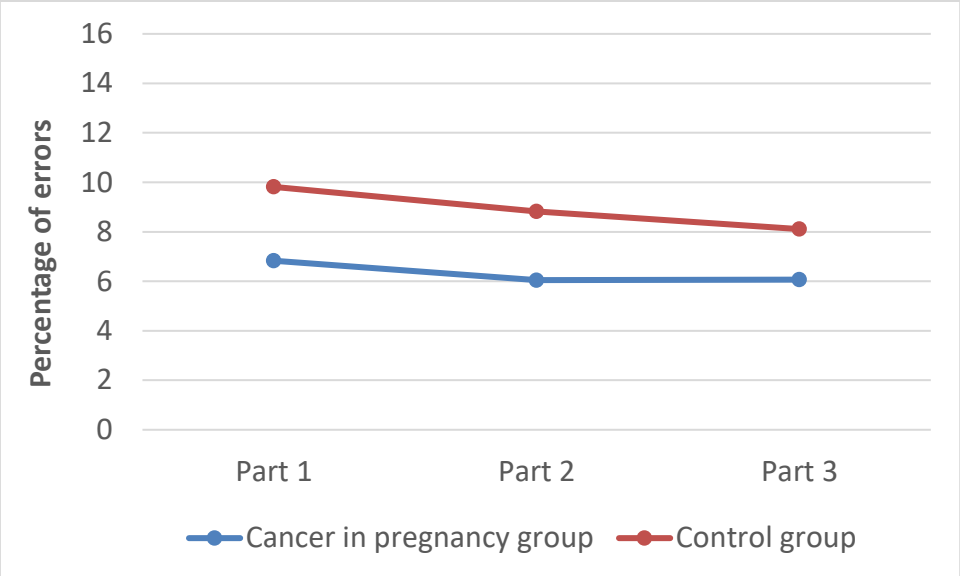
There were no significant between-group differences in the subtests from the TEA-Ch measuring selective attention, attentional control and sustained attention (Supplementary Appendix Table S12) or in the subtests from the ANT measuring alertness, response inhibition, divided attention, selective attention and attentional control (Supplementary Appendix Table S13). No significant between-group differences in accuracy on the tasks were found. However, children from the study group were marginally slower on the Creature Counting subtask of the TEA-Ch, measuring attentional control, and on the divided attention task Memory Search Letters and on the selective attention task Focused Attention 4 Letters of the ANT, although not statistically significant using Bonferroni correction. On the Memory Search Letters task, memory load increased the reaction time equally in both groups (Figure 7), but did not increase the number of errors (Figure 8). On the Focused Attention 4 Letters task, distraction due to irrelevant targets did not significantly increase the reaction time in both groups (compared to the reaction time for the correct rejection of non-targets) (Figure 9), but equally increased the number of errors in both groups (Figure 10).

Figure 7. Comparison of the mean reaction times (ms) on the Memory Search Letters task with increasing memory load from part 1 to part 3 between the cancer in pregnancy group and the control group



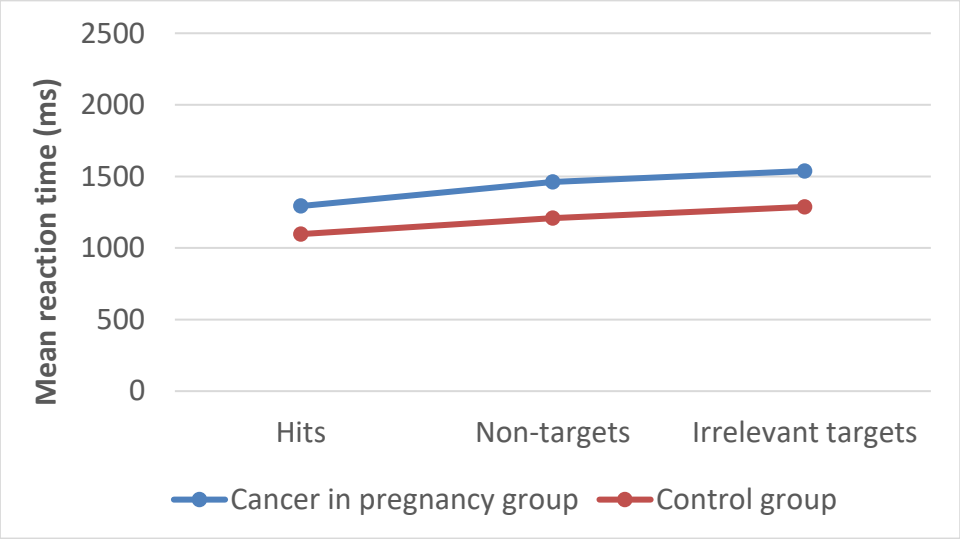
Note: The figure shows estimated marginal means of the overall reaction time of both groups in part 1, 2 and 3 of the subtask. Memory load is increased from 1 target letter in part 1 to 2 letters in part 2 and 3 letters in part 3.

Figure 8. Comparison of the percentage of errors on the Memory Search Letters task with increasing memory load from part 1 to part 3 between the cancer in pregnancy group and the control group



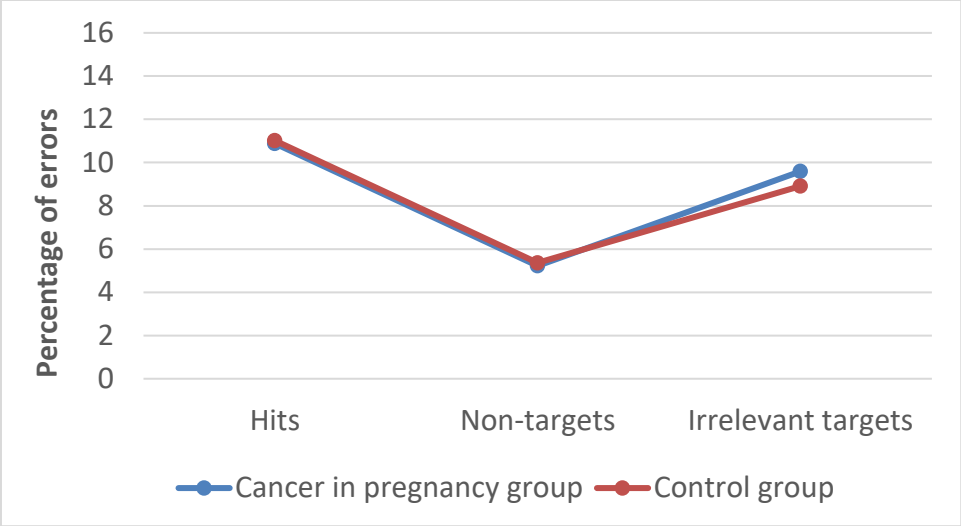
Note: The figure shows estimated marginal means of the percentage of errors of both groups in part 1, 2 and 3 of the subtask. Memory load is increased from 1 target letter in part 1 to 2 letters in part 2 and 3 letters in part 3.

Figure 9. Comparison of the mean reaction times (ms) on the Focused Attention 4 Letters task between the cancer in pregnancy group and the control group



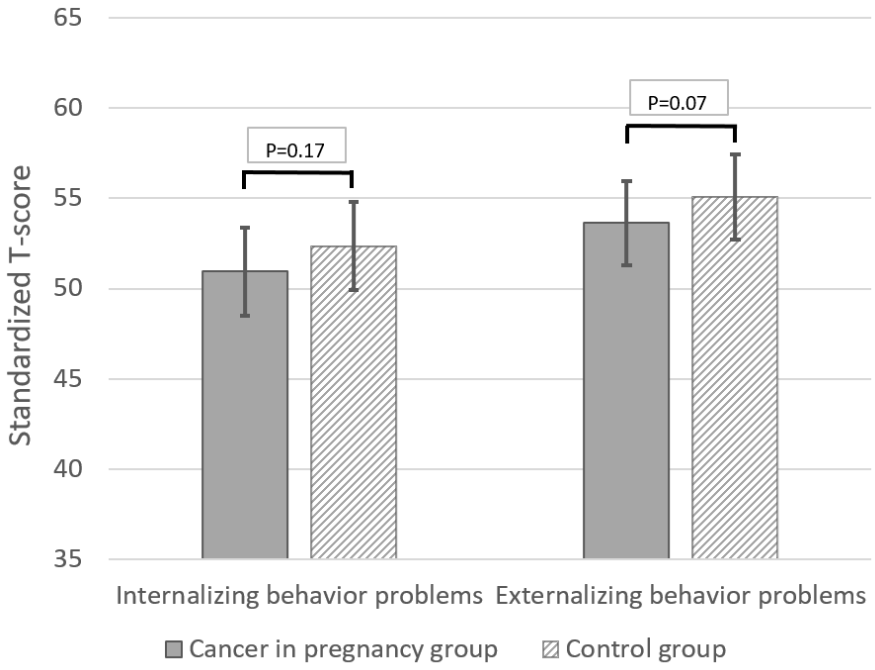
Note: The figure shows estimated marginal means of the averaged reaction time of part 1 and 2 for hits, correct rejection of non-targets and correct rejection of irrelevant targets for both groups.

Figure 10. Comparison of the percentage of errors on the Focused Attention 4 Letters task between the cancer in pregnancy group and the control group



Note: The figure shows estimated marginal means of the averaged percentage of errors of part 1 and 2 for both groups when hits, non-targets and irrelevant targets were presented.

Figure 11. Comparison of the standardized T-scores for internalizing and externalizing behavior problems on the Child Behavior Checklist between the cancer in pregnancy group and the control group



Note on the next page.

Note to Figure 11: The figure shows estimated marginal means with standard errors of the means for each group and variable. Raw P values are presented. The mean of standardized T-scores is 50 with a standard deviation of 15. Higher scores indicate more behavior problems.

Behavior problems

The standardized T-scores for internalizing, externalizing and total problems were not significantly different between the study and control group (Figure 11, Supplementary Appendix Table S14).

DISCUSSION

In this multicenter cohort study, we evaluated the cognitive outcome of 9-year-old children born from pregnancies complicated by maternal cancer and the associated stress, diagnostic imaging and treatments. The results were compared to those of children born after an uncomplicated pregnancy, who were one-to-one matched for age, gestational age at birth, gender, country and language of the tests to the study group. Overall, the cognitive development was reassuring as no significant differences were found between the study and control group.

Comparable to the 6 years cohort study described in the previous chapter, there were no significant between-group differences in Performance IQ, Processing Speed, different aspects of memory and attention and in the incidence of behavior problems. However, at the age of 6 years, we found a significant between-group difference in Full Scale IQ and Verbal IQ, which was not confirmed in the current interim analysis of 9-year-old children. Several factors may contribute to the difference between the two cohorts. First of all, different types and editions of intelligence tests were used, which are in general highly but not perfectly correlated to one another.[206] At the age of 6 years, most children were examined by means of the Wechsler Preschool and Primary Scale of Intelligence – third edition (WPPSI-III)[39], while at the age of 9 years, most children were examined by means of the Wechsler Intelligence Scale for Children – third edition (WISC-III). Differences exist in the subtests that compose the Full Scale IQ, Verbal IQ and Performance IQ factors in the different Wechsler tests. Moreover, correlational research between different types and editions of intelligence tests is usually executed at one time point, while the stability of intelligence is thought to increase with age during childhood.[208] During a test-retest interval of 3 years, differences in test results can be partly explained by instability of the subtests and IQ factors over time, but may also reflect real changes in cognitive abilities that take place.[209] Furthermore, although most of the study children included in the 9 years cohort were also included in the 6 years cohort, the groups of control children included in the two cohorts were totally different, which excludes the possibility of longitudinal comparisons between the groups.

As in our previous studies, more than half of the children (55.8%) were born preterm. Gestational age at birth was moderately correlated to Full Scale IQ in the study and control group, a finding that was also demonstrated in the 1.5 to 3 years cohort, but not in the 6 years cohort. Some of the aforementioned elements of discussion may also contribute to this discrepancy. A larger sample is needed to further investigate this relationship.

The study has some limitations. First, the study is based on an interim analysis on a small study sample, which may not be representative for the total group. Eighteen controls were still lacking at the time of analysis, especially matched controls for French-speaking and Dutch study children, and therefore these study children could not be included in the interim analysis. The study and control groups were also not balanced with respect to parental education levels and the number of children raised bilingual. Further recruitment of study and control children is still ongoing. Additionally, subgroup analyses according to treatment type and small for gestational age birth were regarded as not appropriate due to the small study sample, the large amount of outcome parameters and the heterogeneity of treatment combinations.

In conclusion, 9 years after prenatal exposure to maternal cancer and its treatment, children show normal cognitive development for their gestational age at birth. The results confirm previous research findings in younger age cohorts documenting reassuring cognitive outcomes and strengthen the evidence that oncological treatment in pregnancy for specific cancers and under well-defined circumstances may be possible without major cognitive developmental problems in the child.

SUPPLEMENTARY APPENDIX

1. Methods

1.1 Recruitment of study and control children

Between 2005 and 2018, women diagnosed with cancer during pregnancy and referred to one of the participating centers in Belgium (University Hospitals Leuven) and The Netherlands (VU University Medical Center and Academic Medical Center Amsterdam, University Medical Center Utrecht, Erasmus Medical Center Rotterdam, University Medical Center Groningen and Radboud University Medical Center Nijmegen) were prospectively (during pregnancy) or retrospectively (after delivery but before the child was 9 years old) invited to take part in the study. All children were prospectively examined at University Hospitals Leuven, VU Medical Center Amsterdam, Radboud University Medical Center Nijmegen or at home. Children who were not able to perform the age-specific cognitive tests due to severe intellectual disability were excluded. Parents signed the informed consent at the moment of inclusion. Denial of participation or drop-out were mainly due to the distance to the hospital, difficulties to reach the patient after moving out or death of the mother and fear of overload for the child due to the supplementary examinations. Participants were offered to do (part of) the neuropsychological assessment at home if the distance to the hospital was the main reason for drop-out.

Control children were recruited in Belgium and the Netherlands. Preterm born children were recruited through the screening of birth lists from the participating hospitals. Children born full term were recruited by distributing information letters in schools and by advertising on the webpage of the hospital. All parents who were willing to let their child participate in the study first filled out a questionnaire on general health and prenatal history, in order to check if they met the inclusion criteria. Exclusion was based on all pregnancy-related (e.g., hypertension, severe preeclampsia, gestational diabetes with medical treatment, liver problems, epilepsy …) or neonatal problems (e.g., admission to a neonatal ward because of infections, long-term need of oxygen, malformations, brain lesions …) that may impact on child development. Immediate postnatal oxygen administration (CPAP) was not considered an exclusion criterion. Parents whose child met all the inclusion criteria signed the informed consent consecutively. Reasons for denial of participation or drop-out were the same as for the study children.

1.2 Description of the neuropsychological assessment protocol

The neuropsychological assessment consisted of two parts: an intelligence test of about 1,5 to 2 hours and several attention and memory tests of about 2,5 to 3 hours altogether.

Part 1: intelligence test

The following intelligence tests were used in our study:
Wechsler Intelligence Scale for Children – third edition (WISC-III)[204] (N = 78)
Wechsler Intelligence Scale for Children – fourth edition (French version) (WISC-IV)[205] (N = 4)
Wechsler Intelligence Scale for Children – fifth edition (WISC-V)[40] (N=2)

Different intelligence tests were used due to several reasons:

1. Intelligence tests are regularly revised in order to provide test materials that are adapted to the daily life of today's children and in order to update the norms to correct for the Flynn effect (i.e., the increase of intelligence scores in many parts of the world over the 20th century). The long-term nature of our study therefore implies that tests are revised during the duration of the project.

2. The Wechsler intelligence tests are developed in the United States of America and further translated, adapted and validated in other countries and languages. This implies that certain editions or revisions are not (yet) available in all languages (Dutch versus French) and countries. As our study is a multicenter international study, the currently used edition of the Wechsler test is not always the same in all participating countries.

For WISC-III, Full Scale Intelligence Quotient (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ) and Processing Speed (PS) were calculated. For WISC-IV and WISC-V, only FSIQ and PS were used, as these tests do not provide scores for VIQ and PIQ.

All IQ-tests used in this study have a mean score of 100 with a standard deviation of 15. Higher scores indicate more advanced development. Scores between 90 and 110 are considered average.

Correlations between Wechsler intelligence tests and editions are high. For example, r=0.88 for Full Scale Intelligence (FSIQ) and r=0.82 for Processing Speed measured by means of the Dutch editions of WISC-V and WISC-III.[210]

Part 2: attention and memory tests

Five subtasks from the **Amsterdam Neuropsychological Tasks (ANT)**[195] were used to evaluate different aspects of attention. ANT is a computerized program which enables to measure not only the accuracy of responses but also the reaction times. Prior to each task, the subjects were given verbal instructions and were shown the stimulus material. Next, they received a practice trial before the test of each task.

1. 'Baseline Speed'

   This task assesses **alertness** by measuring simple reaction time to 32 visual stimuli expressed in milliseconds. Subjects have to press a key as soon as a rectangle appears on the screen. The interval between two stimuli is variable in order to induce uncertainty about the timing of the appearance of the next stimulus. Mean reaction time and standard deviation of the reaction time were obtained for the dominant and non-dominant hand.

2. 'GoNoGo'

   This task is a measure of **response inhibition** and inattention. A key has to be pressed when a 'go'-signal (a complete square) is presented. When a 'no-go'-signal (an incomplete square) is presented, this prepotent response has to be inhibited. We used a balanced design with 24 'go'-signals and 24 'no-go'-signals, randomly presented. Mean reaction time of the hits, number of missed targets and number of false alarms were obtained. Response inhibition was measured by the percentage of false alarms.

