Febrile Seizures and Other Paroxysmal Events in Early Childhood

The Generation R Study

Annemarie Visser

Acknowledgements

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The Generation R Study

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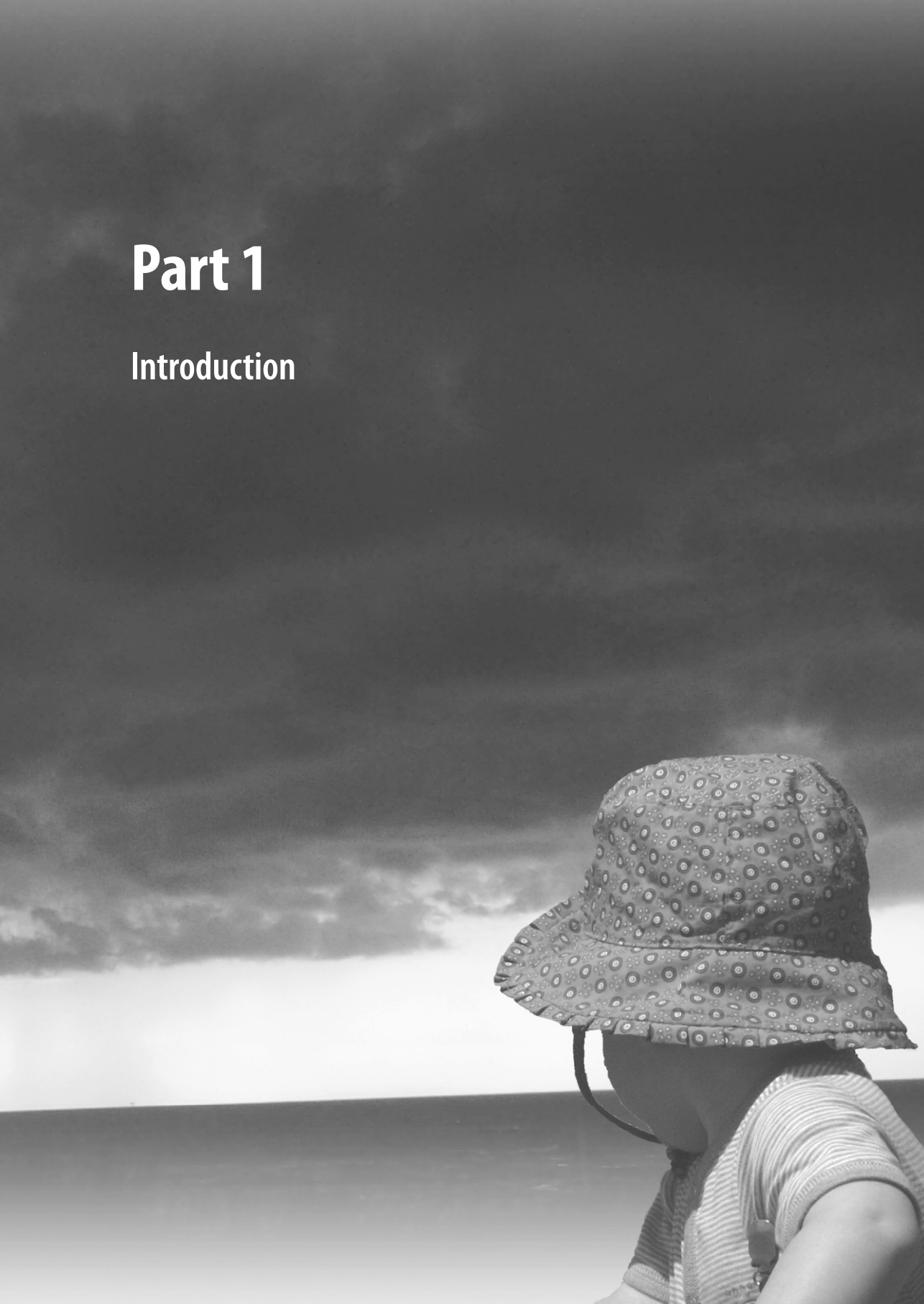
Part 1

Introduction



Seizures and epilepsy are relatively common disorders in childhood[1]. Seizures are characterized by the occurrence of paroxysmal motor, sensory, autonomic and/ or psychic symptoms. Epilepsy is defined as the occurrence of two or more unprovoked epileptic seizures. There are also several other conditions in childhood that can manifest with periodically occurring paroxysmal events[2-4]. It is important to distinguish these non-epileptic paroxysmal events from epileptic seizures. This can be challenging as they may partially share the same clinical manifestations.

NON-EPILEPTIC PAROXYSMAL EVENTS

Non-epileptic paroxysmal events can be due to physiological or exaggerated physiological responses, parasomnias, movement disorders, behavioural or psychiatric disturbances, or to hemodynamic, respiratory or gastro-intestinal dysfunction (**Table 1**)[2-3]. Knowledge of the occurrence of non-epileptic paroxysmal events is to a large part based on studies on children referred to tertiary clinics because of the suspicion of refractory seizures. In these settings, the diagnosis, often based on prolonged observation and video-EEG registrations, appears to be non-epileptic in 20-40%[5-7]. In a small study on 22 children under the age of 1 year referred to a paediatric neurologist because of possible seizures, 59% had non-epileptic paroxysmal events[8]. Not much is known about the incidence of paroxysmal events, and the incidence of different types of events relative to each other, in the general population. In the only study we have found, they were reported in 25% of the children in the first 2 years of life. The majority of these events were innocent events often related to feeding[9]. In the UK National Child Development Study, 6.7% of all children had experienced at least one episode of altered consciousness at the age of 11 years[10].

TABLE 1. Non-epileptic paroxysmal events in childhood

Category of disorder	Example
Physiologic events*	Short apnoea during sleep in newborns, stiffening in reaction to startle or pain
Parasomnias	Benign neonatal sleep myoclonus, pavor nocturnus, head banging
Hemodynamic	Cardiac arrhythmia, vasovagal syncope
Respiratory	Choking, pseudocroup, obstructive sleep apnoea syndrome
Apnoeic spells	Cyanotic spells, reflex anoxic spells (cardiovagal syncope)
Gastro-intestinal	Gastroesophageal reflux, nasopharyngeal reflux (Sandifer syndrome)
Behavioural or psychiatric disturbances	Pseudo-seizures, temper tantrums
Movement disorders	Tics, chorea

*Physiological events were defined as those that are consistent with the normal pattern of behaviour of children that age

EPILEPTIC PAROXYSMAL EVENTS

In epileptic seizures, the suddenly occurring motor, sensory, autonomic or psychic symptoms are caused by a transient dysfunction of the brain or part of the brain, because of a sudden discharge of a group of hypersensitive neurons. Different types of seizures and epilepsy syndromes are distinguished[11-12]. To classify seizures and epilepsy-syndromes the 1981 and 1989 classifications of seizures and the epilepsies by the International League Against Epilepsy (ILAE) are as yet most widely used[11 13], although a revised classification has been published recently[14]. Seizures can be divided in provoked or unprovoked whether or not provoking factors can be identified. Several epidemiological studies have been conducted on the incidence of epilepsy and seizures[1]. The highest incidence of epilepsy has been found in childhood, especially in the first years of life. The most common type of provoked seizures in childhood is the febrile seizure.

FEBRILE SEIZURES

Definition and epidemiology

Febrile seizures are defined as a condition in childhood characterized by seizures occurring during an acute febrile episode but without evidence of intracranial infections or other defined causes, occurring between 3 months and 5 years of age[15]. They are the most common type of seizures in childhood. The cumulative incidence in Western countries is 2-5% of all children in the first 6 years of life[16-23]. In Japan a somewhat higher incidence of 6-9% is reported[24]. The occurrence of febrile seizures exclusively in early childhood suggests a particular sensitivity in this phase of brain development.

Febrile seizures are divided in simple and complex seizures. Simple febrile seizures are defined as seizures that are short in duration (<15 minutes), have a generalized phenotype and do not recur in the same fever episode. Complex febrile seizures are characterized by one of the following features: focal features or onset, duration of more than 15 minutes, or recurrent seizures in the same fever episode. About 20-30% of the seizures have one of these characteristics[18 20 22 25]. Of all febrile seizures 5% present as a status epilepticus[26]. Most children have a febrile seizure only once. About one third of the children experiences a second febrile seizure in a subsequent fever episode, and of those again about half presents with a third febrile seizure[10 16-17 20 22].

Etiology; Pathogenesis

A fever episode is a prerequisite for a febrile seizure. For a long time the raise in temperature of the brain has been held solely responsible for the seizure to take place. Elevated brain

temperature alters many neuronal functions and can influence neuronal excitability[27-28]. In the past decades however, evidence of both clinical and experimental studies has emerged that components of the immune response are directly involved in the pathogenesis of febrile seizures, next to causing an increase in body temperature. Studies have specifically focussed on the pro-inflammatory cytokine interleukin-1 beta(IL-1ß). For example, in an experimental setting an exaggerated IL-1ß production was shown in leukocytes of children with febrile seizures and in brain tissue of a rat model[29-31]. Also it was discovered that children with certain genetic alterations in the interleukin system were more susceptible to febrile seizures[32]. Cytokines are presumed to give rise to an increased body temperature as well as independently to an increased neuronal excitability. The above may explain why antipyretic therapy is not protective for recurrences of febrile seizures whereas GABA-ergic drugs do prevent the seizures[33-34]. It may also explain why the same rise in temperature does not always result in febrile seizures in susceptible children.

Etiology; Risk factors

The direct provoking factor of a febrile seizure is a fever. However, although almost all children have fever episodes in the first years of life, only 2-5 % experience febrile seizures. Apparently some children are more susceptible to febrile seizures than others. The cause of this increased susceptibility is largely unknown. Several epidemiological studies have examined possible risk factors of first and recurrent febrile seizures. These studies support involvement of genetic as well as environmental factors.

Genetic factors

Almost all studies have demonstrated that febrile seizures occur at a higher than expected rate in first, second and third degree relatives of children with febrile seizures[18 35-40]. A positive family history can be elicited in 25-40% of patients with febrile seizures[25 41]. Febrile seizures are reported in 7-18% of the parents and in 8-22% of the siblings of children with febrile seizures[41]. Also twin studies have shown higher concordance rates for febrile seizures for monozygotic than for dizygotic twins[42-43 44-45]. These findings indicate involvement of genetic factors in the pathogenesis of febrile seizures.

Febrile seizures represent a heterogeneous group of disorders. Families with mendelian inheritance are rare. In some families with a high number of cases a single major locus could be involved with autosomal dominant inheritance with reduced penetrance[46-47]. In extensive linkage analysis in febrile seizure families until now 9 genetic loci have been mapped (FEB 1-9)[48-49]. Besides this a number of genetic epilepsy syndromes has been described in which seizures provoked by fever are in due course followed by afebrile seizures: Dravet syndrome, Generalized Epilepsy with Febrile Seizures plus (both usually caused by a mutation of the SCN1A gene) and Epilepsy in Females with Mental Retardation (caused by a mutation of the PCDH19 gene)[49-50].