3. 'Memory Search Letters'

   This **divided attention** task measures **speed and accuracy of memory search processes**. Four letters are presented in a square. Subjects have to press the yes-key when all target letters from the memory set are present. When none or not all target letters are present, subjects have to press the no-key. The letters change positions in each trial. The task consists of 3 parts and memory load is increased with target set size rising from 1 letter in part 1 to 2 letters in part 2 and 3 letters in part 3. Divided attention is needed because all four stimuli are relevant and the subject has to divide the attention over the field of stimuli in order to search for letters from the target set. The reaction time for hits (RT hits) and for correct rejections (RT CR) were measured separately in part 1, 2 and 3. Distinction was made among correct rejection when no letters from the target set are presented (CR 0t), when 1 letter from the target set is presented (CR 1t, only in part 2 and 3) or when 2 letters from the target set are presented (CR 2t, only in part 3). The number and percentage of missed targets (P-MI) and of false alarms in case 0 (P-FA 0t), 1 (P-FA 1t, only in part 2 and 3) or 2 targets (P-FA 2t, only in part 3) are presented were also measured separately in part 1, 2 and 3. The total reaction time was calculated as $(\text{RT hits} + \text{RT CR 0t})_{\text{part1}} + (\text{RT hits} + \text{RT CR 0t} + \text{RT CR 1t})_{\text{part2}} + (\text{RT hits} + \text{RT CR 0t} +$

RT CR 1t + RT CR 2t)$_{part3}$. The total percentage of errors was calculated as [(P-MI + P-FA 0t)$_{part1}$ /2 + (P-MI + P-FA 0t + P-FA 1t)$_{part2}$ /3 + (P-MI + P-FA 0t + P-FA 1t + P-FA 2t)$_{part3}$ /4] /3. The speed and accuracy of memory search processes were measured by calculating the increase in reaction time and error rate during higher memory load. A new variable Load[RT] was constructed as an index of the memory search rate, by calculating mean RT part 3 – mean RT part 1 or (RT hits + RT CR 0t + RT CR 1t + RT CR 2t)$_{part3}$ /4 - (RT hits + RT CR 0t)$_{part1}$ /2. Similarly, a new variable Load[Acc] was constructed as an index of the effect of increasing memory load on accuracy, calculated as % errors part 3 – % errors part 1 or (P-MI + P-FA 0t + P-FA 1t + P-FA 2t)$_{part3}$ /4 - (P-MI + P-FA 0t)$_{part1}$ /2.

4. 'Focused Attention 4 Letters'

   This task is a measure of **selective attention**. Four letters are presented in a square, but attention has to be focused on only 2 letters (the one on the upper left and the one on the lower right location). These letters form the so-called relevant diagonal. The task consists of 2 parts and memory load is increased with target set size rising from 1 letter in part 1 to 3 letters in part 2. Subjects have to press the yes-key if at least one of the target letters (and not all, as was the case in Memory Search Letters) is presented at the relevant diagonal. A no-response is required if one of the target letters is presented at an irrelevant location or if there are no target letters presented. The reaction times for hits (RT hits), correct rejection of irrelevant targets (RT CR [irrelevant target]) and correct rejection of non-targets (RT CR [non-target]) were obtained, together with the number and percentage of missed targets (P-MI), false alarms on irrelevant targets (P-FA [irrelevant target]) and false alarms on non-targets (P-FA [non-target]) for both parts separately. Focused attention is studied by examining the reaction time to targets presented on the irrelevant diagonal, since an attention shift to these targets illustrates a disruption of focused attention. The size of the distraction effect on reaction time was calculated as ((RT CR [irrelevant target]$_{part\ 1}$ + RT CR [irrelevant target]$_{part\ 2}$) – (RT CR [non-target]$_{part\ 1}$ + RT CR [non-target]$_{part\ 2}$))/2. Higher numbers indicate a larger effect of distraction on reaction time. The size of the distraction effect on accuracy was measured as ((P-FA[irrelevant target]$_{part\ 1}$ + P-FA[irrelevant target]$_{part\ 2}$) – (P-FA[non-target]$_{part\ 1}$ + P-FA[non-target]$_{part\ 2}$))/2. Higher numbers indicate a larger effect of distraction on accuracy. The accuracy of task performance is measured as the percentage of total errors, calculated as ((2 x P-MI + P-FA [irrelevant target] + P-FA [non-target])$_{part1}$ + (2 x P-MI + P-FA [irrelevant target] + P-FA [non-target])$_{part2}$) /8. The total reaction time was calculated as (RT hits + RT CR [irrelevant target] + RT CR [non-target])$_{part\ 1}$ + (RT hits + RT CR [irrelevant target] + RT CR [non-target])$_{part\ 2}$ and gives an indication of overall processing speed.

5. 'Shifting Attentional Set – Visual'

   This task is a measure of **attentional control and flexibility**. The test consists of 3 parts, in which a horizontal bar is shown, consisting of 10 grey squares. In the first part, baseline speed and accuracy are measured. A green colored square moves across the bar in a random direction, either to the right or left. Participants are asked to respond in a spatially compatible way by pressing the button that corresponds to the direction in which the stimulus moved. The second part is a measure of inhibition of a prepotent response. A red colored square moves across the bar in a random direction. Participants are asked to respond in a spatially incompatible way by pressing the response button that corresponds opposite to the direction in which the stimulus moved. In the third part, attentional set shifting is measured. The color of the moving square alternates in a random fashion between green and red. Both the direction and color of the square are unpredictable. The color of the square simultaneously changes, as the square moves one position. When the square is green, a compatible response is required (as in part 1). When the square is red, an incompatible response is required (as in part 2). From part 3, the mean reaction time of the compatible and incompatible responses was obtained together with the total percentage of errors in the compatible and incompatible setting.

Additionally, the **Test of Everyday Attention for Children (TEA-Ch)**[51] was used to evaluate different aspects of attention.

Selective attention subtests

1. Sky Search

   In this subtest, children are given a laminated A3 sheet depicting rows of paired spacecraft. Four distinctive types of craft are presented, with most pairs being of mixed type. The children are instructed to try and find all of the target items, defined by a pair of identical craft, as quickly as possible. Twenty targets are distributed among 108 distractors. Termination of the task is self-determined with the child marking a box in the lower right corner when they have finished. Both speed and accuracy are emphasized. In order to control for differences that are attributable to motor speed rather than visual selection, the children complete a motor control version of the task. The A3 stimulus sheet is identical to that of the Sky Search test with the exception that all of the distractor items were removed. The task therefore consisted of circling all 20 target items as quickly as possible and then indicating completion. Time taken to completion and accuracy were recorded for each part of the test. A time-per-target score was calculated (time/targets found). Subtraction of the 'motor control' time-per-target from the

more attentionally demanding Sky Search time-per-item produces an 'attention score' that is relatively free from the influence of motor slowness or clumsiness. Higher scores indicate worse performance.

2. Map Mission

   In this subtest, the children are given a printed A3 laminated city map. Eighty targets (small restaurant knife-and-fork symbols) are randomly distributed across the map. Distracting symbols of a similar size (depicting supermarket trolleys, cups, and cars) are also present. The children are instructed to find and circle with a pen as many target symbols as possible within 1 minute. The raw score is the number of targets correctly marked. Higher scores indicate better performance.

Attentional control subtests

1. Creature Counting

   This subtest consists of 7 trials. In each trial, a number of 'creatures' are depicted in their burrow. Interspersed between the creatures are arrows either pointing up or down. The children are asked to begin counting the creatures from the top down but to use the arrows as a cue to switch the direction of their count. The accuracy of the response and the time to complete the trial are recorded. A timing score is calculated (seconds-per-switch) by dividing the time taken to complete correct items by the number of switches within those items. Higher scores indicate worse performance.

2. Opposite Worlds

   In this task, children are presented with a stimulus sheet showing a mixed, quasi-random array of the digits 1 and 2. In the 'Same World' condition, they are asked to read out the digits aloud as quickly as possible in the conventional manner. In the 'Opposite World' condition, they are asked to say the opposite for each digit ("one" for 2 and "two" for 1) as quickly as possible, inhibiting the prepotent verbal response. Four test pages are run in the order: Same World, Opposite World, Opposite World, Same World. The time taken to complete each condition is recorded. The raw score is the total time to complete the four trials. Higher scores indicate worse performance.

Sustained attention subtests

1. Score!

   In this subtest, 10 items are presented. In each item, between 9 and 15 identical tones are presented, separated by silent interstimulus intervals of variable duration. Children are asked to silently count the tones (without assistance from fingers) and to give the total at the end.

The raw score is the total number of correctly counted tones (ranging from 0 to 10). Higher scores indicate better performance.

2. Score DT

   This is a dual task consisting of 10 items. In each item, the child has to count the number of tones (as in the Score! subtest). In addition, meaningful, auditory speech in the form of news bulletins is simultaneously presented. Children are asked to keep a count of the tones whilst at the same time keeping 'an ear out' for the mention of an animal during the news broadcast. The raw score is the total number of correctly counted tones and the total number of correctly recognized animals (ranging from 0 to 20). Higher scores indicate better performance.

3. Sky Search DT

   In this dual task, children are asked to complete a parallel version of the Sky Search task, which differs only in the location of the targets. During the Sky Search task, they are asked to simultaneously and silently count the number of tones presented within each item of an auditory counting task (comparable to the Score! subtask), giving the total at the conclusion of each item. The test is ended when the child indicates completion of the visual search component. The time taken to find each visual target is calculated (total time / correctly identified targets) (a). Then, the proportion of the counting items with correct totals is calculated (total items correct / total items attempted) (b). Poor counting performance is then used to inflate the time-per-target scores by dividing (a) by (b). Finally, in order to assess the decrement from single task visual search performance, the raw time-per-target score from the Sky Search task is subtracted from this value. Higher scores indicate a higher decrement.

4. Walk Don't Walk

   In this subtest, children are given an A3 sheet showing 'paths' each made up of 14 squares. They are asked to listen to a tape that will play one sound (go tone) if the move to the next square should be made and another (no-go tone) if not. The go and no-go tones are identical for the first part, the no-go tone being marked by a concluding vocal exclamation ("D'oh!"). The task therefore requires children to listen to the entire sound before making their response. The go tones are presented in a regular, rhythmic fashion with the no-go tone occurring unpredictably within the sequence. The raw score is the total number of correct items (ranging from 0 to 20). Higher scores indicate better performance.

5. Code Transmission

   In this task, children are asked to monitor a stream of monotonous digits for the occurrence of a particular target sequence (e.g., 5 5) and then to report the digit that occurred immediately before. The target sequence is constant throughout the test. Following a practice sequence, 40 targets are presented over the 12 minutes of the test. The raw score is the total

number of correctly recognized target sequences (ranging from 0 to 40). Higher scores indicate better performance.

Four subtasks from the **Children's Memory Scale (CMS)**[194] were used to evaluate different aspects of memory.

1. 'Numbers'

   This task is a measure of the **verbal memory span** (repeating numbers forward) and **verbal working memory** (repeating numbers backward). Raw scores range from 0 to 16 (numbers forward) and from 0 to 14 (numbers backward), with higher scores indicating better performance.

2. 'Picture Locations'

   The **visuospatial memory span** is measured as the proportion of correctly recalled picture locations. The number of picture locations is gradually increased during the task, ranging from one to eight pictures. Raw scores range from 0 to 72, with higher scores indicating better performance.

3. 'Dot Locations'

   This task is a measure of **visuospatial learning, short- and long-term visuospatial memory**. Subjects have to learn and recall the location of 8 blue dots. Three learning trials are offered. Next, subjects have to learn and recall a new pattern with 8 red dots in one trial. Immediate recall is measured as the proportion of correctly recalled blue dot locations after the interference of the red dots. Delayed recall is measured after 20 minutes of attention tasks from the ANT and/or TEA-Ch. Raw scores range from 0 to 8 for both the immediate and delayed recall phase, with higher scores indicating better performance.

4. 'Faces'

   This task is a measure of **short- and long-term memory for faces**. In the learning phase, subjects are presented 16 target faces. Next, 48 target and non-target faces are presented in a random order and the subject has to decide whether the face is a target or a non-target. The proportion of correctly recalled faces is a measure of immediate recall. After 20 minutes of attention tasks of the ANT and/or TEA-Ch (delayed recall), subjects are shown another series of 48 target and non-target faces presented in a random order and the subject has to decide again whether the face is a target or a non-target. Raw scores range from 0 to 48 for both the immediate and delayed recall phase, with higher scores indicating better performance.

Additionally, the **Auditory Verbal Learning Test (AVLT)**[207] was used to evaluate verbal learning and memory. The test consists of 5 learning trials of the same word list A (trials A1-A5), consisting of 15 words, followed by an interference list B of 15 new words. In the next trial, the participant is asked to recall the first list again (A6, short-term memory). After a delay of about 20-25 minutes, participants are once more asked to recall the first list (A7, long-term memory) followed by a recognition task. The number of words recalled in the first trial (A1) is interpreted as a measure of the verbal memory span. The total number of words recalled over the first five trials reflects the individual's ability to accumulate words across repeated learning trials. Higher scores indicate better performance. Proactive interference occurs when previously learned material negatively affects the acquisition or recall of new information and is calculated as B/A1. Retroactive interference occurs when subsequent material negatively affects the recall of previously learned material and is calculated as A6/A5. Scores <1 indicate proactive or retroactive interference. The lower the score, the larger the interference effect.

Behavior questionnaire

The parents were asked to fill out a questionnaire on the incidence of **behavior problems** (**Child Behavior Checklist, CBCL**).[176] The items measure a range of emotional and behavioral problems on a three point Likert scale (0 = 'not true', 1 = 'somewhat or sometimes true', or 2 = 'very true or often true'). The questionnaire consists of two empirically derived broadband scales (internalizing and externalizing problems) and several subscales. The total score of all problems results in the overall scale 'total problems'. Raw scores are converted into standardized T-scores (mean 50, standard deviation 10), using computerized software provided by the developers of the questionnaire, which enables to control for gender, age and country.

2. Results

2.1 Maternal tumor types treated during pregnancy (42 mothers, 43 children) and the incidence of small for gestational age (SGA) children (Table S1)

Maternal malignancy	N mothers	% mothers	N mothers deceased	% mothers deceased	N SGA*	% SGA
Breast cancer	20	47.6	3	15.0	1	5.0
Hematological Malignancy	11	26.2	2	18.2	3	27.3
- Acute Lymphoid Leukemia	1	2.4	0	0.0	1	100.0
- Acute Myeloid Leukemia	4	9.5	0	0.0	1	25.0
- Chronic Myeloid Leukemia	1	2.4	1	100.0	0	0.0
- Hodgkin's Disease	3	7.1	0	0.0	1	33.3
- Non-Hodgkin's Disease	2	4.8	1	50.0	0	0.0
Cervical cancer	5 (1 twin pregnancy)	11.9	0	0.0	1	16.7
Ovarian cancer	1	2.4	0	0.0	1	100.0
Brain tumor	2	4.8	0	0.0	0	0.0
Oral cavity and oropharyngeal cavity cancer	1	2.4	0	0.0	0	0.0
Melanoma	1	2.4	0	0.0	0	0.0
Soft tissue sarcoma	1	2.4	1	100.0	1	100.0
TOTAL	42	100.0	6	14.3	7	16.3

2.2 Chemotherapy regimens applied during pregnancy in 27 women (including 1 twin pregnancy) (Table S2)

Chemotherapy scheme	N cycles	N patients	% patients	N SGA	% SGA	GA (median (range))
(F)AC†	42	12	44.4	1	8.3	26.3 (14.4-37.3)
FEC†	6	1	3.7	0	0.0	26.5 (19.0-34.0)
ABVD†	9	3	11.1	1	33.3	29.1 (15.4-35.3)
CHOP†	6	1	3.7	0	0.0	26.1 (18.7-33.7)
Cisplatin (± Epirubicin)†	12	3*	11.1	1	24.0	22.9 (17.3-27.3)
Paclitaxel-Cis/Carboplatin	4	1	3.7	1	100.0	27.6 (23.3-32.1)
Hovon 37	2	1	3.7	1	100.0	23.6 (21.0-26.3)
Temozolomide	4	1	3.7	0	0.0	27.9 (18.0-33.9)
Idarubicin-AraC†	5	2	7.4	1	50.0	20.4 (14.1-26.6)
CMF	4	2	7.4	0	0.0	30.9 (27.1-33.3)
TOTAL	94	27		6	21.4	

Abbreviations: SGA, small for gestational age; GA, gestational age; (F)AC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; Hovon 37, cycle 1 prednisolone, vincristine, daunorubicin, L-asparaginase, methotrexate, and cycle 2 cytarabine, mitoxantrone, intrathecal methotrexate; AraC, cytarabine; CMF, cyclophosphamide, methotrexate, 5-fluorouracil

† including anthracyclines; * including 1 twin-pregnancy

2.3 Overview of registered dosages received per drug (Table S3)

Anti-cancer agent	N patients*	Cumulative dosage (mg/m²): median (range)
Doxorubicin	13/16	180 (50-360)
Epirubicin	1/1	600
Daunorubicin	1/1	45
Idarubicin	2/2	30 (24-36)
Cyclophosphamide	12/16	1900 (600-4500)
5-Fluorouracil	6/8	1900 (600-3000)
Paclitaxel	1/1	2079
Cisplatin	3/3	210 (60-450)
Carboplatin	1/1	700
Vincristine	2/2	5 (1-9)
Bleomycine	3/3	50 (40-80)
Dacarbazine	3/3	1500 (800-3000)
Vinblastine	3/3	30 (24-48)
Cytarabine	3/3	200 (3-300)
Methotrexate	2/3	27.5 (15-40)
Temozolomide	1/1	3000

*Number of patients with registered dosages / Total number of patients receiving this type of anti-cancer agent.

2.4 Overview of radiation exposure in 6 patients and the gestational period of exposure (Table S4)

Patient	Cancer type	Radiation Field	GA (w)	Maternal Dose (Gy)	Estimated Fetal Dose (mGy)
1	NHL	Head	28	33	34
2	Brain	Head	16-19	54	42
3	AML	Left eye	20-22	20	15
4	Soft tissue liposarcoma (tigh)	Left tigh	19	50 (brachytherapy)	2.5
5	Tongue	Head and neck	27-34	66	46
6	Breast	Thoracic wall	15-21	50	247

Abbreviations: GA, gestational age; w, weeks; Gy, Gray; mGy, milliGray; NHL, Non-Hodgkin's disease; AML, acute myeloid leukemia

The dose program "Peridose" developed by van der Giessen was used to estimate the fetal radiation dose.[182]

2.5 Smoking during pregnancy for study and control children (Table S5)

	N of mothers smoked during pregnancy (%)	Median number of cigarettes per week (range)
Cancer in pregnancy group	4 (9.8 %)	15 (5-20)
Control group	1 (2.3 %)	7

Information on smoking during pregnancy was available for 41/43 study children and 43/43 control children.

2.6 Alcohol use during pregnancy for study and control children (Table S6)

	N of mothers drinking alcohol during pregnancy (%)	Reported number of consumptions during pregnancy
Cancer in pregnancy group	3 (7.5 %)	1-2 consumptions per week (N=3)
Control group	4 (9.5 %)	Less than one per month (N=2) Less than one per week (N=2)

Information on alcohol use during pregnancy was available for 40/43 study children and 42/43 control children.

2.7 Fertility treatment to achieve this pregnancy for study and control children (Table S7)

	N of mothers pregnant through fertility treatment (%)	Type of fertility treatment
Cancer in pregnancy group	5 (11.9 %)	Hormonal stimulation (N=3) IUI with donor sperm (N=1) ICSI (N=1)
Control group	7 (17.1 %) (including 1 twin pregnancy)	Hormonal stimulation (N=1) IUI (N=2) IVF (N=3) ICSI (N=1)

Information on the need of fertility treatment to achieve this pregnancy was available for 42/42 mothers of study children (including 1 twin pregnancy) and 41/41 mothers of control children (including 2 twin pregnancies).
Abbreviations: IUI = intra-uterine insemination, IVF = in vitro fertilization, ICSI = intracytoplasmatic sperm injection

2.8 Bilingual education from birth to 9 years for study and control children (Table S8)

	N of children raised bilingual
Cancer in pregnancy group	10 (23.3 %)
Control group	0 (0.0 %)

Children were considered to be raised bilingual if they were equally exposed to two languages at home or if at least half of the classes at school were taught in another language than the child's mother tongue.
Information on bilingual education was available for 43/43 study children and 43/43 control children.

2.9 Intelligence outcomes in children from the cancer in pregnancy group compared to matched controls using ANCOVA with parental education levels as covariates (Table S9)

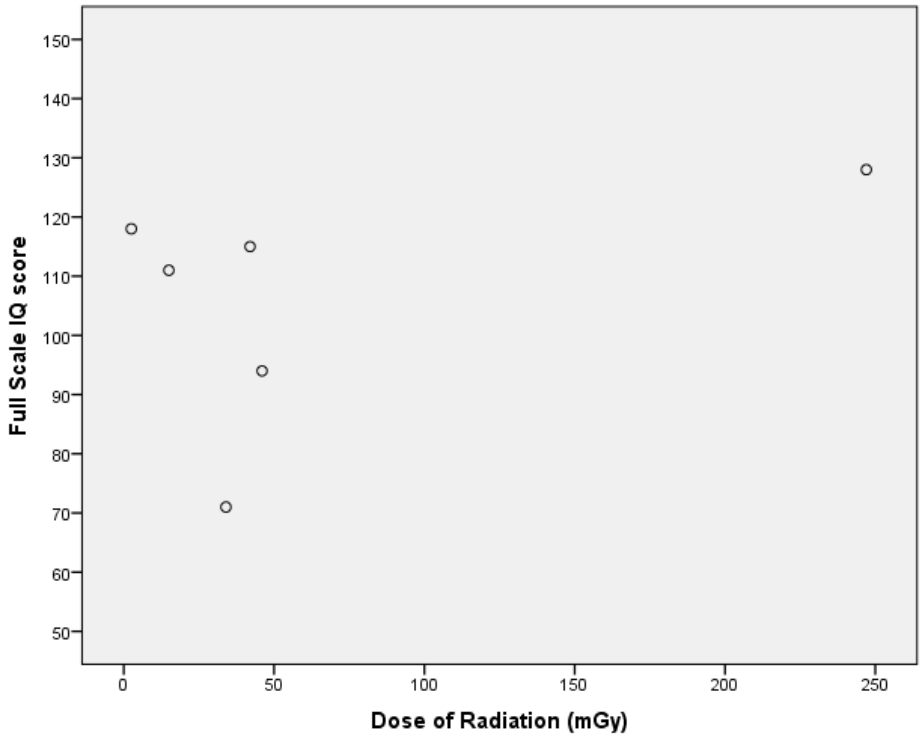
Measurement	No.	Cancer in pregnancy group (N=43)				Control group (N=43)				Type 3 test of fixed effects		
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
				Lower	Upper			Lower	Upper			
Full Scale IQ	82	**100.4**	3.4	93.6	107.2	**101.5**	3.8	94.0	109.0	0.11	0.74	0.002
Verbal IQ	76	**97.4**	4.0	89.5	105.2	**99.3**	4.2	90.9	107.7	0.32	0.57	0.005
Performance IQ	76	**95.7**	4.1	87.5	103.8	**95.2**	4.3	86.6	103.9	0.01	0.91	0.000
Processing Speed	79	**103.6**	3.2	97.3	110.0	**104.4**	3.5	97.3	111.4	0.05	0.83	0.001

Abbreviations: CI, confidence interval; S.E., standard error of the mean

Results are expressed as standardized IQ-scores (M=100, SD=15). Higher numbers indicate better performance.

Raw P values are presented.

2.10 Full Scale IQ in relation to the estimated fetal dose of radiation (expressed in milligrays) for 6 children exposed to radiotherapy during pregnancy (Figure S1)



2.11 Memory outcomes on the Children's Memory Scale (CMS) in children from the cancer in pregnancy group compared to matched controls using ANCOVA with parental education levels as covariates (Table S10)

CMS subtask	Measurement	Minimum to maximum raw score	No.	Cancer in pregnancy group (N=43)				Control group (N=43)				Type 3 test of fixed effects		
						95% CI				95% CI				
				Mean	S.E.	Lower	Upper	**Mean**	S.E.	Lower	Upper	F	P value	Partial eta squared
Numbers forward	Verbal memory span	0-16	83	**6.56**	0.39	5.79	7.34	**7.67**	0.43	6.82	8.53	8.23	0.005	0.099
Numbers backward	Verbal working memory	0-14	83	**3.93**	0.27	3.39	4.47	**4.45**	0.30	3.85	5.04	3.77	0.06	0.048
Picture Locations	Visuospatial memory span	0-72	83	**61.44**	1.30	58.85	64.03	**62.59**	1.43	59.74	65.45	0.80	0.38	0.010
Dot Locations	Visuospatial short-term memory	0-8	83	**6.95**	0.26	6.43	7.47	**7.28**	0.29	6.70	7.85	1.60	0.21	0.021
Dot Locations	Visuospatial long-term memory	0-8	83	**6.96**	0.25	6.47	7.44	**7.23**	0.27	6.69	7.77	1.26	0.27	0.017
Faces	Short-term memory for faces	0-48	83	**38.37**	0.91	36.56	40.19	**36.47**	1.00	34.47	38.47	4.47	0.04	0.056
Faces	Long-term memory for faces	0-48	83	**36.58**	1.02	34.55	38.61	**36.22**	1.12	33.98	38.45	0.13	0.72	0.002

Abbreviations: CI, confidence interval; S.E., standard error of the mean

Results are expressed as raw subtest scores. Higher numbers indicate better performance.

Raw P values are presented.

2.12 Memory outcomes on the Auditory Verbal Learning Test (AVLT) in children from the cancer in pregnancy group compared to matched controls using ANCOVA with parental education levels as covariates (Table S11)

Trial number or composite score	Measurement	No.	Cancer in pregnancy group (N=43)				Control group (N=43)				Type 3 test of fixed effects		
			Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
					Lower	Upper			Lower	Upper			
A1	Verbal memory span	83	**5.60**	0.35	4.90	6.30	**5.25**	0.39	4.47	6.02	1.00	0.32	0.013
A5	Number of words recalled at 5th (last) learning trial	82	**12.59**	0.67	11.26	13.93	**12.86**	0.74	11.38	14.34	0.15	0.70	0.002
Total number of words recalled (A1 to A5)	Total learning	83	**49.29**	2.33	44.65	53.93	**49.04**	2.57	43.92	54.16	0.01	0.91	0.000
A6	Short-term verbal memory	83	**10.70**	0.72	9.27	12.13	**10.81**	0.79	9.23	12.39	0.02	0.88	0.000
A7	Long-term verbal memory	83	**11.18**	0.69	9.81	12.54	**11.14**	0.76	9.63	12.65	0.002	0.96	0.000
B	Number of words recalled from interference word list	83	**5.74**	0.45	4.85	6.63	**5.51**	0.49	4.53	6.49	0.27	0.60	0.004
B/A1	Proactive interference	83	**1.08**	0.08	0.92	1.23	**1.11**	0.08	0.94	1.27	0.16	0.69	0.002
A6/A5	Retroactive interference	82	**0.85**	0.04	0.76	0.94	**0.85**	0.05	0.76	0.95	0.003	0.96	0.000

Abbreviations: CI, confidence interval; S.E., standard error of the mean. Raw P values are presented.

Results of trials A1 to A7 and B are expressed as raw scores ranging from 0 to 15. Total number of words recalled is the sum of trials A1 to A5 with scores ranging from 0 to 75. Higher numbers indicate better performance.

Proactive interference is calculated as B/A1. Retroactive interference is calculated as A6/A5. Scores range from 0 to 15. Scores <1 indicate proactive or retroactive interference. The lower the score, the larger the interference effect.

2.13 Attention outcomes on the Test of Everyday Attention for Children (TEA-Ch) in children from the cancer in pregnancy group compared to matched controls using ANCOVA with parental education levels as covariates (Table S12)

Measurement	No.	Cancer in pregnancy group (N=43)				Control group (N=43)				Type 3 test of fixed effects		
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
				Lower	Upper			Lower	Upper			
Selective attention												
Sky Search – attention score	83	**5.10**	0.35	4.40	5.80	**5.24**	0.39	4.47	6.02	0.17	0.68	0.002
Map Mission - accuracy	83	**23.07**	1.92	19.25	26.89	**21.68**	2.11	17.45	25.88	0.54	0.47	0.007
Attentional control												
Creature Counting – speed (s)	83	**4.88**	0.38	4.12	5.64	**4.10**	0.42	3.27	4.94	4.28	0.04	0.054
Opposite Worlds – speed (s)	83	**58.24**	2.38	53.50	62.97	**54.05**	2.62	48.83	59.27	3.18	0.08	0.041
Sustained attention												
Score! - accuracy	83	**7.42**	0.40	6.63	8.21	**8.04**	0.44	7.17	8.91	2.50	0.12	0.032
Sky Search DT - Dual task decrement	82	**4.77**	1.77	1.24	8.30	**3.08**	1.95	-0.80	6.96	0.92	0.34	0.012
Score! DT - accuracy	83	**14.10**	0.68	12.75	15.44	**15.24**	0.75	13.75	16.72	2.90	0.09	0.037
Walk Don't Walk - accuracy	82	**14.82**	0.82	13.19	16.46	**13.74**	0.91	11.93	15.55	1.76	0.19	0.023
Code Transmission - accuracy	83	**28.48**	1.29	25.91	31.05	**30.12**	1.42	27.29	32.95	1.64	0.20	0.021

Abbreviations: CI, confidence interval; S.E., standard error of the mean

The results are structured using the three-factor structure of Manly.[211]

Results on accuracy are expressed as raw scores. Higher scores indicate better performance.

Results on speed are expressed in seconds (s). Higher scores indicate worse performance.

Sky Search – attention score and Sky Search DT – Dual task decrement are composite scores, calculated according to the TEA-Ch manual. Higher scores indicate worse performance.

Raw P values are presented.

2.14 Attention outcomes on the Amsterdam Neuropsychological Tasks (ANT) in children from the cancer in pregnancy group compared to matched controls using ANCOVA with parental education levels as covariates (Table S13)

ANT subtask	Measurement	No.	Cancer in pregnancy group (N=43)				Control group (N=43)				Type 3 test of fixed effects		
			Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
					Lower	Upper			Lower	Upper			
Baseline Speed	**Alertness**												
	Mean RT of dominant and non-dominant hand (ms)	83	**383.7**	16.1	351.7	415.7	**381.9**	17.8	346.5	417.4	0.01	0.91	0.000
Go-NoGo	**Response inhibition**												
	RT hits (ms)	83	**555.8**	21.5	512.9	598.7	**544.5**	23.8	497.0	592.0	0.28	0.60	0.004
	Number of false alarms (%)	83	**6.8**	2.0	2.8	10.7	**5.5**	2.2	1.1	9.8	0.43	0.51	0.006
Memory Search Letters	**Divided attention**												
	Total RT (ms)	82	**14431**	780	12876	15986	**12499**	869	10767	14230	5.99	0.02	0.075
	Total number of errors (%)	83	**6.3**	2.4	1.4	11.2	**8.9**	2.7	3.5	14.3	1.1	0.29	0.015
	Effect of memory load on RT (ms)	82	**698.2**	79.7	539.4	857.0	**636.2**	88.8	459.3	813.0	0.59	0.44	0.008
	Effect of memory load on accuracy	83	**-0.76**	1.42	-3.59	2.07	**-1.71**	1.58	-4.84	1.43	0.44	0.51	0.006
Focused Attention 4 Letters	**Selective attention**												
	Total RT (ms)	81	**8587**	480	7631	9543	**7183**	533	6121	8244	8.40	0.005	0.103
	Total number of errors (%)	83	**9.1**	3.4	2.4	15.9	**9.1**	3.7	1.6	16.5	0.000	0.99	0.000
	Effect of distraction on RT (ms)	81	**76.8**	39.5	-1.9	155.5	**75.2**	43.9	-12.2	162.6	0.002	0.97	0.000
	Effect of distraction on accuracy	83	**4.37**	2.61	-0.84	9.58	**3.56**	2.89	-2.21	9.32	0.10	0.76	0.001
Shifting Attentional Set - Visual	**Attentional control and flexibility**												
	Mean RT part 3 (ms)	82	**1309**	89	1131	1486	**1283**	99	1087	1480	0.08	0.78	0.001
	Total number of errors part 3 (%)	82	**24.0**	3.9	16.2	31.9	**22.5**	4.4	13.8	31.2	0.15	0.70	0.002

Abbreviations: CI, confidence interval; CR, correct rejections; FA, false alarms; P, percentage; RT, reaction time; S.E., standard error of the mean

Results are expressed as raw subtest scores. Reaction times are expressed in milliseconds (ms), while numbers of errors are expressed in percentages. Higher scores indicate worse performance. Raw P values are presented.

The effect of memory load on reaction time is calculated as mean RT part 3 – mean RT part 1. Higher numbers indicate a larger effect of memory load on reaction time.

The effect of memory load on accuracy is calculated as % errors part 3 - % errors part 1. Higher numbers indicate a larger effect of memory load on accuracy.

The effect of distraction on reaction time is calculated as ((RT CR [irrelevant target] part 1 + RT CR [irrelevant target] part 2) – (RT CR [non-target] part 1 + RT CR [non-target] part 2))/2. Higher numbers indicate a larger effect of distraction on reaction time.

The effect of distraction on accuracy is calculated as ((P-FA[irrelevant target] part 1 + P-FA[irrelevant target] part 2) – (P-FA[non-target] part 1 + P-FA[non-target] part 2))/2. Higher numbers indicate a larger effect of distraction on accuracy.

2.15 Behavior problems in children from the cancer in pregnancy group compared to matched controls using ANCOVA with parental education levels as covariates (Table S14)

Measurement	No.	Cancer in pregnancy group (N=43)				Control group (N=43)				Type 3 test of fixed effects		
		Mean	S.E.	95% CI		**Mean**	S.E.	95% CI		F	P value	Partial eta squared
				Lower	Upper			Lower	Upper			
Internalizing problems	82	**52.7**	2.2	48.3	57.0	**55.6**	2.4	50.8	60.5	1.89	0.17	0.025
Externalizing problems	82	**50.6**	2.1	45.9	55.2	**54.7**	2.6	49.6	59.8	3.3	0.07	0.043
Total problems	82	**52.7**	2.2	48.3	57.1	**56.0**	2.4	51.2	60.8	2.3	0.13	0.030

Abbreviations: CI, confidence interval; S.E., standard error of the mean

Results are expressed as standardized T-scores (M=50, SD=15).