Probably most cases of febrile seizures are genetically complex disorders influenced by variation in several susceptibility genes as well as environmental factors. In recent years, several genetic polymorphisms have been studied in relation to febrile seizures. Associations have been reported with polymorphisms in genes involved in neurotransmission and inhibition as the GABAa receptor gamma 2 subunit gene and the neuronal nicotinic acetylcholine receptor alpha 4 subunit gene. Also associations with polymorphisms in genes involved in the functioning of the immune system are reported, reflecting the possible role of the immune system in the aetiology of febrile seizures. However, most of these associations were found in small populations and could not be replicated in other studies. Until now no consistent and convincing susceptibility genes have emerged that affect the majority of febrile seizures[48-49].

Environmental factors

Several studies have addressed potential environmental risk factors for febrile seizures. A variety of pre-, and perinatal factors have been examined. Preterm birth, low birth weight and maternal complications during pregnancy such as pre-eclampsia have been suggested to be associated with an increased risk of febrile seizures[18 35-37 51-52]. Maternal smoking during pregnancy, the most important adverse fetal exposure in Western countries, has also been reported to be associated with febrile seizures by several authors[36 40 53-55]. Although results of different studies are inconsistent, these findings suggest that adverse fetal environmental exposures during pregnancy may predispose the individual to febrile seizures.

Also environmental factors in early childhood are involved in the occurrence of febrile seizures. The most obvious example is that at least a feverish illness should be present. It appears that also factors related to the illness - the type of underlying infection, the height of the fever and the number of fever episodes - influence the occurrence of first or recurrent febrile seizures. Concerning the type of infection, several studies suggest that viral infections are more frequently involved than bacterial infections and some viral infections more than others. In Western countries the highest association is found with HHV-6 and in Asian countries with Influenza type A[56]. Concerning the number of fever episodes most evidence exists for an association with febrile seizure recurrence[57-60]. One retrospective study found the number of fever episodes to be associated with the occurrence of a first febrile seizure[38]. Indirectly, others reported an association between febrile seizures and breast feeding or day care attendance[39 55].

Risk factors for febrile seizure recurrence

Also risk factors for febrile seizure recurrence have been studied. Factors associated with an increased risk are: 1. First febrile seizure in the first year of life[18 61-63], 2. Relatively low temperature at the start of the seizure[64] 3. Frequent fever episodes[57-60] 4. Positive family history of febrile seizures[64]. A family history of epilepsy was associated with recurrent febrile seizures to a lesser degree[64].

Outcome

Concerning the outcome of febrile seizures two factors can be distinguished; the risk of developing unprovoked seizures or epilepsy, and the risk of an adverse cognitive or behavioural outcome.

Epilepsy

Children with febrile seizures seem to be at increased risk of developing epilepsy. Several population-based studies reported a risk of 2-7% of unprovoked seizures compared to 0.5-2.0% in children without febrile seizures[65-68]. In incidence cohorts of epilepsy antecedent febrile seizures are reported in 13-21%[69-73]. This does not necessarily mean that febrile seizures increase the risk of developing epilepsy. Febrile seizures might just have been the first manifestation of an underlying seizure disorder. This is supported by the fact that a family history of epilepsy increases the risk of subsequent unprovoked seizures. However, indications exist that especially prolonged and focal febrile seizures can produce brain damage. This brain damage might promote subsequent unprovoked seizures. Retrospective studies especially linked a history of prolonged febrile seizures in early childhood to temporal lobe epilepsy[74].

Cognition and behaviour

The behavioural and cognitive outcomes of children with a history of febrile seizures have been subject of many studies. Most population-based cohort-studies did not find clear differences in developmental outcomes between children with and without febrile seizures and suggest that febrile seizures are an essentially benign disorder with a good prognosis[10 22 51 75-78]. Certain subgroups of children with febrile seizures however may have less favourable prognoses. Some studies reported that children with recurrent or prolonged febrile seizures perform worse on neuropsychological tests compared to healthy controls or children with single, simple febrile seizures[79-81]. Also an adverse outcome in children with a first febrile seizure before their first birthday has been suggested[77-78 82]. The majority of the aforementioned population-based studies mainly examined cognitive function in school-aged children. It is still possible that some more subtle aspects of cognitive function or behaviour might be adversely affected in children with febrile seizures. Besides this, minor cognitive or behavioural deficits at young age might have been obscured or overcome in school-aged children.

CONCLUSION

In conclusion, the etiology of febrile seizures is largely unknown. Most cases of common febrile seizures are considered to be multifactorial, influenced by a variation in several susceptibility genes as well as several pre-, and postnatal environmental factors. Cognitive outcome in

school-aged children appears to be good, perhaps with exception of children with recurrent and prolonged febrile seizures, or a first seizure at young age.

Aims of this thesis

Against this background the aims of this thesis are:

1. To examine the incidence of paroxysmal events in infancy in the general population, as well as possibly associated pre-, and perinatal factors.
2. To extend existing knowledge on the pathogenesis of febrile seizures by examining the next possible associated factors:
    a. foetal growth retardation
    b. folic acid supplement use during embryogenesis
    c. the number of fever episodes in early childhood
3. To examine behavioural problems, language development and executive functioning in pre-school children with a history of febrile seizures compared to children without such a history.

Setting of this thesis

All studies described in this thesis were embedded in the Generation R Study, a prospective population-based cohort study from early fetal life onwards. This study is designed to identify early environmental, biological and social determinants of growth, development and health[83]. The Generation R Study is conducted in Rotterdam, the second largest city of the Netherlands comprising about 585,000 inhabitants. All pregnant women living in the study area and with a delivery date from April 2002 until January 2006 were eligible for enrolment in the study. Enrolment was aimed in early pregnancy but was possible until birth of the child. Assessments were planned in early pregnancy (gestational age < 18 weeks), mid pregnancy (gestational age 18-25 weeks) and late pregnancy (gestational age > 25 weeks), and included questionnaires, physical examinations and fetal ultrasound examinations. Postnatal information on growth, development and health of the participating children was obtained from hands-on measurements at the routine child health centres and by questionnaires at the ages of 2, 6, 12, 18, 24, 36 and 48 months.

In total 9.778 mothers were enrolled in the study, of which 8.880 in pregnancy. They gave birth to 9.745 live-born children and 7.893 of these children were included for postnatal follow-up. Of all eligible children at birth, 61% participate in the study[83]. Of 598 children, parents only gave permission to use information obtained from the child health centres. Full consent for the postnatal phase of the Generation R Study, which included obtaining information from the child health centres as well as by postal questionnaires, was obtained from 7295 children and their parents. Of these 6559 already participated in pregnancy. Due to missing data on

determinants and outcomes and because of specific exclusion criteria, the population for analysis differed between the various studies presented in this thesis.

Assessment of paroxysmal events

Paroxysmal events were defined as suddenly-occurring mostly short-lasting events, with altered consciousness, altered behaviour, involuntary movements, altered muscle tone and/or a changed breathing pattern alternating with periods during which the symptoms did not occur. With this definition we aimed to include all epileptic seizures as well as conditions that can mimic them. Information about the occurrence of paroxysmal events was collected by questionnaires at the ages of 2, 6, 12, 24, 36 and 48 months. Each of these questionnaires contained direct questions asking whether any epileptic attack, epilepsy or febrile seizure had occurred. In addition the parents were asked about symptoms that could have been caused by or associated with a seizure or a non-epileptic paroxysmal event with symptoms in common with a seizure, according to our definition (**Appendices, Table 1**). These questions were adapted from previously used screening instruments for epilepsy[18 20 84-86], adjusted for this young age with some questions added that seemed relevant according to expert opinion (WFMA). If one or more of these screening-questions were answered positive, an extended follow-up questionnaire concerning this episode was sent to gather detailed information about this event (**Appendices, Additional questionnaire paroxysmal events**). In this follow-up questionnaire the parents were also asked to describe the event in their own words. If questions remained, the parents were called by phone for additional information. When a physician was consulted, the medical record of this visit and results of supplementary investigation were obtained. Based on this information, the events were classified into one of 8 mutually exclusive categories of paroxysmal events (**Appendices, Table 2**). The events were classified independently by two authors (AMV and WFA). Direct consensus was present in 95%; in the other 5%, discussion led to agreement in about half. If consensus could not be reached, the event was classified as "unknown".

Definition of febrile seizure

A febrile seizure was defined as an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with a fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who had suffered a previous non-febrile seizure or in children with known neurological disabilities were excluded[15]. All seizures were given the annotation 'definite', 'probable' or 'possible' (**Appendices, Table 2**). Because of the degree of uncertainty, febrile seizures with the annotation "possible" were excluded in our analyses on febrile seizures.

Outline of the thesis

Part 1 gives an introduction to the topics described in this thesis. In **part 2**, the incidence of paroxysmal epileptic and non-epileptic disorders in the first year of life is studied. Also possible associated prenatal and perinatal factors that might predict them are examined. The next part addresses febrile seizures. In **chapter 3.1** we report on the validity of parentally reported febrile seizures. Next we describe the association between fetal growth retardation (**chapter 3.2**) and inadequate folic acid supplement use (**chapter 3.3**) in pregnancy, and the risk of febrile seizures. Also results are presented of our study on the association between the number of fever episodes and the risk of first or recurrent febrile seizures (**chapter 3.4**). In **chapter 3.5** we report on the outcome of febrile seizures in pre-school children. In **Part 4** we provide an overview of our main findings and discuss their significance and clinical implications. Also suggestions for further research are presented. **Part 5** provides a summary of the findings in Dutch.