Higher scores indicate more behavior problems.

Raw P values are presented.

PART 2

The impact of a cancer diagnosis and treatment during pregnancy on the couple's distress and coping

Chapter 6

Psychological distress and cognitive coping in pregnant women diagnosed with cancer and their partners

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A slightly modified version of this manuscript has been published:

Vandenbroucke, T., Han, S. N., Van Calsteren, K., Wilderjans, T. F., Van den Bergh, B. R. H., Claes, L., & Amant, F. (2017). Psychological distress and cognitive coping in pregnant women diagnosed with cancer and their partners. *Psycho-Oncology, 26,* 1215-1221. DOI: 10.1002/pon.4301

ABSTRACT

Objective

A cancer diagnosis during pregnancy may be considered as an emotional challenge for pregnant women and their partners. We aimed to identify women and partners at risk for high levels of distress based on their coping profile.

Methods

Sixty-one pregnant women diagnosed with cancer and their partners filled out the Cognitive Emotion Regulation Questionnaire (CERQ) and the newly constructed Cancer and Pregnancy Questionnaire. K-means cluster analysis was performed on the CERQ-scales. Scores on the Cancer and Pregnancy Questionnaire were compared between the women and their partners and between the CERQ-clusters.

Results

Comparison of women and partners on the Cancer and Pregnancy Questionnaire did not reveal significant differences on distress about the child's health, the cancer disease, and the pregnancy or on information satisfaction (P=0.16, P=0.44, P=0.50, P=0.47 respectively). However, women were more inclined to maintain the pregnancy than their partners (P=0.011). Three clusters were retrieved based on the CERQ scales characterized by positive coping, internalizing coping and blaming. Women and partners using internalizing strategies had significantly higher scores on concerns about the child's health (P=0.039), the disease and treatment (P<0.001), and the pregnancy and delivery (P=0.009) compared to positive and blaming strategies. No cluster differences were found for information satisfaction (P=0.71) and tendency to maintain the pregnancy (P=0.35).

Conclusion

Women and partners using internalizing coping strategies deal with the highest levels of distress and may benefit from additional psychosocial support.

INTRODUCTION

One in 1000 pregnant women is diagnosed with cancer during her pregnancy. Until recently, patients were often advised to terminate their pregnancy due to a lack of knowledge of physicians about the possibilities of cancer treatment during pregnancy. Since the last decade, several studies have indicated that chemotherapy may be administered during the second and third trimester of pregnancy,[212] while radiotherapy with lead shielding is possible in the first and second trimester.[181] Surgery can be performed in all stages of pregnancy. The survival appears not to be different between pregnant and non-pregnant women with cancer.[3] Moreover, evidence is accumulating that prenatal exposure to cancer and the associated imaging, surgery, chemo- and/or radiotherapy does not impair the general health, cognitive and cardiac outcome of the children.[11,14,35]

Pregnancy and the transition to parenthood are major life events in a woman's life, which may be associated with heightened levels of emotions.[213] When cancer is diagnosed during pregnancy, the experience of joy of being pregnant and becoming a mother may become intertwined with fear for one's own life and that of the baby. In a study based on self-reports of 74 pregnant women with cancer, 20.9 to 51.5% reported clinically significant levels of distress,[214] compared to 2.3 to 33.3% in healthy pregnant women,[215] and 20 to 40% in non-pregnant breast cancer patients.[216] Although different measures of distress were used, the results indicate that a cancer diagnosis may be considered as an additional emotional challenge for pregnant women.

Anxiety and stress during pregnancy have been associated with adverse birth outcomes (e.g., spontaneous abortion, preterm labor, growth restriction) and cognitive, behavioral and emotional problems in the child.[97,108] Therefore, it is important to have a better understanding of how pregnant women cope with their cancer diagnosis and treatment and the associated emotions and concerns.

Cognitive processes are a way to regulate our emotions and to help us not to become overwhelmed by them during or after a threatening or stressful life event. Garnefski et al. identified nine cognitive emotion regulation or coping strategies, which people use to a higher or lower extent when confronted with a stressor.[217] The first strategy, *self-blame,* refers to thoughts of putting the blame for what you have experienced on yourself, while *blaming others* includes thoughts of putting the blame on the environment or another person. *Focus on thought* or *rumination* means thinking about the feelings and thoughts associated with the negative event. *Catastrophizing* refers to thoughts of explicitly emphasizing the terror of what you have experienced, while *putting into perspective* has to do with thoughts of brushing aside the seriousness of the event or emphasizing the relativity when comparing it to other events. *Acceptance* includes thoughts of accepting what you have experienced and resigning yourself to what has happened. *Positive reappraisal* has to do with attaching a positive meaning to the

event in terms of personal growth. Thinking about joyful and pleasant issues instead of thinking about the actual event has been labeled as *positive refocusing*. Last, *refocus on planning* refers to thinking about what steps to take and how to handle the negative event. Several studies have indicated that cognitive processes may affect the emotional response during and after the experience of a stressful life-event.[218-221] The strategies of acceptance, putting into perspective, positive refocusing, positive reappraisal and refocus on planning have been associated with fewer depressive and anxiety symptoms and are therefore referred to as 'more adaptive' in the literature.[217,218] The strategies of rumination, self-blame, blaming others and catastrophizing have been related to more symptoms of anxiety and depression and are considered as 'less adaptive'.[217,218] Wang et al. investigated the relationship between the use of cognitive emotion regulation strategies and depressive symptoms in 509 newly diagnosed breast cancer patients.[221] Greater acceptance, positive refocusing and positive reappraisal shortly after diagnosis were related to fewer depressive symptoms one month later. Li et al. studied quality of life in 665 newly diagnosed breast cancer patients and found that the frequent use of adaptive versus maladaptive strategies was related to a better versus worse perceived quality of life.[222]

To date, there is a lack of knowledge about the concerns pregnant women diagnosed with cancer and their partners experience, how they deal with these concerns and who is at risk for high levels of distress. Therefore, we formulated the following research questions:

(1) Do pregnant women diagnosed with cancer and their partners experience similar or different concerns and distress levels?
(2) How do pregnant women diagnosed with cancer and their partners cope with their cancer diagnosis and treatment?
(3) Is the way in which pregnant women and their partners cope with their cancer diagnosis and treatment related to their level of distress?

The aims of the present study are threefold: (1) to compare the distress and concerns of the women and their partners, (2) to investigate whether there are subtypes of women and partners using similar cognitive coping strategies when confronted with cancer during pregnancy and (3) to investigate the relationship between these subtypes of women and partners based on their coping strategies and their level of distress and concerns. We hypothesize that partners may experience concerns and distress that is comparable to that of the patients themselves, as the partners are expecting parents confronted with their wife's life-threatening disease and treatment that may possibly be harmful for their unborn child. According to the literature, we hypothesize to find two clusters of cognitive coping strategies: one cluster including more adaptive or positive strategies (acceptance, positive refocusing, positive reappraisal, refocus on planning, putting into perspective) and a second cluster including less adaptive

or negative strategies (self-blame, rumination, catastrophizing, blaming others).[217] We hypothesize that the use of less adaptive coping strategies is related to higher levels of distress and concerns.

METHODS

Participants

Given the rarity of a cancer diagnosis during pregnancy, participants were retrospectively (after delivery) and prospectively (before delivery) recruited from the European cancer in pregnancy registry, organized by the International Network on Cancer, Infertility and Pregnancy (INCIP). Women and their partners from Belgium and The Netherlands were invited to participate in the study.

Procedure

Women identified retrospectively were contacted by their physician in order to explain the study. After agreement, the questionnaires and informed consents were sent to them. In the prospective part, newly diagnosed women and their partners were asked to take part in the study once decisions on treatment were taken.

Instruments

Cancer and Pregnancy Questionnaire

A retrospective questionnaire, consisting of 87 items, and a prospective questionnaire, consisting of 75 items, were developed in Dutch by Prof. dr. Frédéric Amant and Prof. dr. Bea Van den Bergh. The questionnaires were designed to specifically address concerns and issues related to cancer during pregnancy. Twenty-five of these items are part of the Pregnancy Related Anxiety Questionnaire (PRAQ), developed and validated by Prof. dr. Bea Van den Bergh.[223] The other items were constructed based on our own experience with pregnant cancer patients. As cancer during pregnancy is a rare phenomenon, the sample size was too small as compared to the number of items of the questionnaires to perform exploratory factor analysis. The items in common between the retrospective and the prospective questionnaire were thematically organized into subscales. This resulted in six subscales. A reliability analysis on the subscales was performed and the items that resulted in the highest reliability for each subscale were selected. One subscale with items on concerns about the partner was left out because the reliability was too low. In the final questionnaire, five subscales with a total of 40 items were retained (provided in the Supplementary Appendix): concerns about the child's health (16 items,

α=0.95), concerns about the cancer disease and treatment (8 items, α=0.70), concerns about the pregnancy and delivery (6 items, α=0.75), satisfaction with the information and care of the medical team (6 items, α=0.86), and tendency to maintain the pregnancy (4 items, α=0.62). The participants indicated how well the statements corresponded to their thoughts on a 7-point Likert scale, ranging from 1 [not at all] to 7 [very well].

Cognitive Emotion Regulation Questionnaire (CERQ)

The Cognitive Emotion Regulation Questionnaire (provided in the Supplementary Appendix) was developed by Garnefski et al. to measure cognitive emotion regulation strategies that characterize the individual's style of responding to stressful events.[217] We asked the participants to indicate how they think/thought about the cancer diagnosis and treatment during pregnancy. The questionnaire consists of nine subscales with a total of 36 items to be rated on a 5-point Likert scale, ranging from 1 [(almost) never] to 5 [(almost) always]. A shorter 27-item version with three items per subscale was used to prevent patients from overload, with acceptable internal consistency in our sample (α's ranging from 0.62 to 0.83).

Data analysis

To identify subtypes of women and partners who used similar coping strategies to deal with cancer during pregnancy, we performed a K-means cluster analysis on the 122 participants (i.e., 61 women and their partner) using the 9 CERQ-scales. We explored values of K (i.e., the number of clusters) going from 1 up to 8 and used a scree plot to determine the optimal number of clusters. Prior to the analysis, data were transformed into z-scores in order to facilitate the interpretation of the clustering. Differences in scores on the Cancer and Pregnancy Questionnaire between women and their partners and between coping clusters were examined using MANOVA. Retrospective vs. prospective participation and parity (nulliparous vs. multiparous) were explored as possible covariates, but not included in the analysis because of low correlations (ranging from -0.23 to 0.22) with the subscales of the Cancer and Pregnancy Questionnaire. Pearson correlations were used to determine the relationship between stage at diagnosis / prognosis and the subscales of the Cancer and Pregnancy Questionnaire. Only breast cancer patients were included because this is the largest and most homogeneous group and because of the lack of comparability between the stages and the ways of determining the prognosis of the different cancer types.

RESULTS

Patient characteristics

Sixty-one women and their partners were included, 43 (70.5%) retrospectively and 18 (29.5%) prospectively. Retrospective participants filled out the questionnaires at a median of 3.1 years after delivery (range, 0.2-38.0 years). Thirty-four women (55.7%) already had one or more children when diagnosed with cancer during pregnancy (multiparous women), while 27 women (44.2%) were pregnant with their first child (nulliparous women). Median age at cancer diagnosis was 32 years (range, 22-42) and median gestational age was 16 weeks (range, 1-36). Cancer types and treatment modalities are summarized in Table 1.

Retrospective participants scored significantly higher than prospective participants on concerns about the child's health (P=0.015), but not on concerns about the disease and treatment (P=0.83), concerns about the pregnancy and delivery (P=0.38), satisfaction with the information and care of the medical team (P=0.11) or tendency to maintain the pregnancy (P=0.67). Nulliparous parents were more concerned about the pregnancy and delivery (P=0.037) and less satisfied with the information and care of the medical team (P=0.013) compared to multiparous parents, but no significant differences were found for concerns about the child's health (P=0.79), concerns about the disease and treatment (P=0.54) or tendency to maintain the pregnancy (P=0.56). We combined the groups to obtain an adequate sample size in further analyses.

Comparison of women's and partner's levels of distress

Subscale differences between women and their partners on the Cancer and Pregnancy Questionnaire are presented in Figure 1. Women were more inclined to maintain the pregnancy than their partners (P=0.011). However, the strength of concerns about the child's health, about the disease and treatment and about the pregnancy and delivery were not significantly different between women and their partners (P=0.16, P=0.44, P=0.50, respectively). Women and partners were equally satisfied with the information and care provided by the medical team (P=0.47).

Note to Table 1:

[a] The 5-year overall survival prognosis of breast cancer patients was calculated with the predict tool (www.predict.nhs.uk) developed by the Cambridge Breast Unit at the University of Cambridge and the Eastern Cancer Information and Registration Center.

[b] The 5-year overall survival prognosis of women with cervical or ovarian cancer was determined according to the FIGO staging.[224,225]

The prognosis of women with hematological malignancies, tongue cancer, ewing sarcoma or a recurrence during pregnancy was not determined, due to a lack of articles giving information on the 5-year overall survival or because some parameters were missing to provide a reliable prognosis.

Table 1. Cancer types and treatment modalities

	N	%		N	%	
Cancer type			**Stage at diagnosis during pregnancy**			**Median 5 year survival prognosis in % (range)**
Breast cancer	38	62.30				90.60 (61.40-97.70)[a]
			1	8	21.05	94.45 (90.60-97.10)[a]
			2	17	44.74	90.20 (78.20-97.70)[a]
			3	10	26.32	80.85 (61.40-97.70)[a]
			recurrence	3	7.89	-
Hematological malignancies	13	21.31				
Hodgkin lymphoma	5	0.08				
Non-Hodgkin lymphoma	3	4.92				
Acute myeloid leukemia	3	4.92				
Acute lymphoblastic leukemia	2	3.28				
Cervical cancer	4	6.56				89.10[b]
			1	4	100.00	-
Ovarian cancer	3	4.92				89.60 (46.70-89.60)[b]
			1	2	66.67	-
			3	1	33.33	-
Tongue cancer	1	1.64				
Ewing sarcoma	1	1.64				
Gastrointestinal stromal tumor	1	1.64	recurrence			
Treatment during pregnancy						
Surgery only	5	8.20				
Chemotherapy only	17	27.87				
Radiotherapy only	2	3.28				
Surgery + chemotherapy	27	44.26				
Surgery + radiotherapy	2	3.28				
Surgery + chemotherapy + radiotherapy	4	6.56				
No treatment during pregnancy	3	4.92				
Herceptin	1	0.02				

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Figure 1. Differences in distress/concerns, information satisfaction and tendency to maintain the pregnancy (Cancer and Pregnancy Questionnaire) between women and their partners

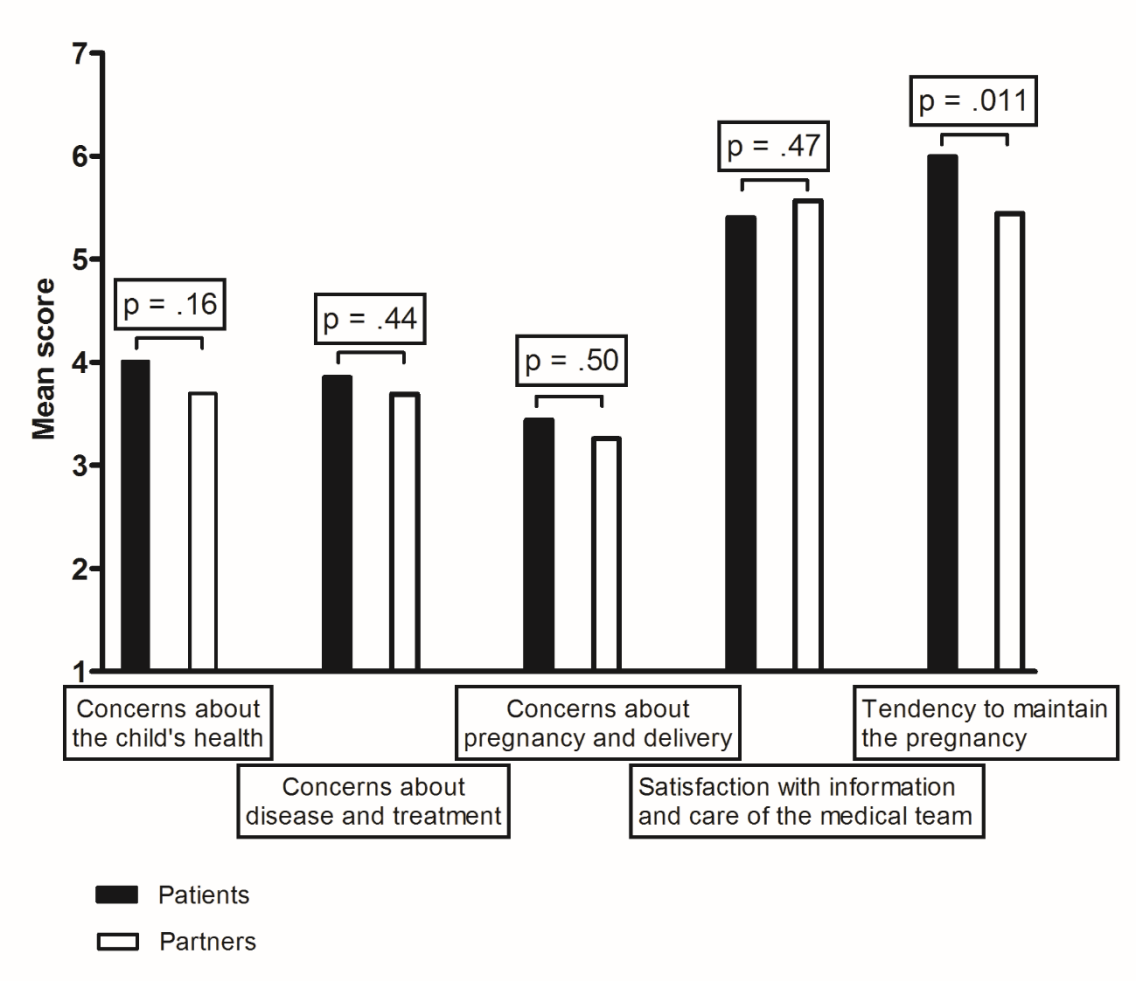
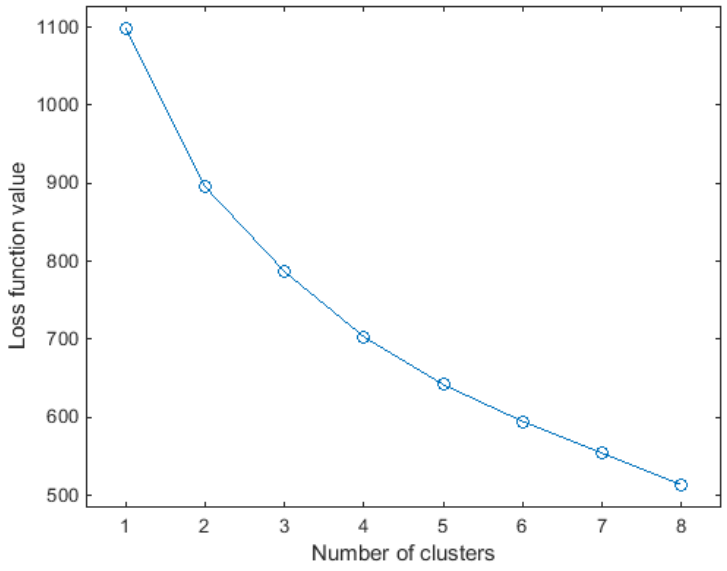


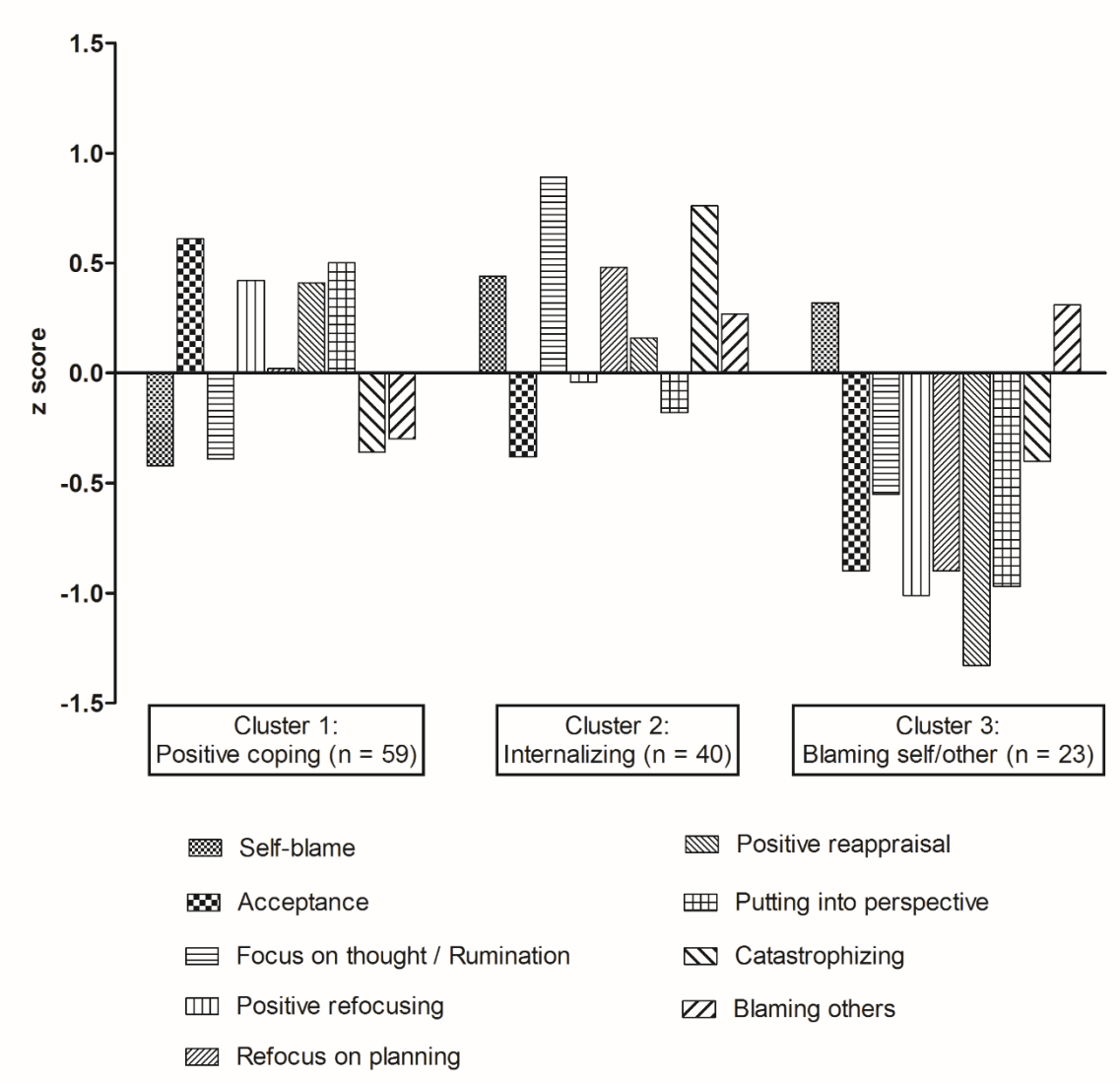
Figure 2. Scree plot (number of clusters against mis–fit value) for the K-means analysis based on the CERQ-scales



Clusters of cognitive emotion regulation strategies

When looking at a scree plot of the number of clusters against the (mis)fit-value of each solution (Figure 2), the clearest elbow appears at the solution with two clusters and a less pronounced elbow is encountered for the three- and four-cluster solution. The solution with four clusters was not used because it contains a very small cluster (N=3) and therefore cannot be considered as stable. The three-cluster solution (Figure 3) was chosen because it is a refinement of the solution with two clusters (i.e., one cluster is split into two separate clusters) that makes more sense from a substantive point of view.

Figure 3. Three-cluster solution based on the CERQ-scales for women (N=61) and their partners (N=61)



Note: positive and negative z-values are shown to present relative differences between the clusters. Positive z-values indicate that participants in this cluster use these strategies more than participants in the other clusters. Negative z-values indicate that participants in this cluster use these strategies less than participants in the other clusters.

The first cluster of women and partners is characterized by positive z-scores on the CERQ-subscales acceptance, putting into perspective, positive refocusing and positive reappraisal, and negative z-scores on self-blame, rumination, catastrophizing and blaming others (N=59, 48.3%). We labeled this cluster as positive coping. The second cluster includes women and partners with positive z-scores on rumination, catastrophizing, refocus on planning, self- and other-blame and positive reappraisal, and negative z-scores on acceptance and positive refocusing (N=40, 32.8%). We labeled it as the internalizing coping cluster. The third cluster is characterized by positive z-scores on self- and other-blame, and negative z-scores on all other strategies (N= 23, 18.9%). We labeled this cluster as blaming self/other. Retrospective and prospective cases were equally distributed in the clusters (P=0.20), as well as women and partners (P=0.37), and nulliparous and multiparous parents (P=0.15) (Tables 2-4).

Table 2. Distribution of the prospective and retrospective cases in the three-cluster solution

	Cluster 1: positive coping	**Cluster 2: internalizing coping**	**Cluster 3: blaming self/other**	**Total**
Prospective	13 (36.1%)	14 (38.9%)	9 (25.0%)	36 (100.0%)
Retrospective	46 (53.5%)	26 (30.2%)	14 (16.3%)	86 (100.0%)
Total	59	40	23	122

Table 3. Distribution of the patients and partners in the three-cluster solution

	Cluster 1: positive coping	**Cluster 2: internalizing coping**	**Cluster 3: blaming self/other**	**Total**
Patients	33 (54.1%)	19 (31.1%)	9 (14.8%)	61 (100.0%)
Partners	26 (42.6%)	21 (34.4%)	14 (23.0%)	61 (100.0%)
Total	59	40	23	122

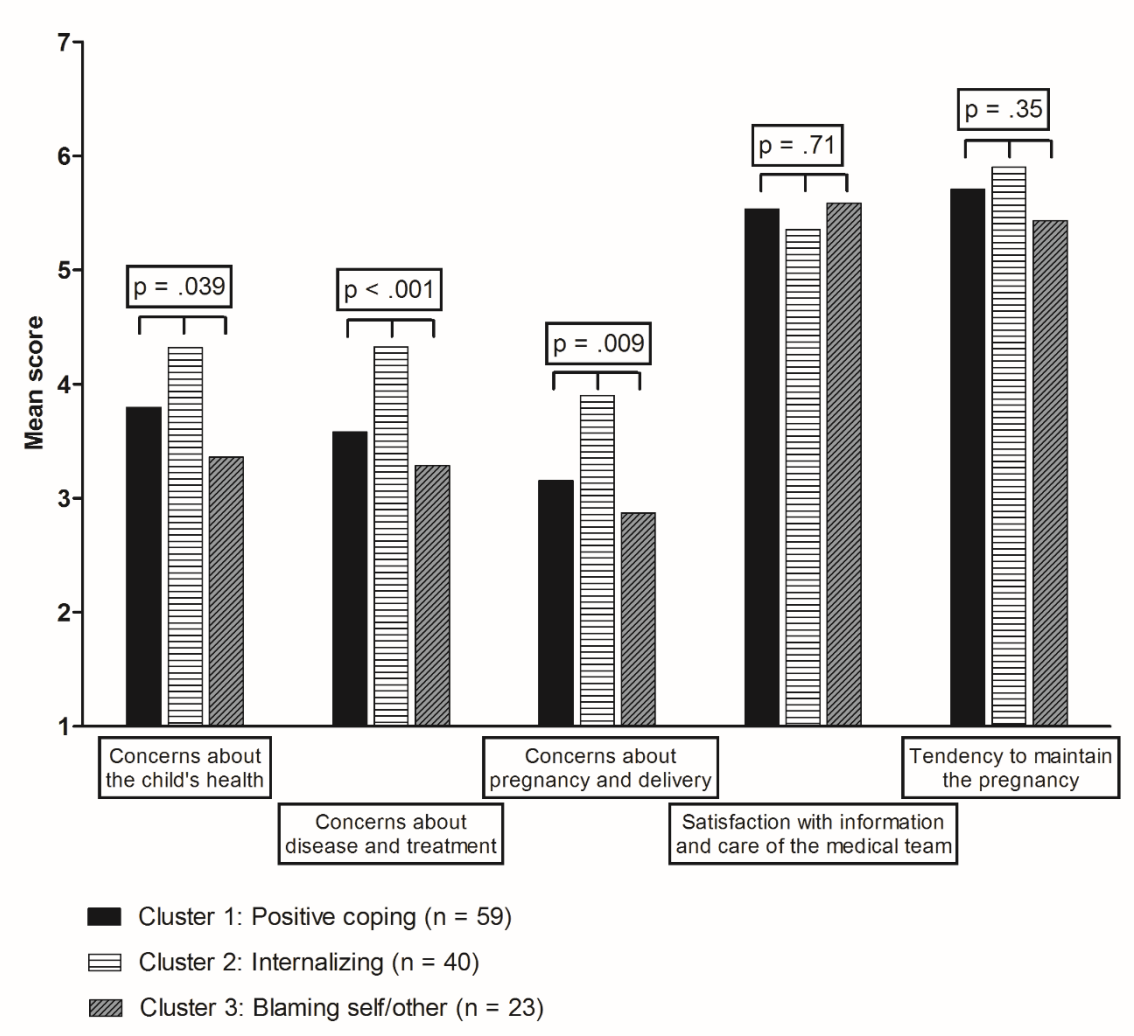
Table 4. Distribution of the nulliparous and multiparous parents in the three-cluster solution

	Cluster 1: positive coping	**Cluster 2: internalizing coping**	**Cluster 3: blaming self/other**	**Total**
Nulliparous	21 (38.9%)	22 (40.7%)	11 (20.4%)	54 (100.0%)
Multiparous	38 (55.9%)	18 (26.5%)	12 (17.6%)	68 (100.0%)
Total	59	40	23	122

Cluster differences in distress

Significant differences in distress levels were found between the three clusters (Figure 4). Women and partners mainly using internalizing coping strategies (cluster 2) had significantly higher levels of concerns than those using positive coping strategies (cluster 1) or those who blame themselves and others for what happened (cluster 3). This was true for concerns about the child's health (P=0.039), concerns about the disease and treatment (P<0.001) and concerns about the pregnancy and delivery (P=0.009). No cluster differences were found for information satisfaction (P=0.71) or tendency to maintain the pregnancy (P=0.35).

Figure 4. Differences in distress/concerns, information satisfaction and tendency to maintain the pregnancy (Cancer and Pregnancy Questionnaire) between CERQ-clusters



Distress and coping in relation to disease characteristics

A subgroup analysis of women with breast cancer showed that a higher stage of disease at diagnosis was related to more concerns about the disease and treatment (P=0.05), but not about the child's health (P=0.71) or about the pregnancy and delivery (P=0.54). This relationship was not found for the partners (P=0.11, P=0.82, P=0.67 respectively). However, the higher the stage at diagnosis, the more partners were inclined to maintain the pregnancy (P=0.042). This was not true for the women (P=0.47). No relationship was found between stage at diagnosis and information satisfaction for both women and partners (P=0.43, P=0.16 respectively). Moreover, the 5-year overall survival prognosis of women with breast cancer was not related to their level of concerns about the child's health (P=0.97), the disease and treatment (P=0.30) and the pregnancy and delivery (P=0.98) or to information satisfaction (P=0.95) or to the tendency to maintain the pregnancy (P=0.36).

Women with different stages of breast cancer and their partners were equally distributed in the coping clusters (P=0.79), indicating that the use of coping strategies was not different for those having a lower or a higher stage of the disease at diagnosis.

DISCUSSION

To the best of our knowledge, this is the first study addressing the particular concerns and coping strategies of pregnant women diagnosed with cancer and their partners. An association between the use of cognitive coping strategies and the level of distress was found. Women and partners mainly using internalizing coping strategies had the highest levels of distress and concerns, compared to those using positive or blaming coping strategies.

We aimed to compare the level of distress and concerns between the women and their partners. Interestingly, women and their partners reported similar levels of distress about the child's health, about the cancer disease and treatment and about the pregnancy and delivery. Nulliparous parents were more concerned about the pregnancy and delivery than multiparous parents, which is consistent with the literature.[226] Satisfaction with the information and care provided by the medical team were quite high in our sample and this was not significantly different for women and partners. However, women were more inclined to maintain the pregnancy than their partners. Our findings underscore the importance of evaluating the level of distress and concerns for both the women and their partners in order to identify who may benefit from additional psychosocial support.

Given our combined retrospective and prospective design, results of the groups were compared. Retrospective participants reported higher levels of concerns about the child's health as compared to prospective participants. A possible explanation may be that evidence on fetal safety after prenatal

exposure to cancer treatment is growing. Women diagnosed nowadays can thus be better informed about the safety and risks for their child, which may lower their level of distress.

Moreover, a higher stage of the disease at diagnosis was related to more concerns about the disease and treatment of women with breast cancer, but not for their partners. Surprisingly, there was no relationship with the 5-year overall survival prognosis. It is likely that physicians informed their patients about the stage of their disease, but not always communicated the percentage of overall survival. In general, the prognosis of women with breast cancer in our study was high. This is in part a result of the inclusion of retrospective cases with a history of cancer during pregnancy, who were still alive at the moment of completion of the questionnaire, and therefore might have had a good prognosis. Partners of women with a higher stage of breast cancer at diagnosis were more inclined to maintain the pregnancy than those of women with a lower stage at diagnosis, which was not true for the women themselves. It might be that partners who are afraid to lose their wife from cancer adhere to the baby as a way of searching for consolidation, connection to their partner and future prospects.

The second aim of our study was to identify subtypes of women and partners who use similar cognitive coping strategies when confronted with cancer during pregnancy. In our sample, we identified three subtypes: 48.3% of women and partners preferably used positive coping strategies (acceptance, putting into perspective, positive refocusing, positive reappraisal), 32.8% mainly used internalizing coping strategies (rumination, catastrophizing, refocus on planning, blaming self and others, a lack of acceptance and of positive refocusing) and 18.9% mainly blamed themselves and others for what happened. The internalizing and blaming clusters are comparable in their use of the strategies self-blame and blaming others, but highly differ in their scores on the strategies of rumination and catastrophizing. The first cluster is different to cluster two and three in the frequent use of positive or adaptive strategies and the absence of negative or maladaptive strategies (which are present in cluster two and three).