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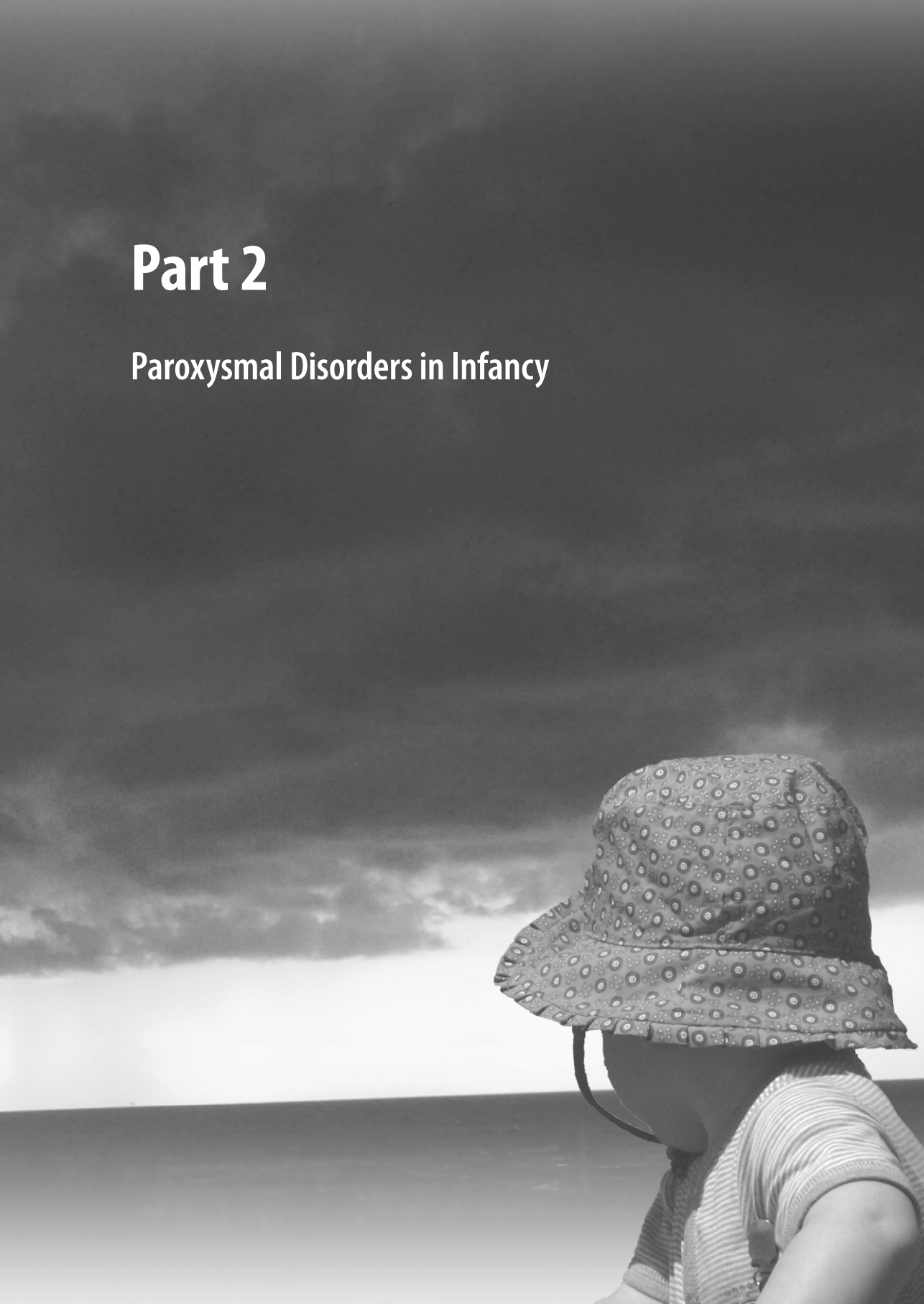
Part 2

Paroxysmal Disorders in Infancy



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Chapter 2.1

Paroxysmal disorders in infancy and their risk factors in a population-based cohort

ABSTRACT

We examined the incidence of paroxysmal epileptic and non-epileptic disorders and the associated prenatal and perinatal factors that might predict them in the first year of life in a population-based cohort. This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards. Information about the occurrence of paroxysmal events, defined as suddenly-occurring episodes with an altered consciousness, altered behaviour, involuntary movements, altered muscle tone and/or a changed breathing pattern, was collected by questionnaires at the ages of 2, 6 and 12 months. Information on possible prenatal and perinatal determinants was obtained by measurements and questionnaires during pregnancy and after birth. Information about paroxysmal events in the first year of life was available in 2860 participants (1410 males, 1450 females). We found an incidence of paroxysmal disorders of 8.9% (n=255) in the first year of life. Of these participants, 17 were diagnosed with febrile seizures and two with epilepsy. Non-epileptic events included physiological events, apnoeic spells, loss of consciousness by other causes then epileptic seizures or apnoeic spells, parasomnias and other events. Preterm birth ($p < 0.001$) and low Apgar scores at 1 minute ($p < 0.05$) were significantly associated with paroxysmal disorders in the first year of life. Continued maternal smoking during pregnancy and preterm birth were significantly associated with febrile seizures in the first year of life ($p < 0.05$). Our results suggest that paroxysmal disorders are frequent in infancy. They are associated with preterm birth and a low Apgar score. Epileptic seizures only form a minority of the paroxysmal events in infancy. In this study, children whose mothers continued smoking during pregnancy had a higher reported incidence of febrile seizures in the first year of life. These findings may generate various hypotheses for further investigations.

INTRODUCTION

Seizures and epilepsy are a common problem in childhood[1]. There are also many conditions that can mimic them[2-4]. It is important to distinguish non-epileptic paroxysmal events from epileptic seizures. In epileptic seizures, the suddenly occurring motor, sensory, autonomic or psychic symptoms are caused by a transient dysfunction of the brain or part of the brain, because of a sudden discharge of a group of hypersensitive neurons. Different types of seizures and epilepsy syndromes are distinguished[5-6]. Non-epileptic paroxysmal events can be due to physiological or exaggerated physiological responses, parasomnias, movement disorders, behavioural or psychiatric disturbances, or to haemodynamic, respiratory or gastrointestinal dysfunction[2-3]. They seem to be frequent in early childhood[4 7].

Several epidemiological studies have examined the incidence of epilepsy and seizures[1]. Few data exist on the incidence of non-epileptic paroxysmal events and the relative frequency of the different types of events in the general population. In one study, they were reported in 25% of the children in the first 2 years of life. Most of these events were innocent events often related to feeding[7]. In UK National Child Development Study, 6.7% of all children had experienced at least one episode of altered consciousness at the age of 11 years[8].

As physicians are often confronted with paroxysmal disorders in young children, we wanted to determine how often these disorders occur in the first year of life in an unselected population in the Netherlands, and what part is accounted for by epilepsy and seizures. We hypothesized that the incidence of various types of paroxysmal disorders would be considerable, but that epileptic seizures would only account for a small minority of them. We also examined whether pre-defined prenatal and perinatal variables were associated with any or all of these disorders.

METHOD

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life until young adulthood. This study is being conducted in Rotterdam, the second largest city in The Netherlands. It is designed to identify early environmental and genetic determinants of growth, development and health in fetal life, childhood and adulthood and has been described previously in detail[9-10]. Enrolment took place in early pregnancy. Assessments during pregnancy included questionnaires, physical examinations and fetal ultrasound examinations. Postnatal information on growth and development of the participating children was obtained by questionnaires and from information obtained routinely in young children in Dutch child health centres.

This study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from the legal representatives of all participants.

Assessment of paroxysmal events

We defined paroxysmal events as suddenly-occurring mostly short-lasting events, with altered consciousness, altered behaviour, involuntary movements, altered muscle tone and/or a changed breathing pattern alternating with periods during which the symptoms did not occur. With this definition we aimed to include all epileptic seizures as well as conditions that could mimic them. Information about the occurrence of paroxysmal events was collected by questionnaires at the ages of 2, 6 and 12 months. Each of these questionnaires contained direct questions asking whether any epileptic attack, epilepsy or febrile seizure had occurred. In addition, the parents were asked about symptoms that could have been caused by or associated with a seizure, or a non-epileptic paroxysmal event with symptoms in common with a seizure, according to our definition (**Table 1**). These questions were adapted from previously used screening instruments for epilepsy[11-13], adjusted for this young age with some questions added that seemed relevant according to the opinion of the last author (WFMA). If one or more of these questions were answered positive, an extended follow-up questionnaire about this episode was sent to the parents to gather detailed information about the event. In this follow-up questionnaire the parents were also asked to describe the event in their own words. If questions remained, the parents were telephoned for additional information**.** When a physician was consulted, the medical record of this visit and results of supplementary investigations were obtained. Based on this information, the events were classified into one of 8 mutually exclusive

TABLE 1. Screening questions

1.	Has your child had an epileptic attack during this period or has your child been diagnosed as having epilepsy?
2.	Has you child had feverish fits or convulsions during this period?
3.	Has your child sometimes suddenly lost consciousness, either partially or completely, during this period and failed to react when spoken to?
4.	Has your child had periods during these months in which he or she was suddenly distracted, and you could no longer make contact with him or her?
5.	Has your child ever had an attack of muscular spasms or trembling that started suddenly or any other involuntary movements of the entire body or part thereof (arms, legs, hands, face, torso, tongue) during this period?
6.	During this period has your child become completely rigid or tense or contrary to this, completely limp?
7.	Has your child had a period during these months when it suddenly stopped breathing or had a different breathing pattern?
8.	Have there been occasions during this period when your child suddenly started to show strange behaviour or made strange movements while asleep?

categories of paroxysmal events (**Table 2**). When participants reported at least one of a certain paroxysmal event, they were classified as having this paroxysmal disorder independent of how often the event had occurred. The events were classified independently by the first (AMV) and last author (WFMA). Direct consensus was present in 95%; in the other 5%, discussion led to agreement in about half of the events. If consensus could not be reached, the event was classified as "unknown".

Events that did not correspond to our definition of a paroxysmal event were classified as "no paroxysmal event". Physiological events were defined as those that were consistent with the normal pattern of behaviour of children that age; most often reported were a short apnoea during sleep in newborn babies or sudden stiffening in reaction to startle or pain.

For the epileptic seizures, the classification of seizures by the International League Against Epilepsy was used [5 6]. Febrile seizures were defined as a condition in childhood characterized by seizures occurring during an acute febrile episode but without evidence of intracranial infections or other defined causes[15]. Epilepsy was defined as a disorder characterized by recurrent unprovoked seizures. Neonatal seizures were defined as seizures within the first 4 weeks of life. All other seizures were categorised as "seizure, other". All seizures were given the annotation "definite", "probable" or "possible".

Apnoeic spells included cyanotic spells, provoked by anger and crying, and reflex anoxic spells (cardiovagal syncope), provoked by sudden pain or fright. Episodes of losing consciousness due to other causes than an epileptic seizure or apnoeic spell (for example vasovagal syncope) were placed in category 5. The parasomnias included arousal disorders, sleep-wake transition disorders and other parasomnias (mainly benign neonatal sleep myoclonus)[16].

All events that did not fit into one of the aforementioned categories were defined as "other". Most of these were related to the respiratory or gastrointestinal system (choking, pseudocroup, reflux). In some cases there was insufficient information to classify the event into one of the aforementioned groups, or the event remained unclear even after thorough examination.

TABLE 2. Classification of events

1. No paroxysmal event	Does not fulfil our definition of a paroxysmal event
2. Physiologic event	Behaviour that can be normally seen in children of this age group
3. Seizure disorder [a]	Including epilepsy, neonatal seizures, febrile seizures, other seizures
4. Apnoeic spell	Cyanotic spells or reflex anoxic spells
5. Loss of consciousness	not caused by a seizure or a breath holding spell
6. Parasomnia	Benign neonatal myoclonus, repetitive movements, arousal disorder
7. Other	Paroxysmal events not belonging to one of the other categories
8. Unknown	Insufficient data to classify in one of the aforementioned groups

[a] definite: diagnosis confirmed by a physician; probable: diagnosis "probable seizure" according to a physician or history characteristic for a seizure; possible: diagnosis "possible seizure" according to a physician or history that could point to a seizure but not characteristic. Possible seizures were categorised in group 8 "unknown ".

These events were classified as unknown. Because of the degree of uncertainty, episodes that had been classified as "possible seizures" were reclassified into the "unknown" group.