Thirdly, we aimed to investigate the relationship between these subtypes of women and partners based on their cognitive coping strategies and the level of distress and concerns. Participants mainly using internalizing emotion regulation strategies had significantly higher levels of distress and concerns than those who used positive coping strategies or searched for someone to blame. This is partly consistent with the literature, as women and partners in the positive coping cluster mainly use strategies that are labeled as ‘more adaptive’ and thus are expected to have lower levels of distress.[217] Also, the strategies that are considered as ‘less adaptive’ in the literature were highly present in our group of participants who used internalizing coping strategies.[217] Surprisingly, participants who mainly searched for someone to blame for their cancer situation had the lowest levels of concerns and distress. One hypothesis is that these women and partners deny or avoid their emotions and thoughts

and as a consequence report low levels of concerns and distress. Moreover, it is likely that other ways of emotion regulation, such as physiological (e.g., rapid pulse, rate of breathing, muscle tension), social (e.g., expression of feelings, distraction), behavioral (e.g., withdrawing, crying, angriness, information seeking) and other conscious and unconscious cognitive processes (e.g., selective attention, projection) are intertwined with the cognitive emotion regulation processes investigated in this study.

Our study has some limitations. First, recall bias may confound the results when including retrospective cases. Retrospective participants may evaluate or remember the event in a different way because of their experiences that have followed the cancer during pregnancy period, e.g. a positive or negative treatment outcome, a positive or negative outcome of the child. We dealt with this limitation by comparing the retrospective and prospective results. As a cancer diagnosis during pregnancy is a rare event, the inclusion of retrospective cases adds to a better understanding of the distress, concerns and coping of pregnant women with cancer and their partners. Another limitation is the heterogeneity of the study group in terms of variation in diseases, timing of diagnosis during pregnancy, prognosis, and treatment options. Lastly, the results are based on the validated CERQ and a new constructed Cancer and Pregnancy Questionnaire, which is not yet validated. Therefore, the results should be interpreted with caution. As this is the first questionnaire specifically addressing the psychological burden of cancer during pregnancy, it may provide useful information for both physicians and psychosocial workers in this field.

As a future project, we plan to validate the newly constructed Cancer and Pregnancy Questionnaire to improve the evaluation of distress and concerns and to implement it as a tool for distress screening and psychosocial care of pregnant women diagnosed with cancer and their partners.

Based on these results and on our experience, we summarize some clinical recommendations for physicians and psychosocial caregivers confronted with pregnant cancer patients and their families. First, the women in our study underscore the importance of clear information about the disease, treatment and prognosis of the mother and about the available evidence on the outcome of children after prenatal exposure to cancer treatment. Therefore, it is recommended that personalized information is provided in a format that the woman will understand in a process of shared decision-making about the cancer treatment and continuation of pregnancy. Second, as women and their partners may be confronted with uncertainty, a lot of questions and diverse emotions, it is important to evaluate their levels of distress and concerns and their coping strategies. Therefore, it is advisable to organize at least one consultation with a psychologist. The results in our study indicate that women and partners who use internalizing coping strategies may benefit from additional psychosocial support. Although women and partners who mainly search for someone to blame had the lowest levels of distress, denial and avoidance of emotions may be underlying mechanisms. In that case, psychosocial

support may also be advised to help them to recognize and express emotions and to teach them coping strategies that are more adaptive in the long term. Lastly, a cancer diagnosis during pregnancy is a very particular stressful life-event. Women confronted with this situation often do not feel completely understood by others. Contact with other families who have experienced cancer during pregnancy may help some of them to cope more easily with their emotions, thoughts and concerns.

SUPPLEMENTARY APPENDIX

1. Subscales and items of the Cancer and Pregnancy Questionnaire

Concerns about the child's health
I sometimes worry that our child will be weak.
I am afraid that our child will have a physical abnormality.
I am afraid that our child will be born with a physical disability requiring a lot of support in daily life.
I am concerned that our child will not be able to grow up normally with his/her peers due to the cancer treatment.
I am afraid that there will be serious complications during the pregnancy due to the cancer treatment.
I am afraid that the results of the tests carried out on our baby shortly after birth will be abnormal.
I am afraid that our child will be brain damaged or will have a mental disability.
I am afraid that our child will suffer growth retardation due to the cancer treatment.
I am concerned that our child will have learning difficulties at school due to the cancer treatment.
I am concerned that the cancer treatment will affect our child's physical appearance, making him/her less attractive, and I fear the reactions of others.
I am concerned that the examinations performed, to determine the type and the extent of the tumor, will have a detrimental effect on our child's health.
I am scared that our child will die before, during or shortly after birth.
I am afraid that our child will have difficulty doing sporting activities as a result of the cancer treatment.
I am always nervous when an ultrasound is performed that an abnormality will be found.
I am afraid that our child will be admitted to the specialized baby unit shortly after birth.
I am concerned that the cancer treatment may be harmful to our unborn child.
Concerns about the disease and treatment
I am afraid that the cancer treatment given to me during pregnancy will not be as effective as the treatment given to non-pregnant women.
I am concerned about the extent of the physical exhaustion caused by the treatment.
I am concerned that not all the tests, to determine the type and extent of the tumor, can be carried out due to the pregnancy.
I often wonder whether the cancer would have been detected earlier had I not been pregnant.
I am often concerned about my chances of survival.
I often wonder whether the cancer would have been detected had I not been pregnant.
I often wonder whether I would have had cancer had I not been pregnant.
I am often concerned about the cost of my cancer treatment.
Concerns about the pregnancy and delivery
I am concerned that I have become irritable, overly sensitive and that I react in a different way than I would like.
I am concerned about my sudden mood swings.
I am afraid that there will be complications during labor and delivery.
I am concerned that I am too preoccupied with myself and will become withdrawn.
I often worry that my pregnancy is so different to that of other pregnant women.
I sometimes worry that becoming a mother will change me a lot and for example, make me feel old.
Satisfaction with the information and care provided by the medical team
I am satisfied with the information I received from my physician regarding the current health state of mothers who underwent cancer treatment during pregnancy.
I am satisfied with the information I received from my physician about the possible risks of the cancer treatment to our child.

I am satisfied with the information I received from my physician regarding the follow-up plan for our child after birth. I am satisfied with the information I received from my physician about the possible (side) effects of my cancer treatment. I am comfortable asking my physician for detailed explanations of difficult medical terms and treatments. The medical team is caring and supportive regarding my wellbeing.
Tendency to maintain the pregnancy
I will do everything I can to save our baby. I have no right to endanger the life of our unborn child. I have an overwhelming urge to protect our child. I seriously considered having my pregnancy terminated.

2. Factors and items of the Cognitive Emotion Regulation Questionnaire (CERQ)[217]

Self-blame
I feel that I am the one to blame for it.
I feel that I am the one who is responsible for what has happened.
I think about the mistakes I have made in this matter.
I think that basically the cause must lie within myself.
Acceptance
I think that I have to accept that this has happened.
I think that I have to accept the situation.
I think that I cannot change anything about it.
I think that I must learn to live with it.
Focus on thought / Rumination
I often think about how I feel about what I have experienced.
I am preoccupied with what I think and feel about what I have experienced.
I want to understand why I feel the way I do about what I have experienced.
I dwell upon the feelings the situation has evoked in me.
Positive refocusing
I think of nicer things than what I have experienced.
I think of pleasant things that have nothing to do with it.
I think of something nice instead of what has happened.
I think about pleasant experiences.
Refocus on planning
I think of what I can do best.
I think about how I can best cope with this situation.
I think about how to change the situation.
I think about a plan of what I can do best.
Positive reappraisal
I think I can learn something from the situation.
I think that I can become a stronger person as a result of what has happened.
I think that the situation also has its positive sides.
I look for the positive sides to the matter.
Putting into perspective
I think that it all could have been much worse.
I think that other people go through much worse experiences.
I think that it hasn't been too bad compared to other things.
I tell myself that there are worse things in life.
Catastrophizing
I often think that what I have experienced is much worse than what others have experienced.
I keep thinking about how terrible it is what I have experienced.
I often think that what I have experienced is the worst that can happen to a person.
I continually think how horrible the situation has been.
Blaming others
I feel that others are to blame for it.
I feel that others are responsible for what has happened.
I think about the mistakes others have made in this matter.
I feel that basically the cause lies with others.

Chapter 7

General discussion and future perspectives

In this chapter, we will first summarize the main findings of our studies and discuss them in the light of our hypotheses and the international literature. Second, the strengths of our studies will be highlighted. Third, we will address the limitations of our studies, and fourth, we will provide suggestions for future research. In the fifth section, clinical implications and recommendations will be formulated, based on our findings. Final conclusions are provided in the last section.

1. SUMMARY AND DISCUSSION OF THE MAIN FINDINGS

In subsection 1.1, we will summarize and discuss the main findings of the cohort studies, investigating the impact of maternal cancer diagnosis and treatment during pregnancy on the cognitive development and behavior of the child. First, in subsection 1.1.1, a summary of each cohort study will be provided. Second, in subsection 1.1.2, the results of the different age cohorts will be integrated and discussed, according to the research questions formulated in chapter 2.

In subsection 1.2, we will summarize and discuss the results of our study on the psychological distress and coping of pregnant women with cancer and their partners, according to the research questions formulated in chapter 6.

1.1 Cognitive and behavioral development after prenatal exposure to maternal cancer and its treatment

In Chapters 3 to 5, we investigated the effects of prenatal exposure to maternal cancer and its treatment on the cognitive development in infancy and early toddlerhood (1.5-3 years), and on the cognitive development and behavior in early childhood (6 years) and in middle childhood (9 years). The results were compared to those of a control group, one-to-one matched to the study group for country, test age, gestational age at birth, and in the 6 years and 9 years cohort also for gender and language of the tests.

1.1.1 Summary

Cognitive development in infancy and early toddlerhood

In infancy and early toddlerhood (1.5-3 years), 129 children born from pregnancies complicated by maternal cancer were included, together with 129 controls. The children were examined by means of the mental or cognitive scale of the Bayley Scales of Infant (and Toddler) Development – second or third edition. The cognitive outcome on the Bayley test was not significantly different between the

study and control group. Subgroup analyses according to treatment type (no treatment, surgery alone, chemotherapy, radiotherapy) or to the type of chemotherapy (anthracyclines, taxanes, platin-based treatment) also did not reveal significant differences compared to the control group, although caution is needed as some subgroups were very small. The number of chemotherapy cycles administered during pregnancy and the estimated fetal dose of radiation were not related to the cognitive outcome. However, prematurity was related to a worse cognitive outcome and this effect was comparable in the study and control group.

Cognitive development and behavior in early childhood

In early childhood (6 years), we included 132 children born to mothers diagnosed with cancer during pregnancy and 132 controls. The children were subjected to a comprehensive neuropsychological test battery, including intelligence, attention and memory tests, and a parent-report behavior questionnaire. No significant between-group differences were found in Performance IQ, Processing Speed, alertness, selective attention, divided attention, response inhibition, verbal and visuospatial memory span, verbal working memory , short- and long-term memory for visuospatial information and faces, and internalizing and externalizing behavior problems. However, children from the study group scored significantly lower on Full Scale IQ (5 points difference) and Verbal IQ (8 points difference) than their matched controls, although the values were within the normal range. Significant between-group differences in Full Scale IQ and Verbal IQ were also found in the subgroup of 97 chemotherapy-exposed children and their matched controls. The size of the between-group difference in Full Scale IQ and Verbal IQ was comparable for children exposed to anthracyclines, taxanes or platin-based treatment, compared to their matched controls, indicating that the type of chemotherapy was not related to the cognitive outcome. Full Scale IQ was not associated with the number of chemotherapy cycles or with the estimated fetal dose of radiation. In both the study and control group, no linear relationship was found between Full Scale IQ and the gestational age at birth.

Cognitive development and behavior in middle childhood

In middle childhood (9 years), we included 43 children prenatally exposed to maternal cancer and its treatment, together with 43 controls in an interim analysis of the data. Cognitive development was examined using an intelligence test and several attention and memory tests. Additionally, the parents filled out a questionnaire on behavior problems. The groups did not significantly differ on any of the tests measuring Full Scale IQ, Verbal IQ and Performance IQ, Processing Speed, alertness, sustained attention, selective attention, divided attention, attentional control, response inhibition, verbal and

visuospatial memory span, verbal working memory, verbal proactive and retroactive interference, verbal and visuospatial short- and long-term memory, and short- and long-term memory for faces. The number of parent-reported internalizing and externalizing behavior problems was not significantly different between children from the study and control group. No subgroup analyses according to treatment type or type of chemotherapy were performed, due to the small overall sample size. No linear relationship was found between Full Scale IQ and the number of chemotherapy cycles or the estimated fetal dose of radiation. Full Scale IQ was moderately correlated to gestational age in both the study and control group.

1.1.2 Integration and discussion of the findings over the age cohorts

Research questions 1, 2 and 3: What is the impact of prenatal exposure to cancer and its treatment (especially chemotherapy) on the cognitive development in infancy and early toddlerhood (1.5 and 3 years) and on the cognitive and behavioral development in early childhood (6 years) and middle childhood (9 years)?

In our studies, cognitive development was investigated in depth by including a large number of measures of specific cognitive functions. Overall, most of these measures were not significantly different between the study and control group throughout the different age cohorts, which is consistent with previous studies documenting reassuring outcomes.[11,14,150,152,162] However, we found that children from the study group had significantly lower Full Scale and Verbal IQ scores than their matched controls at the age of 6 years, although the values were within the normal range. Verbal intelligence depends in particular on acquired knowledge with respect to vocabulary, information and understanding of social situations, and is therefore highly dependent on postnatal environmental factors for the stimulation of the innate verbal potential.[199] We found that parents of children in the control group were on average more highly educated than those of children in the study group. Although we added the education level of the parents as a covariate in our analyses, a possible effect of factors that are associated with education level cannot be ruled out, such as socio-economic status and parenting style. These factors were not measured in our studies. Larger samples with a more balanced control group with respect to education level of the parents are needed to further delineate whether the encountered group differences can be allocated to the prenatal exposure to maternal cancer and its treatment or should be considered as an artefact due to a selection bias of children in the control group.

The between-group differences in Full Scale IQ and Verbal IQ encountered in the 6 years cohort were not found in our interim analysis of 9-year-old children. Several factors may contribute to this

difference between the two cohorts. First, within and between the age cohorts, we used different tests to measure intelligence. Although the correlations between IQ scores measured by the different tests are high, they are not perfect.[206] Furthermore, during a test-retest interval of 3 years, real changes in cognitive abilities can take place.[209] Last, the control groups included in the 6 years and 9 years cohort were different, and therefore longitudinal evaluation of the between-group differences from the age of 6 years to the age of 9 years was not possible. Longitudinal research in larger samples and further evaluation at older ages is needed to evaluate the evolution of these findings.

Given the limited number of studies that were previously published on this subject, our studies were considered as exploratory in nature. However, based on studies reporting chemotherapy-induced cognitive sequelae in children and adults with cancer and the protective role of the placenta during chemotherapy administration in pregnancy, we expected to find only subtle cognitive differences. This hypothesis was confirmed for the measures of general cognitive development in infancy and early toddlerhood and the measures of Performance IQ, Processing Speed, attention, memory and behavior problems in early and middle childhood, as these measures did not significantly differ between the study and control group. The hypothesis was not confirmed for the 5-points difference in Full Scale IQ and the 8-points difference in Verbal IQ at the age of 6 years, which can be considered as a large difference.

Research question 4: Is the type of chemotherapy (anthracyclines, taxanes, platin-based treatment) related to the cognitive outcome?

Previous research has shown that the transplacental passage of chemotherapy varies according to the type of chemotherapeutic agent. As the transplacental passage of platin-based treatments (up to 57% for carboplatin)[10] is much higher than the transplacental passage of anthracyclines (4% for epirubicin and 8% for doxorubicin)[9] and taxanes (1% for paclitaxel and not detectable for docetaxel)[10], we hypothesized to find differential effects according to treatment type, with larger effects on cognitive development in children exposed to platin-based treatments and smaller effects in children exposed to anthracyclines and taxanes. The data in our 1.5-3 years and 6 years cohort did not support this hypothesis. However, the results should be interpreted with caution as they were based on small subgroups of children, which was especially the case for children exposed to taxanes and/or platin-based treatments, and the fact that different types of chemotherapy are in some cases parallel or serially administered. Larger samples are needed to further explore whether a differential impact of different types of chemotherapy exist on the longitudinal development of specific cognitive functions.

Research question 5: Is the number of chemotherapy cycles administered during pregnancy related to the cognitive outcome?

The use of some types of medication in pregnancy (e.g., valproate for the treatment of epilepsy)[177] has been associated with worse cognitive outcomes in a dose-response relationship. Hence, it is possible that the effects of prenatal exposure to chemotherapy on the cognitive outcome are also dose-dependent. Due to the heterogeneity and combinations of chemotherapeutic schemes used in the treatment of cancer during pregnancy, it is difficult to examine the relationship between the dose of a specific chemotherapeutic agent and the cognitive outcome. Therefore, we hypothesized to find a linear relationship between the number of chemotherapy cycles administered during pregnancy and the cognitive outcome. Our data did not support this hypothesis, as we did not find a linear relationship between general cognitive development (in infancy and early toddlerhood) or Full Scale IQ (in early and middle childhood) and the number of chemotherapy cycles administered during pregnancy. Notwithstanding, an interaction between the type of chemotherapy, the dosage and the timing of exposure may exist. Larger samples are needed to further explore this relationship.