When participants reported the same event in different questionnaires, we registered this event only once at the youngest age of occurrence.

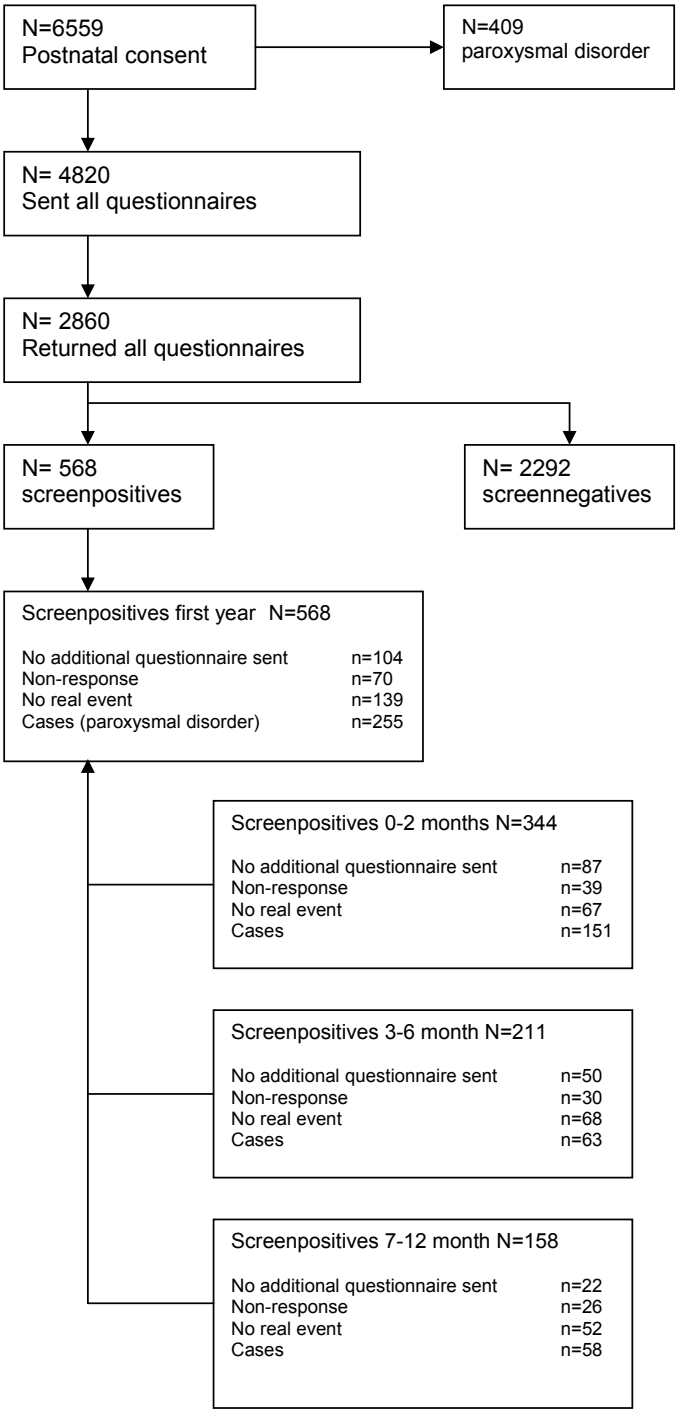
Prenatal and perinatal risk factors

Information about ethnicity and parity as well as the medical history of the mother were obtained by the first questionnaire at enrolment in the study. Maternal smoking habits were assessed in each questionnaire. Smoking during pregnancy was defined as continued smoking after the pregnancy was known. Gestational age was established by fetal ultrasound examination. At the ultrasound in the third trimester of pregnancy (after 25 wks) fetal weight was estimated and head circumference was measured. A low estimated fetal weight or a small head circumference were defined as an estimated fetal weight or head circumference under the 10th percentile of the whole group, adjusted for gestational age. Date of birth, birth weight, Apgar scores and gender were obtained from midwife and hospital registries. Preterm birth was defined as birth before 37 completed weeks of gestation. A low Apgar score was defined as an Apgar score below 7. Head circumference was measured prenatally at 30 weeks gestation and postnatally at about 8 weeks of age. Head circumference at birth was not available in all children.

Study population

In total, 6559 of the prenatally included children were enrolled for the postnatal phase (**Figure 1**). Owing to logistic constraints not all participants were sent all questionnaires. In total, 6015 participants were sent the 2-month questionnaire, 5576 participants the 6-month questionnaire and 6492 the 12-month questionnaire. The response on these questionnaires was about 80%. There were 650 (13.6%) screen-positives in the 2-month questionnaire, 341 (8.6%) in the 6-month questionnaire and 288 (6.4%) in the 12-month questionnaire. Altogether, 4770, 3984 and 4522 participants returned the 2-, 6- and 12- months questionnaire respectively, as well as the follow-up questionnaire for these sampling-periods for screen-positives. When the three questionnaires were combined, 409 participants reported a paroxysmal event in at least one of these sampling periods. Of all participants, 4820 were sent the 2-, 6-, as well as the 12-months questionnaire. Of these, 2860 returned all three questionnaires. In total, 2292 participants were screen-negative in all sampling periods and 568 were screen-positive at least once. Of those, 104 (18%) were not sent the follow-up questionnaire owing to logistic constraints; of those who did receive the follow-up questionnaire, 70 (15%) did not return it and 139 (24%) did not fulfil our criteria of a paroxysmal event. Therefore, 255 of the 2680 participants returning all three screening questionnaires reported at least one paroxysmal event in the first year of life.

FIGURE 1. Flow diagram of the study population (complete cases)



Subgroup analysis showed that participants whose parents or carers did not return their questionnaires were more often of another origin than Dutch, their mothers were not as well-educated and more often had continued smoking during pregnancy.

Statistical analysis

The incidence of paroxysmal disorders, that is the percentage of children with a paroxysmal disorder in the first year of life, was calculated. For this calculation only participants who returned all three questionnaires in the first year of life, were used (n=2860). As the profile of positively answered screening questions of the responders and of the non-responders on the follow-up questionnaire was similar (data not shown), we also calculated the estimated incidence assuming that the distribution of events in the non-responders was similar as in the responders. For each sampling period the distribution of the different disorders was calculated. For this calculation the participants who answered the questionnaires concerning this sampling period were used, irrespective of whether they answered the other questionnaires (0-2 months n=4770; 3-6 months n=3984; 7-12 months n=4522). To calculate the distribution of the different disorders in the entire first year only participants who answered all questionnaires were used (n=2860). Exploratory analyses examined whether prenatal or perinatal factors were associated with the occurrence of paroxysmal disorders in the first year of life. For this calculation we used participants who reported at least one paroxysmal event in one of the sampling periods as cases, irrespective of whether they answered the other questionnaires in the first year of life (n=409). The participants who were screen-negative in all questionnaires were used as controls (n=2292). First unadjusted odds ratios were calculated. Afterwards we included all variables that were associated with the risk of paroxysmal events in univariable models (p-value < 0.1) for multivariable logistic regression analysis. This was done to determine whether any apparent associations between explanatory variables and the risk of paroxysmal events might have instead been caused by correlations with other associated explanatory variables. All statistical analyses were performed using the Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Paroxysmal events

Table 3 shows the distribution of the different types of paroxysmal disorders in the first year of life. Paroxysmal events were reported most frequently in the first 2 months of life, declining over the 3- to 6- month and the 7- to 12- month periods. The incidence of paroxysmal disorders, that is the percentage of children with a paroxysmal disorder in the first year of life, was 255

TABLE 3. Paroxysmal disorders in the first year of life

	0-2 months, N=4770 N (%)	3-6 months, N=3984 N (%)	7-12 months, N= 4522 N (%)	First year of life N=2860 N (%)
Physiologic events	150 (62%)	40 (45%)	15 (18%)	133 (52%)
Seizures	7 (3%)	7 (8%)	23 (27%)	24 (9%)
Febrile seizure	1**	7	20	17
Epilepsy	1	-	2	2
Neonatal seizure	5	-	-	4
Other		-	1	1
Loss of consciousness	18 (8%)	16 (18%)	7 (8%)	26 (10%)
Apnoeic spells	5 (2%)	6 (7%)	11 (13%)	12 (4%)
Parasomnias	8 (3%)	5 (5%)	3 (4%)	10 (4%)
Paroxysmal events, other	40 (17%)	11 (12%)	11 (13%)	36 (14%)
Unknown	12 (5%)	5 (5%)	14 (17%)	18 (7%)
Total	240	90	84	259*

Numbers represent the number of participants with the specific event at least once in this period. Calculation of the distribution of different paroxysmal disorders in the three sampling periods was based on participants who answered at least the 2 months (n=4770), 6 months (n=3984) and 12 months questionnaire (n=4522) respectively. Calculation of the distribution of paroxysmal disorders in the first year of life was based on participants who answered all questionnaires in the first year of life (n=2860). * number represents event-types, 259 event-types in 255 participants. ** seizure associated with fever

out of 2860 (8.9%) of which 133 out of 255 (52%) were physiologic events. Probably this value of 8.9% is an underestimation as not all screen positives returned the follow-up questionnaire. Extrapolating the distribution of events in the responders to the non-responders on the additional questionnaire would result in a percentage of paroxysmal disorders in the first year of life of 12.9%.

In the first 6 months of life most events consisted of physiologic events, whereas in the 7 to 12 months age category physiologic events constituted less then 20% of the reported paroxysmal events. In the first year of life 24 children had at least one seizure and most of these (n=17) were febrile. They occurred especially between 6 and 12 months of age. Neonatal seizures occurred in four children. Epilepsy was diagnosed in two children in the first year of life.

Risk factors

Table 4 shows that children who are born preterm (OR 2.44; 95% confidence interval [CI] 1.61-3.70) or have a low Apgar score at 1 minute (OR 1.98; 95% CI 1.29-3.04) have a higher incidence of paroxysmal disorders in the first year of life. Physiologic events are reported more often in first born children (OR 1.93; 95% CI 1.40-2.66). As these events form a large part of the paroxysmal

TABLE 4. Relations between pre-, and perinatal variables and the occurence of a paroxysmal disorder in the first year of life

	Paroxysmal disorders, all n=409 OR (95% CI)	Non-physiological events, n= 174 OR (95% CI)	Physiological events, n=205 OR (95% CI)	Febrile seizures, N=28 OR (95% CI)	Apnoeic spells, n=22 OR (95% CI)	Loss of consciousness, n=41 OR (95% CI)
Maternal determinants						
Smoking during pregnancy	1.15 (0.83-1.59)	1.06 (0.65-1.73)	1.08 (0.69-1.69)	2.72 (1.05-7.00)***	1.13 (0.33-3.84)	0.44 (0.11-1.86)
Primiparous	1.50 (1.20-1.88)***	1.08 (0.79-1.49)	1.93 (1.40-2.66)***	1.19 (0.55-2.58)	1.42 (0.58-3.49)	1.28 (0.67-2.44)
History of febrile seizures	1.31 (0.67-2.54)	1.03 (0.37-2.87)	1.45 (0.62-3.43)	1.89 (0.25-14.35)	2.12 (0.28-15.2)	1.12 (0.15-8.30)
Child determinants						
Male	1.01 (0.82-1.24)	1.10 (0.81-1.49)	0.99 (0.74-1.32)	1.62 (0.75-3.46)	1.04 (0.45-2.41)	1.34 (0.72-2.49)
Ethnicity, Dutch	1.07 (0.85-1.34)	1.17 (0.83-1.65)	1.00 (0.74-1.36)	1.67 (0.68-4.15)	0.79 (0.33-1.90)	1.24 (0.62-2.49)
EFW 30 weeks pregnancy SDS[a]< 10th percentile	1.21 (0.87-1.70)	1.53 (0.98-2.41)***	0.94 (0.58-1.54)	2.04 (0.77-5.40)	2.08 (0.70-6.18)	1.29 (0.50-3.32)
HC 30 weeks pregnancy SDS< 10th percentile	1.08 (0.77-1.54)	1.31 (0.81-2.10)	0.95 (0.58-1.55)	2.59 (1.04-6.44)**	0.93 (0.22-4.02)	1.01 (0.36-2.86)
Preterm birth	2.44 (1.61-3.70)***	2.27(1.29-3.99)***	2.03 (1.17-3.51)***	2.72 (0.81-9.14)***	-	0.55 (0.08-4.06)
Birthweight SDS < 10th percentile	1.13 (0.80-1.59)	1.21 (0.75-1.97)	1.00 (0.62-1.61)	1.18 (0.35-3.95)	0.43 (0.06-3.19)	1.61 (0.67-3.86)
Apgarscore at 1 min <7	1.98 (1.29-3.04)***	2.04 (1.14-3.64)**	1.69 (0.95-3.00)*	1.70 (0.40-7.23)	1.04 (0.14-7.82)	3.13 (1.21-8.13)**
Apgarscore at 5 min <7	2.33 (0.96-5.65)*	2.95 (1.00-8.73)*	1.11 (0.26-4.75)	-	-	2.87 (0.38-21.74)

N=2701; participants who reported a paroxysmal event in the first year of life (n=409) or who were screen negative at all questionnaires in the first year of life (n=2292).
EFW= estimated fetal weight, HC=head circumference, SDS= standard deviation score, Prematutity = gestational age < 37 weeks at birth
All variables associated with the risk of paroxysmal events in univariate models (p-value < 0.1) were included for multivariable analysi* p-value< 0.10 in univariable analyses, ** p-value< 0.05 in univariable analyses, *** p-value<0.05 in multivariable analyses

disorders in the first year of life this remains a significant factor when all disorders are taken together (OR 1.50; 95% CI 1.20-1.88). In multivariable logistic regression analysis preterm birth and a low estimated fetal weight at ultrasound examination in late pregnancy are significantly associated with non-physiological paroxysmal disorders in the first year of life.

Table 4 also shows the results for some subgroups of paroxysmal disorders. Children with a small head circumference on the ultrasound examination at 30 weeks' gestation had a higher incidence of febrile seizures in the first year of life (OR 2.59; 95% CI 1.04-6.44) and the same was true for children whose mother continued smoking during pregnancy (OR 2.72; 95%CI 1.05-7.00) or who were born preterm. Also children whose mothers had a history of febrile seizures themselves tended to have febrile seizures more often; however, this was not significant. In multivariable regression analysis the association with head circumference was no longer statistically significant (OR 1.89; 95% CI 0.63-5.67). None of the risk factors studied predisposed for apnoeic spells in the first year of life. Children with a low Apgar score 1 minute after birth more often had an episode with loss of consciousness.

DISCUSSION

In this prospective population-based study we found that paroxysmal disorders, defined as disorders characterized by suddenly-occurring episodes with an altered consciousness, altered behaviour, involuntary movements, altered muscle tone and/or a changed breathing pattern, are common in the first year of life with an estimated incidence of 8.9 to 12.9%. The largest group of these events are innocent, physiologic events. Epileptic seizures only form a small minority of these events. Preterm birth and low Apgar scores were associated with paroxysmal disorders in the first year of life. Physiologic events were reported more often in first-born children. Children with a small head circumference at 30 weeks' gestational age, who were born preterm or whose mothers continued smoking during pregnancy had a higher incidence of febrile seizures in the first year of life.

We found an incidence of paroxysmal disorders, i.e. the percentage of children with a paroxysmal disorder in the first year of life, of 8.9 to 12.9%. The only other study on different types of paroxysmal events in the general population that we are aware of reported a prevalence of 25% in the first two years of life[7]. That study also found preterm birth and a low Apgar score at birth to be associated with paroxysmal events in early life. This may partly be a result of more anxiety and attention among parents of children with a difficult start, but these children may also be more vulnerable for some of these events. It is remarkable that low Apgar scores are associated with paroxysmal disorders in the first year of life, as it is well established that early Apgar scores at 1 and 5 minutes have no substantial predictive value on neurological outcome[18]. That physiological events are reported more for first-born children is probably explained by parents with their first child not yet being familiar with certain events in young children.

We found that children who had a small head circumference on the ultrasound examination in late pregnancy had a higher incidence of febrile convulsions in the first year of life. This could point to negative influences on brain development during pregnancy rendering the child more susceptible to febrile convulsions later in life. Possibly the smoking behaviour of the mother might play a role in this as it is known that smoking during pregnancy has a negative impact on brain development[19]. We found that mothers of children with febrile convulsions more often had continued smoking during pregnancy. After adjusting for smoking during pregnancy the association between head circumference and febrile seizures became smaller suggesting that smoking might be part of the causal pathway. The literature on the association of smoking during pregnancy and febrile seizures in the offspring shows conflicting results. In the largest study a small increase in the incidence of febrile convulsions was found in the offspring of mothers smoking more than 10 cigarettes a day during pregnancy[20-21]. The relation between maternal smoking, fetal brain development and febrile convulsions deserves further investigation.

We found that epileptic seizures only form a small subgroup of paroxysmal events in the first year of life. This is important to realise as an erroneous diagnosis of epilepsy can have negative consequences, both because of unnecessarily prescribed medication with possible adverse effects and because of the negative implications this diagnosis might have for daily life[22].

The strength of this study is the population-based cohort with a large number of subjects studied from early pregnancy. Our data were collected prospectively and are, therefore, less dependent on parental recall. Our study also has some limitations. In the first place, no validated screening instrument for epilepsy or seizures exists for this young age. In the past different screening questionnaires have been used for seizure-disorders, few of which had been validated before[11-13 17]. Our screening questions were partly based on these existing questionnaires, adjusted for this low age group, and extended with some questions that appeared relevant according to an experienced child neurologist. We found only two children diagnosed with epilepsy in the first year. However, in this relatively small population, this is compatible to what might be expected for a relatively infrequent disorder like epilepsy[1]. The specificity of our questions for epileptic events was low and most of the paroxysmal events did not concern seizures. We used these events to estimate the incidence of non-epileptic paroxysmal disorders in the general population.

Information on paroxysmal events was missing in about 20% of the participants in the three sampling-periods (0-2, 3-6 and 7-12 months) and only 2860 participants received and returned all screening questionnaires in the first year of life. About 25% of all screen-positives, did not receive or return the supplementary questionnaire. Subgroup analysis showed that participants whose parents or carers did not return the questionnaires were more often of another origin than Dutch, their mothers were less educated and more often had continued smoking during pregnancy. Therefore our results should be only cautiously extrapolated to this group. The estimated incidence of paroxysmal disorders in the first year of life might be affected. Some parents might not report a physiologic event as they already feel the event was innocent or

they did not pay attention to it. This could lead to an underestimation of the incidence of physiological events. Using the complete cases only for the first year analysis might have introduced bias in the subdivision of paroxysmal disorders. However, as the subdivision of paroxysmal disorders in the three sampling periods was similar for participants who participated in the full year analysis as for those who did not, this seems unlikely. Our effect estimates for the associations of prenatal and perinatal factors with paroxysmal disorders would be biased if these associations differed between those with and without complete data. This cannot be excluded but seems unlikely.

In conclusion, we found that paroxysmal events are seen frequently in early childhood. Many of these events are innocent physiologic events, especially in the first 6 months of life. Epileptic seizures only form a minority of the paroxysmal events in the first year of life. This information seems to us to be very relevant. It may be of help in developing rational investigation strategies in infants who present with paroxysmal events. Moreover, we found preterm birth, low birth weight, and low Apgar scores to be associated with paroxysmal disorders in the first year of life. Children with a small head circumference in the third trimester of pregnancy have a higher incidence of febrile seizures in the first year of life. Maternal smoking during pregnancy might be partly responsible for this finding. However, as there was multiple testing, our results should be considered as hypothesis generating rather than suggesting direct causal associations. Further studies are needed to explain these associations.

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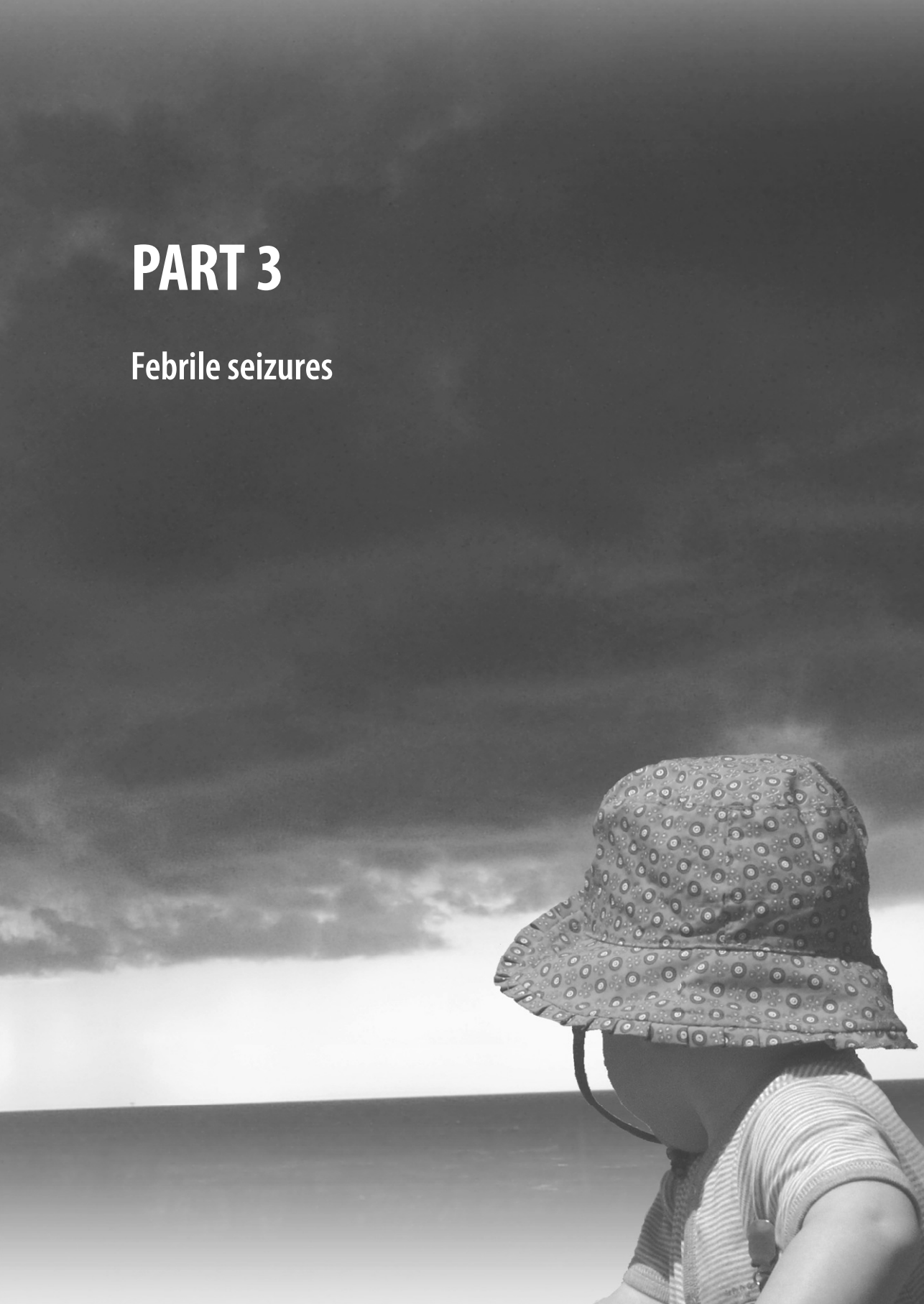
PART 3