Research question 6: Is the estimated fetal dose of radiation related to the cognitive outcome?

According to studies in children prenatally exposed to ionizing radiation from atomic bombs,[137] we hypothesized to find a linear relationship between the estimated fetal dose of radiation and the cognitive outcome. This hypothesis was not supported by our data. A possible explanation may rely in the fact that the estimated fetal dose of radiation as a result of radiotherapy treatment in the children from our study sample was much lower than the exposure to ionizing radiation from atomic bombs. Moreover, only few children in our studies were exposed to radiotherapy, and in about half of the cases, radiotherapy was supplemented with chemotherapy, possibly masking the true relationship between radiotherapy exposure and cognitive development. Due to the small overall sample of radiotherapy-exposed children and the limited number of cases exposed in the first trimester of pregnancy, we were not able to investigate the interaction between the dose of radiation and the timing of exposure. As research has shown that the most sensitive period of the developing brain to radiation is between 8 and 15 weeks of gestation,[137] stronger effects on cognition can be expected when exposed to radiation during this sensitive period. Again, larger samples are needed to further explore this interaction effect.

Research question 7: Is prematurity related to the cognitive outcome?

In our studies, the number of preterm born children was high (55.8% to 61.2%, as compared to 6.8 to 8.0% in the general population), with late preterm born children representing the largest group of preterm born children in our study population. Previous studies already highlighted the possible long-term impact of preterm birth on cognitive development, with a higher risk of worse outcomes with decreasing gestational age.[178-180] Therefore, we hypothesized to find a linear relationship between the gestational age at birth and the cognitive outcome. In the 1.5-3 years cohort, gestational age was indeed related to the cognitive outcome in both the study and control group, with better outcomes in term born children. This is not surprising as most studies in infancy and early toddlerhood have found worse outcomes in preterm versus term born children.[180,227-229] However, as children grow older, it is possible that they partly grow out of their deficits, for example by taking remedial classes, and that the differences between preterm and term born children become more subtle. Inconsistent findings at older ages have been published, although most studies still found one or more cognitive functions to be impaired on the long-term.[112,115,117,200,201,230] In our study, Full Scale IQ was not correlated to the gestational age in 6-year-old children, but was moderately correlated in 9-year-old children. Some of the aforementioned elements of discussion with respect to the difference in control groups and the use of different intelligence tests may also contribute to the encountered difference between the age cohorts. We did not investigate the relationship between gestational age and other cognitive outcomes, as this was not the scope of our studies.

Additionally, during the course of our studies, we discovered that cancer and its treatment may have an adverse impact on the fetal growth, resulting in a higher number of children born small for gestational age (16.3% to 22.0% in our cohort studies, compared to 10% in the general population). In our 6 years cohort study, Full Scale IQ was not significantly different between children who were born small for gestational age and those who were not. Other cognitive outcomes were not compared, as this was not the scope of our study. Previous studies have reported inconsistent findings on the impact of small for gestational age birth on cognitive development and suggest a possible interaction with prematurity and/or postnatal catch-up growth.[121,122,124,126,127]

1.2 Psychological distress and cognitive coping in pregnant women diagnosed with cancer and their partners

In this study, we evaluated the psychological distress and the use of cognitive coping strategies in 61 patients and their partners. Patients and their partners retrospectively (70.5%, after delivery) or prospectively (29.5%, during pregnancy) filled out the validated Cognitive Emotion Regulation

Questionnaire (CERQ) and the newly constructed Cancer and Pregnancy Questionnaire. We formulated three research questions: (1) Do pregnant women diagnosed with cancer and their partners experience similar or different concerns and distress levels? (2) How do pregnant women diagnosed with cancer and their partners cope with their cancer diagnosis and treatment? (3) Is the way in which pregnant women and their partners cope with their cancer diagnosis and treatment related to their level of distress? In the next subsections, we will summarize and discuss the results for each of the three research questions, respectively.

Research question 1: Do pregnant women diagnosed with cancer and their partners experience similar or different concerns and distress levels?

Cancer diagnosis influences both patients and their closest relatives. Previous studies already highlighted that psychosocial distress levels of cancer patients and their partners may be similar.[231,232] In accordance with the hypothesis in our study, the levels of distress and concerns with regard to the child's health, the disease and treatment, and the pregnancy and delivery were comparable between the women and their partners. Specifically in the case of cancer during pregnancy, the partners do not only have to cope with the psychological burden of their wife's life-threatening disease and treatment, but also with concerns about the course of the pregnancy and delivery and the possible harmful impact of the cancer treatment on their unborn child. In our study, the women were more inclined to maintain the pregnancy than their partners and the women and their partners were equally satisfied with the information and care provided by the medical team. Additionally, we found that expecting parents who were pregnant with their first child (nulliparous parents) were more concerned about the pregnancy and delivery than parents who already had children (multiparous parents). This has also been demonstrated by other studies[226,233] and can be explained by the fact that uncertainty about the course of the pregnancy and delivery is higher in nulliparous parents as they have no idea of what to expect. Furthermore, a higher stage of the disease at diagnosis was related to more concerns about the disease and treatment in women with breast cancer, but not in their partners. We did not find a relationship with the 5-year overall survival prognosis. A possible explanation may be that physicians inform their patients about the stage of their disease, but not always communicate the percentage of overall survival. Moreover, the 5-year overall survival of the women in our study was high, which may be a consequence of the inclusion of retrospective participants who survived at the moment of completion of the questionnaires and therefore may have had a good prognosis at diagnosis. Partners of women with a poor prognosis were more inclined to maintain the pregnancy than partners of women with a good prognosis, a relationship that was not found for the women in our study.

Adherence to the baby as a way of searching for consolidation, connection to their partner and future prospects may be a way of coping with the possibility of losing their wife.

Given the rarity of cancer during pregnancy, we used a combined retrospective and prospective study design and compared the results of the retrospective and prospective groups. We found that the groups only differed in their level of concerns related to the child's health, with retrospective participants reporting more concerns. A possible explanation may be that women diagnosed nowadays and their partners can be better informed about the possible risks and safety for their unborn child as evidence on the fetal safety has been growing in the recent years.

Research question 2: How do pregnant women diagnosed with cancer and their partners cope with their cancer diagnosis and treatment?

According to the literature, we hypothesized to find two subtypes or clusters of cognitive coping strategies: one cluster including more adaptive or positive strategies (acceptance, positive refocusing, positive reappraisal, refocus on planning, putting into perspective) and a second cluster including less adaptive or negative strategies (self-blame, rumination, catastrophizing, blaming others).[217] In our study, the data supported a two- or three-cluster solution. We chose for the three-cluster solution, because it was a refinement of the two-cluster solution, splitting one cluster into two different clusters. Using this cluster analysis, we identified three subtypes: 48.3% of women and partners preferably used positive coping strategies (acceptance, putting into perspective, positive refocusing, positive reappraisal), 32.8% mainly used internalizing coping strategies (rumination, catastrophizing, refocus on planning, blaming self and others, a lack of acceptance and of positive refocusing) and 18.9% mainly blamed themselves and others for what happened. The internalizing and blaming clusters include strategies that can be considered as less adaptive, while the positive coping cluster includes strategies that are more adaptive.[217]

Research question 3: Is the way in which pregnant women and their partners cope with their cancer diagnosis and treatment related to their level of distress?

Several studies have shown that less adaptive coping strategies, such as self-blame, rumination, catastrophizing and blaming others, (vs. more adaptive strategies) are related to more symptoms of anxiety and depression and to lower quality of life in cancer patients.[217,218,221,222] Therefore, we expected that women and partners mainly using internalizing or blaming strategies would deal with the highest levels of distress. In accordance to our hypothesis, women and partners using internalizing coping strategies reported indeed the highest levels of concerns and distress. However, in contrast to

our hypothesis, women and partners who mainly searched for someone to blame reported the lowest levels of concerns and distress. Possibly, denial and avoidance of emotions may be underlying mechanisms in this group of participants, and as a consequence they may have reported lower levels of concerns and distress. Moreover, it is likely that other ways of emotion regulation, such as physiological (e.g., rapid pulse, rate of breathing, muscle tension), social (e.g., expression of feelings, distraction), behavioral (e.g., withdrawing, crying, angriness, information seeking) and other conscious and unconscious cognitive processes (e.g., selective attention, projection) are intertwined with the cognitive emotion regulation processes investigated in this study.

2. STRENGTHS

Our studies have several strengths, which will be highlighted in this section.

The incidence of cancer diagnosed during pregnancy is estimated at 1 in 1000 pregnant women. This creates the need but also the opportunity to conduct an international multicenter study. Our three cohort studies were based on collaborations between members of the International Network on Cancer, Infertility and Pregnancy (INCIP). This enabled the inclusion of children from Belgium, the Netherlands, the Czech Republic and Italy. Before the start of this PhD project, only a few studies had been published on the follow-up of children born to mothers diagnosed with cancer during pregnancy. The sample sizes of these studies were smaller, most studies did not include a control group and/or did not investigate the cognitive development in depth by using a comprehensive neuropsychological test battery. The added value of the cohort studies included in this PhD project is five-fold:

First, our 1.5-3 years and 6 years cohort studies included the largest sample of children born to mothers diagnosed with cancer during pregnancy. Second, the results were compared to those of a matched control group of children. Additionally, the children were one-to-one matched for a large number of characteristics, such as country, test age, gestational age at birth, and in the 6 years and 9 years cohort also for gender and language of the tests. Third, information on other factors that may influence child development was gathered in the 6 years and 9 years cohort, among others information on substance abuse during pregnancy, the use of reproductive medicine to achieve the pregnancy, birth characteristics, parental education levels and bilingual education. Fourth, the children were subjected to a comprehensive neuropsychological assessment, including a test of general cognitive development in infancy and early toddlerhood, and tests of intelligence, attention and memory and a parent-report behavior questionnaire in early and middle childhood. This comprehensive protocol enabled to examine the cognitive development of these children in depth. Fifth, our studies provided evidence on

the long-term outcomes, evaluated up to 9 years after prenatal exposure to maternal cancer and its treatment.

To date, the psychological burden of pregnant women diagnosed with cancer and their partners received very limited attention in research projects. Our study on the psychological distress and use of cognitive coping strategies was the first quantitative study on this subject and adds to a better understanding of the concerns and distress that these couples experience and how they deal with these thoughts and emotions. Another strength of the study was the inclusion of both patients and partners, as no previous studies have investigated the experience of the partners.

3. LIMITATIONS

Besides the strengths of our studies, they have also some limitations which need to be discussed. In the following subsections, we will give an overview of the most important limitations related to the sample characteristics, the study design and the assessment instruments.

3.1 Sample characteristics

The coincidence of cancer and pregnancy is rather uncommon. Although we conducted the cohort studies as international multicenter studies, the overall sample size of each study was still limited and mainly children from Belgium and the Netherlands were included. Additionally, the cancer types diagnosed during pregnancy are heterogeneous, with breast cancer and hematological malignancies being the most frequently diagnosed cancer types in pregnancy. The preferred treatment options vary across different cancer types. Moreover, several treatment modalities (surgery, chemotherapy, radiotherapy) or chemotherapeutic schemes are often combined and children are exposed at different time points in pregnancy. Therefore, it is challenging to disentangle the effects of single factors on child development. Subgroup analyses according to treatment modality or type of chemotherapy were rendered inappropriate in the interim analysis of 9-year-old children, due to the low total sample size. We performed some subgroup analyses in the 1.5-3 years and 6 years cohort. However, these analyses were only exploratory as the sample sizes of the subgroups were very small. In the study on the psychological distress and coping of the couples, the small sample size also did not allow to control for the variation in diseases, the timing of diagnosis during pregnancy, the prognosis and the treatment options.

3.2 Design of the studies

In a cohort study, comparing the outcome of children prenatally exposed to maternal cancer with the outcome of children born after uncomplicated pregnancies, the selection of control subjects is of utmost importance. We have chosen for a one-to-one match of study and control subjects for country, test age, gestational age at birth, and in our 6 years and 9 years cohort also for gender and language of the tests. Matching for gestational age was introduced because of the high prevalence of prematurity in pregnancies complicated by maternal cancer, and because prematurity is known by itself to influence neurocognitive development. Premature delivery in pregnancies complicated by maternal cancer results from spontaneous preterm labor, which may have variable cancer-related and cancer-non-related causes, or from elective induction of delivery as part of treatment strategies to limit ongoing exposure of the fetus to cancer treatment. The variety of causal factors may intrinsically and to a variable extent impact on neurocognitive development. In fact, this holds for the ex-premature control subjects as well. The objective of matching for gestational age was to control for the independent and intrinsic effect of premature birth on neurocognitive development, irrespective of its cause. However, one can argue that a pregnancy that ends in a premature delivery cannot be considered as an uncomplicated pregnancy. In the selection of premature control subjects from the hospital birth lists, we screened for factors that may have an adverse impact on child development and considered them as exclusion criteria. Furthermore, we used both advertisement and screening of hospital birth lists as ways to recruit control subjects. Although the screening of hospital birth lists provides the opportunity to select control subjects on a more random basis, selection bias cannot be ruled out and one might question whether the sample of control subjects is representative for the normal population. Parents who are highly educated are often more interested and willing to participate in scientific research projects. On the other hand, parents who are concerned about their child's development are also interested to let their child take part in this kind of studies. This can have induced a selection bias. In the three cohort studies, we noticed that parents of children from the control group were on average more highly educated than parents of children from the study group. A possible solution relies in the inclusion of brothers and sisters of study children as control subjects. However, this was not possible as we preferred to match for gestational age and given the high incidence of prematurity. Moreover, women who are pregnant with their first child when diagnosed with cancer do not always have the option to have another pregnancy after cancer treatment. Another limitation of our studies relies in the use of different control groups for the different age cohorts. Therefore, longitudinal analyses were not possible at this moment. Ideally, both study and matched control subjects would have been included during pregnancy and followed until adulthood. However,

this was not possible as the study started in 2005 with the inclusion of study subjects only. Hence, we retrospectively identified and matched control subjects to the study group.

In our study on the psychological distress and cognitive coping of pregnant women and their partners, we included both retrospective and prospective cases. The inclusion of retrospective participants may have led to recall bias. Retrospective participants may evaluate or remember the event in a different way because of their experiences that have followed the cancer during pregnancy period, e.g. a positive or negative treatment outcome, a positive or negative outcome of the child. Moreover, the inclusion of mainly retrospective participants may have led to a selection bias, including mainly patients with a good prognosis at diagnosis as they survived at the moment of completion of the questionnaires. Unfortunately, we were not able to determine who was still in ongoing treatment at the moment of completion of the questionnaires, because many women were treated and followed-up in their regional hospital. We dealt with this limitation by comparing the retrospective and prospective results. As a cancer diagnosis during pregnancy is a rare event, the inclusion of retrospective cases adds to a better understanding of the distress, concerns and coping of pregnant women with cancer and their partners.

3.3 Instruments

In our cohort studies, we used standardized and validated test instruments to examine cognitive development. However, due to the long-term nature of our study design, test instruments are regularly revised and updated. This is particularly the case for intelligence tests. The different Wechsler tests and editions are highly but not perfectly correlated to one another.[206] We dealt with this limitation by using the same intelligence test and edition for each pair of matched study and control children. Furthermore, in the most recent Wechsler editions, the distinction between Verbal IQ and Performance IQ was abandoned and replaced by index scores, based on factor analysis. The tests and editions used in most children in our studies (especially WPPSI-III at the age of 6 years) did not allow to include index scores. According to the 6 years cohort, we preferred to use IQ scores instead of index scores in the 9-year-old cohort as well, which enables the comparison of the scores over the age groups.

In our study on the psychological distress and coping of the couples, we used a newly constructed Cancer and Pregnancy Questionnaire. This questionnaire is not yet validated, as the sample size and number of items did not allow to perform exploratory factor analysis. Therefore, the results should be interpreted with caution. As this is the first questionnaire specifically addressing the psychological

burden of cancer during pregnancy, it may provide useful information for both physicians and psychosocial workers in this field.

4. FUTURE RESEARCH

In this section, suggestions for future research are formulated. In the first subsection, we will address future research topics with regard to the effects of maternal cancer diagnosis and treatment during pregnancy on neuropsychological child development. In the second subsection, we will focus on future research with regard to the psychological burden of cancer during pregnancy for the couples.

4.1 Follow-up of children exposed to maternal cancer and its treatment in pregnancy

In general, cognitive development and behavior after prenatal exposure to maternal cancer and its treatment were reassuring until the age of 9 years. Although follow-up up to 9 years after an event can be considered as long-term follow-up, further follow-up of this unique cohort until adolescence and adulthood would be very useful, since adolescence is a critical period of structural brain reorganization and maturation of cognitive abilities. It is therefore possible that cognitive problems related to the development of these brain regions may become more manifest in adolescence, when school demands increase and become more challenging.[234]

Furthermore, as the transplacental passage of chemotherapeutic drugs can vary substantially between different chemotherapeutic agents, differential effects on child development might be expected. Future research including larger samples may therefore focus on the differential effects according to the type of chemotherapy. Notwithstanding, different types of chemotherapeutic agents are often combined and chemotherapy might be supplemented by diagnostic imaging, surgery, radiotherapy, supportive drugs, and maternal stress. Thus, it is challenging to disentangle the effects of single factors on child development. Moreover, studies documenting the outcome of children after in-utero exposure to radiotherapy, targeted therapy, or hormonal therapy are scarce. To date, the sample sizes were also too small to differentially explore the effects on child development with regard to the timing of exposure in pregnancy. Larger prospective cohort studies are needed to address the long-term effects of different types of maternal cancer treatment and different timings of exposure in pregnancy on child development until adulthood. Longitudinal cohort studies following a study and matched control group from birth until adulthood would be very valuable, as this allows to follow and evaluate the evolution of group differences over time. This enables to investigate whether children grow into or out of deficits over time. Further inclusion of study and control subjects is therefore needed and

collaborations with other medical centers through the INCIP network may contribute to the inclusion of larger samples of children.