Febrile seizures



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Chapter 3.1

Validity of parentally reported febrile seizures

ABSTRACT

We examined the validity of febrile seizures as reported by the parents. This study was embedded in a population-based prospective cohort study from early fetal life onwards. Information on paroxysmal events was obtained by screening questions at the age of 1, 2 and 3 years. One of these questions was: "Did your child have a febrile seizure?". In case screen-positive an extensive additional questionnaire was sent and the medical record consulted. Based on this information paroxysmal events were classified by an experienced paediatric neurologist as febrile seizure or other event. The validity of a positive reply to the screening question on febrile seizures was assessed taking this classification as reference standard. Analyses were based on 610 subjects. The sensitivity of the positive reply to the question "Did your child have a febrile seizure?" for the diagnosis of febrile seizures was 92%, the specificity 72%, the positive predictive value 41% and the negative predictive value 98%. Among the false-positives, an isolated fever, shivering during a fever episode and vasovagal collapse were the most frequent diagnoses. In conclusion, sensitivity of the question "Did your child have a febrile seizure?" is high and specificity moderate. The positive predictive value is only 41%. Although this question may be appropriate as screening instrument for febrile seizures, a second stage of evaluation is necessary to identify true cases.

INTRODUCTION

Febrile seizures are the most common type of seizures in childhood, affecting 2-5% of all children between 3 months and 5 years of age[1-7]. The etiology remains largely unknown but genetic as well as environmental factors likely play a role. A family history of febrile seizures is the most consistently identified risk factor for febrile seizures[8-13]. The prognosis of febrile seizures seems to be good, although the risk of developing epilepsy appears to be increased[13-18]. To increase insight in pathogenesis and outcome, febrile seizures are subject of several epidemiological and genetic studies. For research purposes, the correct identification of febrile seizure-cases is crucial. Case identification in large populations can be done prospectively by interviewing and examining all participants or by surveillance of hospital admissions and medical records. Although in this way cases are most likely to be accurately diagnosed, it can be time-consuming and expensive. Also cases who do not consult a physician might be missed. An efficient and inexpensive alternative is provided by a questionnaire survey. Concerns may exist however with regard to the accuracy of self-reported information.

In a prospective population-based cohort study, we assessed the validity of parentally reported febrile seizures, as compared to a physician-made diagnosis. We also assessed which of 8 screening questions on paroxysmal disorders had the highest predictive value for febrile seizures. We further examined what disorders were most often diagnosed in connection with a false-positive answer to the screening question on febrile seizures.

METHODS

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life until young adulthood in Rotterdam, The Netherlands[20]. Enrolment was aimed in early pregnancy. Follow up assessments in parents and children included questionnaires, physical and ultrasound examinations, and use of medical records. This study has been approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from the legal representatives of all participants.

Assessment of paroxysmal events

Information about the occurrence of paroxysmal events was collected by questionnaires at the ages of 12, 24 and 36 months. Each of these questionnaires contained the direct question: "Did your child have a febrile seizure / febrile convulsion" (two generally used Dutch terms for febrile seizures "koortsstuip/ koortsconvulsie" were used). In addition the questionnaire contained 7

other questions about paroxysmally occurring symptoms and signs (**Table 1**). If one or more of these questions were answered positive, an extended questionnaire concerning this episode was sent to gather detailed information about this event. When a physician was consulted, the medical record of this visit and results of supplementary investigations were obtained. Based on this information the events were independently classified in one of eight categories of paroxysmal events by the first author and an experienced paediatric neurologist (WFA) (**Table 2**). If consensus could not be reached, the event was classified as "unknown".

Febrile seizures (FS) were defined as a condition in childhood characterized by seizures occurring during an acute febrile episode but without evidence of intracranial infections or other defined causes. They were classified as physician confirmed FS, probable FS or possible FS. Because of the degree of uncertainty, episodes that had been classified as "possible FS" were reclassified into the "unknown" group.

TABLE 1. Screening questions on paroxysmal events

	Febrile seizures N=107 % (n)*
1. Has your child had an epileptic attack during this period or has your child been diagnosed as having epilepsy?	3% (2)
2. Has you child had feverish fits or convulsions during this period?	92% (98)
3. Has your child sometimes suddenly lost consciousness, either partially or completely, during this period and failed to react when spoken to?	23% (25)
4. Has your child had periods during these months in which he or she was suddenly distracted, and you could no longer make contact with him or her?	12% (13)
5. Has your child ever had an attack of muscular spasms or trembling that started suddenly or any other involuntary movements of the entire body or part thereof (arms, legs, hands, face, torso, tongue) during this period?	27% (29)
6. During this period has your child become completely rigid or tense or contrary to this, completely limp?	21% (23)
7. Has your child had a period during these months when it suddenly stopped breathing or had a different breathing pattern?	14% (15)
8. Have there been occasions during this period when your child suddenly started to show strange behaviour or made strange movements while asleep?	10% (11)

*percentage (number) of caregivers of all 107 children with true febrile seizures, that answered these screening questions with "yes"

TABLE 2. Classification of events, reported as febrile seizures by the parents

	Screen-positives[1]		
Classification	12 months questionnaire N=72	24 months questionnaire N=102	36 months questionnaire N=99
1. No paroxysmal event	34% (24)	19% (20)	34% (33)
2. Physiologic event	3% (2)	12% (12)	8% (8)
3. Seizure disorder			
a. Febrile seizure	35% (25)	48% (49)	29% (29)
b. Febrile seizure, possible	6% (4)	5% (5)	5% (5)
c. Seizure disorder other	3% (2)	1% (1)	4% (4)
4. Apnoeic spell			1% (1)
5. Loss of consciousness	8% (6)	7% (7)	6% (6)
6. Parasomnia	1% (1)	1% (1)	3% (3)
7. Other		4% (4)	5% (5)
8. Unknown	11% (8)	3% (3)	5% (5)

[1] participants who answered the question "Did your child have a febrile seizure?" with "yes" in the 12, 24 or 36 months questionnaire and returned the additional questionnaire

Population for analysis

In total 882 participants answered one or more screening questions positively in at least one of the three questionnaires on the first three years of life, and they were eligible for the present study. In 272 of these, the event could not be classified as the participants did not receive or return the additional questionnaire and these participants were excluded from further analysis. Of the remaining 610 participants, 244 at least once gave a positive answer to the question "Did your child have a febrile seizure?" (**Table 3**).

Data-analysis

First we calculated sensitivity (percent true febrile seizures reported as febrile seizures), specificity (percent true no febrile seizures reported as no febrile seizures), positive predictive value

TABLE 3. Positive screening question on febrile seizures versus a diagnosis of febrile seizures in children with paroxysmal events

	Febrile seizure	No febrile seizure	Total
Screen positive	98	143	241
Screen negative	9	360	369
Total	107	503	610*

*N= 610 participants answered at least one of the screening questions on paroxysmal events positively, of which 244 participants answered the question "Did your child have a febrile seizure?" with "yes" (screen-positive). N=107 of these participants were diagnosed as a febrile seizure, as based on the combination of 8 screening questions and the additional questionnaire

(PPV; percent reported as febrile seizure, that is, true febrile seizure) negative predictive value (PNV; percent reported as no febrile seizure, that is, true no febrile seizure) and likelihood ratio of the question "Did your child have a febrile seizure?". The classification of paroxysmal events by an experienced paediatric neurologist, based on the extended questionnaire and if available on the medical record, was taken as the reference standard. This concerned events of participants who were screen-positive on at least one of 8 screening questions. Next, we calculated which of these screening questions had the highest sensitivity for febrile seizures next to the direct question on febrile seizures and whether including a second screening question would improve the validity of the screening instrument. Finally, we assessed which disorders were diagnosed most often in connection with a false-positive screening question on febrile seizures.

RESULTS

Non-response analyses showed that participants who did not return their questionnaires were more often not from Dutch origin and were less well educated.

Table 4 shows that sensitivity of the screening question: 'Did your child have a febrile seizure?" was high (92%) and specificity moderate (72%). The negative predictive value is nearly 100%. The positive predictive value was 41%. The likelihood ratio of a positive answer was 3.2, and of a negative answer 0.1. Of all screening questions the direct question on febrile seizures had the highest sensitivity to detect febrile seizures. In children with febrile seizures, involuntary movements, loss of consciousness and suddenly turning rigid or limp were reported in 27, 23 and 21 percent respectively (**Table 1**). Using the question on febrile seizures together with the question on involuntary movements as screening instrument increased sensitivity to 94%. Specificity became lower (61%) and the positive predictive value diminished to 34%.

The majority of children reported to have experienced a febrile seizure by their parents did not have a true febrile seizure according to our classification. In participants who did not have a febrile seizure the most frequent diagnoses were no paroxysmal event (mostly a fever

TABLE 4. Sensitivity, specificity, positive predictive value and negative predictive value of self-reported febrile seizures compared to doctor-diagnosed febrile seizures

Sensitivity	92%
Specificity	71%
Positive predictive value	40%
Negative predictive value	98%
Likelihood ratio positive	3.2
Likelihood ratio negative	0.1

without accompanying symptoms), physiological events (most often chills with fever) or loss of consciousness otherwise (mostly vasovagal collapse) (**Table 2**).

DISCUSSION

We found that sensitivity of parentally reported febrile seizures was high (92%) and specificity moderate (72%). The positive predictive value was 41%.

Several population-based studies on seizures have used a screening instrument to identify cases[3 5 7 21]. Most studies did not report on the validity of the used screening instrument to identify participants with a history of seizures. Valid screening questions however are crucial for epidemiological studies. There have been some attempts to validate screening questionnaires on epilepsy or seizures in general[22-23]. Febrile seizures are a distinct condition, however, given their relative frequent occurrence as compared to epilepsy, and given their exclusive, fever-related occurrence in early childhood. Because of this, parents of young children might be more familiar with this type of seizure. Besides this, their mostly generalized and/ or tonic-clonic character might render them easier to recognize. We hypothesized that asking caregivers whether a febrile seizure has occurred might be sufficient to identify cases, but we also wanted to make sure that this screening question yielded valid responses.

We observed a high sensitivity and moderate specificity, but a low positive predictive value. This is in accordance with the findings of the earlier mentioned screening questionnaires on epilepsy or seizures in general[23]. Adding the question with the second highest sensitivity for febrile seizures ("Has your child ever had an attack of muscle spasms or trembling that started suddenly or any other involuntary movements of the entire body or part thereof ?") increased sensitivity only slightly while further diminishing positive predictive value. As the incidence of febrile seizures is only 2-5%, even a small false-positive rate still will result in a large proportion of screen-positives who are not truly affected. This means that a second stage of screening is unavoidable and that the replies of those answering positive need to be evaluated in further detail. However, case-identification will be nearly complete, which is essential for estimating incidence.

Next to the context of scientific research, the question whether a child or a family member has experienced febrile seizures will also frequently be asked in the consulting room by the family-physician, the paediatrician or paediatric neurologist. As a positive family-history is a well-known risk factor for febrile seizures and as the risk of epilepsy seems to be increased in children with a history of febrile seizures, this might support the diagnosis or help understanding the etiology of seizures in some patients. Our findings suggest however that this information is less reliable when provided by not medically educated subjects.

Some methodological considerations of our study need to be discussed. The strength of our study is the population-based cohort with a large number of subjects. Data collection was on a yearly basis and therefore less dependent of parental recall. However there are also some limitations. Information on paroxysmal events was not available in all participants. Subgroup analysis showed that non-response was selective; participants who did not return their questionnaires were more often not from Dutch origin and were lower educated. This will likely have influenced our results and limits the generalizability of our findings. Second, we compared the direct question on febrile seizures with a diagnosis based on a combination of 8 screening questions, an expert judgement based on the answers to an extended questionnaire on the event, and a medical record when available. To be diagnosed as a febrile seizure at least one of 8 screening questions had to be answered positively. Although we tried to identify all cases by questioning on several possible symptoms and signs of febrile seizures it is possible that children with febrile seizures have been missed in our study. However, the cumulative incidence of febrile seizure in our study was about 2.8% at the age of 36 months. As this is comparable to findings of other studies it seems unlikely that this would concern a large amount of cases.

We only studied the validity of parentally reported febrile seizures in young children and this can not automatically be extrapolated to other situations. In one study on the accuracy of family-history information on seizure disorders for example, a sensitivity of 56% was found for febrile seizures in general and 80% for febrile seizures in the offspring. However numbers were small[24]. Finally, we studied the validity of parentally reported febrile seizures only in participants who reported a paroxysmal event; the specificity will be much higher in the general population.

In conclusion, the sensitivity of the question "Did your child have a febrile seizure?" is high., and the specificity moderate. However, the positive predictive value is only 41%. This means we should be cautious interpreting this information provided by not medically educated people. Although this question satisfies as screening instrument for febrile seizures, a second stage of evaluation is necessary to identify true cases. This is especially true when the answer to this question would have consequences for the results of scientific research, but it is also useful to keep this in mind when asking the parents of your patient in the consulting room.

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Chapter 3.2

Fetal growth retardation and the risk of febrile seizures

ABSTRACT

The objective of this study was to examine the associations between fetal growth characteristics in different trimesters of pregnancy and the occurrence of febrile seizures in early childhood. This study was embedded in a population-based, prospective, cohort study from early fetal life onwards. Fetal growth characteristics (femur length, abdominal circumference, estimated fetal weight, head circumference, biparietal diameter and transverse cerebellar diameter) were measured with ultrasonography in the second and third trimesters of pregnancy. Information on the occurrence of febrile seizures was collected with questionnaires at the ages of 12 and 24 months. Analyses were based on data for 3372 subjects. In the second trimester, children in the lowest tertile of transverse cerebellar diameters were at increased risk of developing febrile seizures compared to children in the highest tertile (odds ratio 2.87 [95% confidence interval 1.31-6.28]). In the third trimester, children in the lowest tertile of all general growth characteristics (femur length, abdominal circumference, estimated fetal weight) were at increased risk of developing febrile seizures. This association was strongest for children in the lowest tertile of estimated fetal weight (odds ratio: 2.57 [95% confidence interval: 1.34-4.96]). Children in the lowest tertile of biparietal diameter in the third trimester also were at increased risk of febrile seizures. Similar but not statistically significant tendencies were observed for head circumference and transverse cerebellar diameter. These findings suggest that fetal growth retardation is associated with increased risk of febrile seizures in the first two years of life. Adverse environmental and genetic factors during pregnancy may be important in the development of febrile seizures.

INTRODUCTION

Febrile seizures are the most common type of seizures in childhood, affecting 2 to 5% of all children between the ages of 3 months and 5 years. The highest incidence has been observed during the first 2 years of life[1-7]. The cause of febrile seizures remains largely unknown. Genetic factors as well as environmental factors may be important[8-11].

Several prenatal and perinatal factors have been studied in relation to febrile seizures. Maternal complications during pregnancy, preterm birth and low birth weight have been suggested to be associated with an increased risk of febrile seizures. Maternal smoking during pregnancy also has been reported to be associated with febrile seizures. Although results are inconsistent[4 10-18], these findings suggest that adverse fetal environmental exposures may predispose children to febrile seizures. Low birth weight is generally considered a marker of an adverse fetal environment. The same birth weight might result from different fetal growth trajectories. To our knowledge, fetal growth has not been studied previously in relation to febrile seizures. Maternal smoking might be involved in the pathways leading from fetal growth retardation to an increased risk of febrile seizures. Continued maternal smoking during pregnancy is associated with a reduced fetal growth rate[19] and also seems to lead to small structural changes in the brain[20]. Smoking may lead to an increased risk of febrile seizures through suboptimal brain development.

For the present study, we hypothesized that fetal growth retardation (more specifically, retarded head and brain growth) would be associated with greater risk of febrile seizures in childhood. We assessed whether fetal growth retardation in the second and third trimester of pregnancy, as well as maternal smoking, led to an increased risk of febrile seizures.

METHODS

Design and study population

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onward. This study is designed to identify early environmental and genetic determinants of growth, development and health and was described in detail previously[21]. The Generation R Study is conducted in Rotterdam, the second-largest city of the Netherlands. Eligible mothers were mothers who were residing in the study area on their delivery dates and had delivery dates from April 2002 until January 2006. Enrolment was targeted for early pregnancy but was possible until the birth of the child. In total, 9.778 mothers were enrolled in the study, 8.880 during pregnancy. They gave birth to 9.745 live children, and 7.893 of those children were included for postnatal follow-up evaluations. Of all children who were eligible at birth, 61% participated in the study[22]. Assessments were planned in early pregnancy

(gestational age of < 18 weeks), middle pregnancy (gestational age of 18-25 weeks) and late pregnancy (gestational age of > 25 weeks) and included questionnaires, physical examinations and fetal ultrasound examinations. These measurements were considered as first-, second-, and third- trimester measurements, respectively. Postnatal information on growth and development of the participating children was obtained through questionnaires and hands-on measurements at the routine child health centers.

For this study on fetal growth and febrile seizures, participants who were included during pregnancy and who gave full consent for postnatal follow-up evaluations were selected (n=6559). Twins and children who were not born at term were excluded. Of the resulting 5797 participants, the 12-month questionnaire was mailed to 5653 and the 24-month questionnaire to 5677. Both questionnaires were mailed to 5641 participants. The response rates for the 12- and 24-month questionnaires were 72% and 75%, respectively. In total, 3647 participants returned both questionnaires. In addition, 275 participants were excluded because they did not answer the screening questions or the additional questionnaire in screen-positive cases. In total, 259 mothers participated with >1 child in the study. Because results did not differ after random exclusion of 1 of the siblings, the siblings were included in the analyses. Analyses were based on 3372 subjects, of whom 67 (2.0%) were diagnosed as having febrile seizures.

This study was approved by the medical ethics committee of the Erasmus Medical Center (Rotterdam, Netherlands). Written informed consent was obtained from all participants.

Fetal growth characteristics

Ultrasound examinations were performed in the first, second and third trimester of pregnancy. First-trimester measurements were not included because these fetal ultrasound examinations were used primarily to establish gestational age[23]. Fetal growth measurements used for the present study included biparietal diameter from outer to outer skull, transverse cerebellar diameter (TCD), head circumference, abdominal circumference and femur length in the second and third trimesters. Estimated fetal weight was calculated using the formula of Hadlock et al, that is, log(estimated fetal weight) = 1.326 - 0.00326 * abdominal circumference * femur length + 0.0107 * head circumference + 0.0438 * abdominal circumference + 0.158 * femur length [24]. The brain-parameter TCD was not measured for all participating women because this parameter was added to the study protocol during data collection. The missing TCD data were assumed to be distributed randomly across participants.

Febrile seizures assessment

Information about the occurrence of febrile seizures was collected with questionnaires at the ages of 12 and 24 months. In addition to direct questions regarding febrile seizures, the parents were asked about symptoms that might have been caused by a seizure[25]. If one or more of these

questions were answered positively, then an extended questionnaire concerning this episode was sent to collect detailed information about the event. If a physician was consulted, then the medical records for the visit were obtained. Febrile seizures were defined as a condition in childhood characterized by seizures occurring during an acute febrile episode but without evidence of intracranial infections or other defined causes[26]. According to this definition, seizures with fever in children with known neurological disabilities were not considered febrile seizures. On the basis of the available information, events were classified as febrile seizures or other events by 2 authors (Drs Visser and Arts). If consensus could not be reached, the events were classified as unknown.

Maternal smoking during pregnancy

Maternal smoking habits were assessed with questionnaires in each trimester and were categorized as no smoking during pregnancy (never smoked or quit smoking before pregnancy or in the first trimester) or smoking during pregnancy (continued smoking after the pregnancy was known). Passive smoking was defined as daily smoking at work or in the house.

Covariates

Date of birth, birth weight and gender were obtained from midwife and hospital registries. Information about the educational level of the mother, the parents' ethnicity, and the parents' medical histories was obtained with questionnaires at enrolment in the study. The height and weight of the mother were assessed at the first visit during pregnancy, and BMI was calculated. Information on fever episodes was obtained with the 12- and 24-months questionnaires. Frequent fever episodes were defined as >2 fever episodes in the periods from 6 to 12 months and from 12 to 24 months.