Furthermore, as studies in children and adults treated with chemotherapy have shown that chemotherapy may lead to changes in white matter integrity, MRI studies of the brain supplementing neuropsychological assessment may also have an added value in children prenatally exposed to chemotherapy.[141,235] An MRI study of the brain is currently ongoing in children aged 9 years or older by the INCIP.

4.2 Evaluation of the psychological distress and coping in pregnant women with cancer and their relatives

With regard to our study on the psychological distress and coping of the couples, future research may focus on the validation of the newly constructed Cancer and Pregnancy Questionnaire in order to improve the evaluation of distress and concerns and to implement it as a tool for distress screening and psychosocial care for pregnant women diagnosed with cancer and their partners. In a new project, the results that were obtained in our mainly retrospective study may be compared to those obtained in a full prospective sample, which will also allow to include a more balanced group of patients with regard to the prognosis. Last, as distress and the use of coping strategies may vary throughout pregnancy and cancer treatment, evaluation at more than one time point in pregnancy and in the postpartum period would add to a better understanding of the psychological distress and use of coping strategies in pregnant women with cancer and their relatives. A thorough evaluation of the maternal distress in pregnancy would also permit to study the impact of prenatal stress on the cognitive development and behavior of the child.

5. CLINICAL IMPLICATIONS AND RECOMMENDATIONS

The studies of this PhD project have important clinical implications. Until recently, many physicians were reluctant to start cancer treatment during pregnancy due to the limited availability of long-term fetal safety data. This has resulted in delay of maternal cancer treatment, termination of pregnancy or preterm induction of delivery, with possible adverse effects for both mother and child, such as maternal disease progression, neonatal morbidities and long-term neurocognitive problems in the child. The results of the different cohort studies presented in this PhD project strengthen the evidence that cancer treatment during pregnancy for specific cancer types and under well-defined circumstances is possible without major long-term consequences for the cognitive development of the children, although caution is always indicated. Thanks to these studies, newly diagnosed patients can

be better informed about their treatment options and about the possible risks and safety of these treatments for their child. This will help them to make a well-informed decision about the continuation of pregnancy and the treatment options.

Pregnant women with cancer need support from a multidisciplinary team of caregivers, including oncologists, obstetricians, neonatologists/pediatricians, psychologists, sexologists and social workers. Based on the results of our study on the psychological distress and coping of the couples, we summarize some clinical recommendations for physicians and psychosocial caregivers confronted with pregnant cancer patients and their families. First, we found that pregnant women with cancer and their partners experience concerns about the child's health, the disease and treatment and the pregnancy and delivery. Additionally, they have to consider whether or not to continue the pregnancy. The diagnosis of cancer during pregnancy may be associated with uncertainty, a lot of questions and diverse emotions. Therefore, it is advisable to organize at least one consultation with a psychologist to evaluate their concerns, distress and the use of coping strategies. Second, the levels of distress of the partners were comparable to those of the women themselves. Hence, it is recommended to involve the partners in psychosocial support sessions as well. Last, the results in our study indicate that women and partners who use internalizing coping strategies experience the highest levels of concerns and distress and may benefit from additional psychosocial support. Although women and partners who mainly search for someone to blame had the lowest levels of distress, denial and avoidance of emotions may be underlying mechanisms. In that case, psychosocial support may also be advised to help them to recognize and express emotions and to encourage them to acquire coping strategies that are more adaptive in the long term.

6. CONCLUSIONS

It has become clear that for specific cancers and under well-defined circumstances, cancer treatment during pregnancy is possible. In our three cohort studies, the cognitive development of children aged 1.5 to 3 years, 6 years and 9 years can be in general considered as normal for their gestational age. However, Full Scale and Verbal IQ were significantly lower in the study versus control group at the age of 6 years, although the values were within the normal range and these differences were not found in our interim analysis of 9-year-old children. Moreover, more than half of the children were born preterm and prematurity may be related to worse cognitive outcomes. Further research in larger samples and at older ages is needed to evaluate the evolution of these findings and to explore whether a differential impact of different types of maternal cancer treatment exist on the longitudinal development of specific cognitive functions.

Our study on the psychological distress and use of cognitive coping strategies in pregnant women diagnosed with cancer and their partners indicates that the diagnosis of cancer may be an emotional challenge for pregnant women and their partners, which is associated with concerns about the child's health, about the disease and treatment and about the pregnancy and delivery. In a combined retrospective and prospective design, we found that especially women and their partners who mainly use internalizing coping strategies (e.g., rumination, catastrophizing, refocus on planning, blaming self and others, a lack of acceptance and of positive refocusing) deal with the highest levels of concerns and distress and may benefit from additional psychosocial support. Future research may focus on the validation of the newly constructed Cancer and Pregnancy Questionnaire in a prospective sample in order to implement it as tool for distress screening and psychosocial care in pregnant women diagnosed with cancer and their relatives.

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Curriculum Vitae

PERSONALIA

Name	Tineke Vandenbroucke
Date of birth	May 16th, 1988
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EDUCATION

2013 – 2018 **Doctoral studies in Psychology, KU Leuven**
Doctoral School Humanities & Social Sciences
Cancer during pregnancy: Impact on neuropsychological child development and on the couple's distress and coping
Promotor: Prof. Dr. Frédéric Amant, Copromotor: Prof. Dr. Laurence Claes

2014 – 2016 **Permanent Training Programme "Psycho-Oncology", UGent**

2011 – 2013 **Master of Science in Human Sexuality Studies, KU Leuven**
Magna cum laude
Seksuele opvoeding in gezinnen. Een exploratief onderzoek naar patronen van ouder-adolescent communicatie en het verband met demografische factoren, gezinsinteractiefactoren en psychosociale factoren.
Promotor: Prof. Dr. Paul Enzlin

2009 – 2011 **Master of Science in Clinical and Health Psychology, KU Leuven**
Magna cum laude
Mindfulness voor jongeren. Onderzoek naar de effectiviteit op vlak van algemene psychische klachten, cognitieve kwetsbaarheidsfactoren en mindfulnessvaardigheden.
Promotor: Prof. Dr. Filip Raes

2006 - 2009 **Bachelor of Science in Psychology, KU Leuven**
Cum laude

PROFESSIONAL CAREER

2013 – 2018 PhD researcher at KU Leuven (2013-2015) and Research Foundation - Flanders (FWO) (2015-2018)

2014 – 2016 Clinical psychologist in psycho-oncology training at UZ Leuven
Specialization in hematology and medical oncology

2013 Sexologist in training at Bourgognecentrum Hasselt
Counseling of couples for termination of pregnancy

2010 – 2011	Clinical psychologist in training at Psychiatrische Kliniek Broeders Alexianen Tienen, section 'Pathways' Residential treatment of adolescents with substance use disorders

AWARDS AND GRANTS

2015 – 2018	Research fellow grant 'aspirant' at the Research Foundation - Flanders (FWO)
2017	Laureate 'best research abstract' at the Fourth Congress in Psychosocial Oncology in Mechelen, Belgium, organized by the Cédric Hèle Instituut (CHI) *Neuropsychologische en gedragsmatige opvolging van kinderen na kankerdiagnose en kankerbehandeling tijdens de zwangerschap*
2015	Abstract selected in the category of 'best oral presentations' at the European Society of Gynaecological Oncology (ESGO) Congress in Nice, France *Pediatric outcome after maternal cancer diagnosed during pregnancy*

List of publications

1. INTERNATIONAL PEER-REVIEWED PAPERS

Vandenbroucke T, Verheecke M, Van Calsteren K, Han SN, Claes L, & Amant F (2014). Fetal outcome after prenatal exposure to chemotherapy and mechanisms of teratogenicity compared to alcohol and smoking. *Expert Opinion on Drug Safety, 13,* 1653-1665. DOI: 10.1517/14740338.2014.965677

Han SN, Verheecke M, **Vandenbroucke T**, Gziri MM, Van Calsteren K, & Amant F (2014). Management of gynecological cancers during pregnancy. *Current Oncology Reports, 16*, 415. DOI: 10.1007/s11912-014-0415-z

Vandenbroucke T, & Amant F (2015). Development of children born to mothers with cancer during pregnancy: Comparing in utero chemotherapy-exposed children with nonexposed controls [letter to the editor]. *American Journal of Obstetrics and Gynecology, 212,* 830-831. DOI: 10.1016/j.ajog.2015.01.035

Amant F, Han SN, Gziri MM, **Vandenbroucke T**, Verheecke M, & Van Calsteren K (2015). Management of cancer in pregnancy. *Best Practice and Research in Clinical Obstetrics and Gynaecology, 29,* 741-753. DOI: 10.1016/j.bpobgyn.2015.02.006

Amant F*, **Vandenbroucke T***, Verheecke M*, Fumagalli M, Halaska MJ, Boere I, Han S, Gziri MM, Peccatori F, Rob L, Lok C, Witteveen P, Voigt JU, Naulaers G, Vallaeys L, Van den Heuvel F, Lagae L, Mertens L, Claes L, & Van Calsteren K (2015). Pediatric outcome after maternal cancer diagnosed during pregnancy. *New England Journal of Medicine*, *373,* 1824-1834. DOI: 10.1056/NEJMoa1508913

Lishner M, Avivi I, Apperley JF, Dierickx D, Evens AM, Fumagalli M, Nulman I, Oduncu FS, Peccatori FA, Robinson S, Van Calsteren K, **Vandenbroucke T**, Van den Heuvel F, & Amant F (2015). Hematologic malignancies in pregnancy: Management guidelines from an international consensus meeting. *Journal of Clinical Oncology*, *34,* 501-508. DOI: 10.1200/JCO.2015.62.4445

Vandenbroucke T, Van Calsteren K, & Amant F (2016). Pediatric outcome after maternal cancer diagnosed during pregnancy [reply to letter to the editor]. *New England Journal of Medicine*, *374,* 692-693. DOI: 10.1056/NEJMc1515462

Vandenbroucke T, Han SN, Van Calsteren K, Wilderjans TF, Van den Bergh BRH, Claes L, & Amant F (2017). Psychological distress and cognitive coping in pregnant women diagnosed with cancer and their partners. *Psycho-Oncology*, *26*, 1215-1221. DOI: 10.1002/pon.4301

Boere I*, Lok C*, **Vandenbroucke T*,** & Amant F (2017). Cancer in pregnancy: safety and efficacy of systemic therapies. *Current Opinion in Oncology*. DOI: 10.1097/.0000000000000386

Vandenbroucke T, Verheecke M, Fumagalli M, Lok C, & Amant F (2017). Effects of cancer treatment during pregnancy on fetal and child development. *The Lancet Child and Adolescent Health, 1,* 302-310. DOI:10.1016/S2352-4642(17)30091-3

2. BOOK CHAPTERS

Vandenbroucke T, Verheecke M, Vercruysse D, & Amant F (2016). Neonatal and long-term consequences of in utero exposure to systemic anticancer treatment. In H. Azim Jr. (Red.), *Managing cancer during pregnancy* (pp. 97-110). Springer International Publishing. DOI: 10.1007/978-3-319-28800-0_9

Vandenbroucke T, Aerts L, Hasenburg A, Weis J, & Schwab R (2017). Psychological challenges and support for pregnant women diagnosed with cancer and their family. In F. Amant (Red.), *Textbook Cancer in Pregnancy* (pp. 47-51) by the European Society of Gynaecological Oncology.

Verheecke M, & **Vandenbroucke T** (2017). Pediatric long-term outcome after in utero exposure to cancer treatment. In F. Amant (Red.), *Textbook Cancer in Pregnancy* (pp. 61-65) by the European Society of Gynaecological Oncology.

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List of presentations

1. ORAL PRESENTATIONS AT (INTER)NATIONAL CONFERENCES

Vandenbroucke T. "Gevolgen van kankerbehandeling tijdens de zwangerschap?". International Symposium on Cancer in Young Women, Leuven, February 5, 2015.

Vandenbroucke T, Han SN, Van Calsteren K, Wilderjans TF, Van den Bergh BRH, Claes L, & Amant F. "Cognitive emotion regulation in pregnant cancer patients and their partners and the relationship with anxiety and concerns". European Society of Gynaecological Oncology Congress, Nice, October 26, 2015.

Vandenbroucke T. "Psychological aspects of cancer during pregnancy". International Psycho-Oncology Society Congress, Dublin, October 20, 2016.

Vandenbroucke T. "Pediatric outcome after maternal cancer diagnosed during pregnancy". International Network on Cancer, Infertility and Pregnancy Congress: Cancer in pregnancy and fertility sparing management of gynecological cancers, Prague, February 23, 2017.

Vandenbroucke T. "Paediatric outcome after maternal cancer diagnosed during pregnancy". Spring Conference of the Royal College of Physicians of Ireland, Dublin, March 10, 2017.

Haim N*, **Vandenbroucke T***, Trefoux Bourdet A, Amant F, Koskas M. "Quality of information and decision regret during fertility sparing management for atypical hyperplasia and endometrial cancer". World Congress of Psycho-Oncology, Berlin, August 18, 2017.

Vandenbroucke T. "Challenges and support for pregnant women with cancer and their family". European Society of Gynaecological Oncology Congress, Vienna, November 5, 2017.

Vandenbroucke T. "Effects of prenatal exposure to chemotherapy on child development". European Society for Medical Oncology Asia Congress, Singapore, November 17, 2017.

Vandenbroucke T. "Kanker tijdens de zwangerschap: invloed van behandeling tijdens de zwangerschap op de ontwikkeling van het kind". Cédric Hèle Instituut congres, Mechelen, December 11, 2017.

Vandenbroucke T. "Kanker tijdens de zwangerschap: invloed van behandeling tijdens de zwangerschap op de ontwikkeling van het kind". PXL Healthcare congres, focus op oncologie, Hasselt, June 5, 2018.

Vandenbroucke T. "Effects of maternal cancer diagnosis and treatment during pregnancy on cognitive development in toddlerhood". European Pediatric Psychology Conference, Ghent, September 20, 2018.

2. POSTER PRESENTATIONS AT (INTER)NATIONAL CONFERENCES

Amant F, **Vandenbroucke T**, Verheecke M, Ottevanger PB, Fumagalli M, Mertens L, Han SN, Van Calsteren K, & Claes L. "Cancer during pregnancy: A case-control interim analysis of mental development and cardiac functioning of 38 children prenatally exposed to chemotherapy". European Society for Medical Oncology Congress, Madrid, September 27, 2014.

Amant F, **Vandenbroucke T**, Verheecke M, Gziri MM, Han SN, Van den Heuvel F, Lagae L, Willemsen MA, Kapusta L, Ottevanger PB, Mertens L, Claes L, & Van Calsteren K. "Long-term neuropsychological and cardiac follow-up of children and adults who were antenatally exposed to radiotherapy". European Society for Medical Oncology Congress, Madrid, September 27, 2014.

Vandenbroucke T, Han SN, Van Calsteren K, Wilderjans TF, Van den Bergh BRH, Claes L, & Amant F. "Cognitive emotion regulation in pregnant cancer patients and their partners and the relationship with anxiety and concerns". World Congress of Psycho-Oncology, Washington DC, July 30, 2015.

Vandenbroucke T, Han SN, Van Calsteren K, Wilderjans TF, Van den Bergh BRH, Claes L, & Amant F. "Cognitive emotion regulation in pregnant cancer patients and their partners and the relationship with anxiety and concerns". Cédric Hèle Instituut congres, Mechelen, December 1, 2015.

Amant F*, **Vandenbroucke T***, Verheecke M*, Fumagalli M, Halaska MJ, Boere I, Han S, Gziri MM, Peccatori F, Rob L, Lok C, Witteveen P, Voigt JU, Naulaers G, Vallaeys L, Van den Heuvel F, Lagae L, Mertens L, Claes L, & Van Calsteren K. "Pediatric outcome after maternal cancer diagnosed during pregnancy". European Conference on Developmental Psychology, Utrecht, September 1, 2017.

3. PRESENTATIONS / COURSES ON 'CANCER IN PREGNANCY'

January 18, 2016: Presentation entitled "Pediatric outcome after maternal cancer diagnosed during pregnancy" at UMC St-Pierre hospital Brussels.

January 30, 2017: Presentation entitled "Pediatric outcome after maternal cancer diagnosed during pregnancy" at the Intervision Group on 'Neuropsychology for children' at UZ Leuven.

March 7, 2017: Lecture entitled "Borstkanker tijdens de zwangerschap" in the training 'Banaba in de oncologische zorg' at UCLL.

June 28, 2018: Presentation entitled "Cancer during pregnancy: effects of prenatal exposure to cancer treatment on neurocognitive development" at the Focus Group on 'Cancer and Cognition' at KU Leuven.

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