Data analysis

To examine whether nonresponse was selective, we compared baseline characteristics of participants with and without information on febrile seizures.

Next, we examined the associations of fetal growth characteristics in the second and third trimesters of pregnancy with the risk of developing febrile seizures in the first 2 years of life. To take the gestational age of the fetal measurements into account, we constructed gestational age-adjusted SD scores (SDSs) by using data from the whole study population. We categorized these SDSs for the different fetal growth characteristics into tertiles and performed logistic regression analyses to calculate the risks (odds ratio [OR]) of developing febrile seizures during the first 2 years of life, with the highest tertile as reference. These models were used for each growth characteristic in the second and third trimesters. We adjusted for baseline characteristics

(fetal gender and ethnicity, and maternal height, BMI, and educational level) known to influence fetal growth. Because adjustment also for paternal anthropometric features did not change our results, those were not included in the model. We also performed tests for trend by introducing the SDSs of the growth characteristics as continuous variables into the models. Subsequently, to assess whether maternal smoking during pregnancy was an intermediate in the association, models were also adjusted for active and passive smoking during pregnancy. Next we also adjusted for frequent fever episodes of the child, because this might be an intermediate.

Finally, we used the repeatedly measured growth parameters during pregnancy to examine whether fetal growth trajectories of children with febrile seizures differed from those without febrile seizures. We used repeated regression models to account for the dependency between measurements in the same subject. First, the best-fitting models with the outcomes (SDSs of the growth characteristics) as functions of gestational age were constructed by using fractional polynomials[23]. Next, febrile seizures were brought into the model as the main predictor of fetal growth. In this way, a regression coefficient is obtained that reflects the difference in SDS changes per pregnancy week between children with and without febrile seizures.

Statistical analyses were performed by SPSS 15.0 for Windows (SPSS Inc, Chicago, IL, USA) and SAS 9.2 (Stata Corporation, College Station, TX, USA).

RESULTS

Nonresponse analyses showed that participants without information on febrile seizures more often were of other than Dutch origin and their mothers had lower educational levels and more often continued smoking during pregnancy. Characteristics of the participants are presented in **Table 1**. Children with febrile seizures more often had lower birth weights and their mothers had lower educational levels.

General growth parameters in the second trimester were not associated with the risk of febrile seizures in the first two years of life (**Table 2**). In the third trimester, children in the lowest tertile of femur length (OR: 2.32 [95% confidence interval [CI] : 1.20-4.48]), abdominal circumference (OR: 2.01 [95%CI: 1.06-3.80]) and estimated fetal weight (OR: 2.57 [95%CI: 1.34-4.96]) were at an increased risk of febrile seizures compared to children in the highest tertile. Regarding the growth characteristics of the head and brain, smaller TCDs in the second trimester were associated with an increased risk of febrile seizures (**Table 3**). The ORs for febrile seizures for the lowest and middle tertiles of TCDs, compared with the highest tertile were 2.87 (95% CI: 1.31-6.28) and 2.36 (95% CI: 1.07-5.18), respectively. In the third trimester, small biparietal diameters were associated with the development of febrile seizures (OR: 1.93 [95% CI: 1.00-3.72]). Similar tendencies were observed for third-trimester head circumferences (OR: 1.39 [95% CI: 0.74-2.63]) and TCDs (OR: 1.67 [95% CI: 0.87-3.22]), but these associations were not statistically significant. The test for trend was significant for TCDs also in the third trimester. We repeated the analyses

TABLE 1. Subject characteristics

	No febrile seizures (N = 3305)	Febrile seizures (N = 67)	P
Maternal characteristics			
Age, mean (SD), y	31.4 (4.4)	31.1 (4.9)	.618
Height, mean (SD), cm	169.2 (7.3)	168.4 (7.1)	.382
Weight, mean (SD), kg	69.3 (12.2)	70.9 (13.1)	.275
Body Mass Index, mean (SD), kg/m^2	24.2 (4.0)	25.0 (4.1)	.107
Educational level (%)			.050
Primary	4.4	10.4	
Secundary	36.0	29.9	
High	59.6	59.7	
Nulliparous (%)	59	64	.427
Pre-eclampsia (%)	1.0	3.0	.122
Smoking during pregnancy (%)	13.0	17.2	.340
Febrile seizures mother (%)			.689
Yes	2.8	3.2	
No	91.5	93.5	
Don't know	5.7	3.2	
Child characteristics			
Gender, male (%)	48.6	47.8	.897
Origin, Dutch (%)	68.9	64.2	.362
Birthweight, mean (SD), g	3506 (485)	3439 (487)	.263
Lowest 25% of sds birthweight	24.9%	35.8%	.041

Data were missing for febrile seizures in the mothers (N=376), maternal smoking in pregnancy (N = 293), pre-eclampsia (N = 85), maternal educational level (N = 59)
P-values were based on chi-square statistics for categorical variables and independent t-tests for continuous variables.

for simple and complex febrile seizures separately. The effect sizes for the associations were similar for simple febrile seizures (n=50). For complex febrile seizures (n=11) the effect estimates for the associations between small TCDs and biparietal diameters and febrile seizures increased; however, because of the small numbers, this was not statistically significant (see **Supplemental Table 4** and **Supplemental Table 5**). Adjustment also for maternal active and passive smoking during pregnancy only slightly influenced the association between small fetal size and febrile seizures, which suggests that continued maternal smoking during pregnancy did not mediate these associations (see **Supplemental Table 6** and **Supplemental Table 7**). Additional adjustment for frequent fever episodes in the first or second year of life also did not influence the associations found.

Repeated measurement analyses showed that fetal growth trajectories of children with febrile seizures deviated from those of children without febrile seizures. For this analysis we

TABLE 2. Associations of general second and third trimester fetal growth characteristics with the risk of febrile seizures.

	Risk of febrile seizures Odds ratio (95% confidence interval)	
	Second trimester	Third trimester
Estimated fetal weight		
Lowest tertile	1.04 (0.56-1.95)	2.57 (1.34-4.96)
Mid-tertile	1.18 (0.64-2.17)	1.24 (0.60-2.56)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.498*	*0.007*
Abdominal circumference		
Lowest tertile	1.13 (0.59-2.16)	2.01 (1.06-3.80)
Mid-tertile	1.50 (0.81-2.76)	1.13 (0.57-2.25)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.820*	*0.029*
Femur length		
Lowest tertile	1.27 (0.67-2.41)	2.32 (1.20-4.48)
Mid-tertile	1.42 (0.76-2.64)	1.30 (0.66-2.56)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.390*	*0.009*

Values represent odds ratios (95% confidence interval) for febrile seizures for each tertile of the fetal growth characteristics compared to children in the highest tertile. Multiple logistic regression models were adjusted for fetal gender and ethnicity and maternal body mass index, height and educational level.

used the SDSs of the growth characteristics. **Figure 1** shows the differences in SDS changes per pregnancy week between children with febrile seizures and control subjects. For this purpose, the SDS changes per week for the growth characteristics of the control subjects were set to 0.

DISCUSSION

We found that reduced fetal growth was associated with increased risk of febrile seizures in the first 2 years of life. Except for TCDs, the strongest associations were observed in the third trimester. In general, the associations were stronger for body than head or brain growth characteristics.

Febrile seizures represent a heterogeneous condition with currently unclear pathophysiological and genetic bases. The importance of genetic factors has long been recognized. A family history of febrile seizures is the most-consistently identified risk factor for febrile seizures[4]

TABLE 3. Associations of second and third trimester fetal growth characteristics of the head and the risk of febrile seizures.

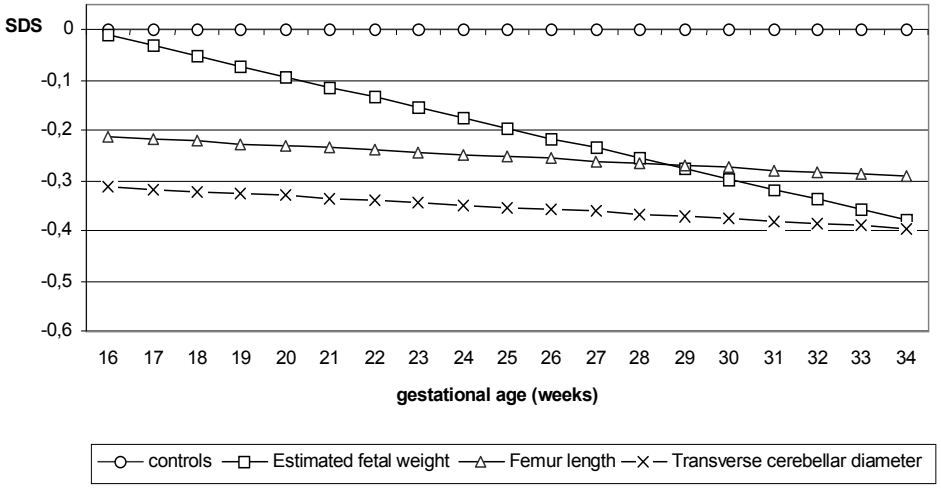
	Risk of febrile seizures Odds ratio (95% confidence interval)	
	Second trimester	Third trimester
Head circumference		
Lowest tertile	1.04 (0.56-1.94)	1.39 (0.74-2.63)
Mid-tertile	0.94 (0.51-1.73)	1.05 (0.54-2.01)
Highest tertile	0.97 (0.75-1.26)	0.79 (0.60-1.03)
p-trend	*0.831*	*0.082*
Biparietal diameter		
Lowest tertile	1.37 (0.66-2.85)	1.93 (1.00-3.72)
Mid-tertile	1.57 (0.78-3.15)	1.23 (0.62-2.43)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.431*	*0.087*
Transverse cerebellar diameter		
Lowest tertile	2.87 (1.31-6.28)	1.67 (0.87-3.22)
Mid-tertile	2.36 (1.07-5.18)	1.09 (0.53-2.22)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.009*	*0.080*

Values represent odds ratios (95% confidence interval) for febrile seizures for each tertile of the fetal growth characteristics compared to children in the highest tertile. Multiple logistic regression models were adjusted for fetal gender and ethnicity and maternal body mass index, height and educational level.

Several prenatal factors have been studied in relation to febrile seizures. The results of different studies are conflicting but suggest that adverse exposures during pregnancy might predispose children to febrile seizures. Low birth weight is considered to be a marker of an adverse fetal environment. Low birth weight was found to be associated with increased risk of febrile seizures in some studies[10-11 13]. However, birth weight is only a crude proxy indicator of intrauterine growth. Different fetal growth patterns might lead to the same birth weights.

In our population, 2% of the children experienced a febrile seizure in the first two years of life. This proportion is comparable to findings of other studies[1 4-5]. We found that children in the lower tertiles of general third-trimester fetal growth characteristics more often presented with febrile seizures. Because these measures of fetal growth are highly correlated, the same trends can be expected. Repeated-measurement analyses showed that children with febrile seizures had lower fetal growth rates than the control subjects (**Figure 1**). Our findings support the hypothesis that adverse exposures during pregnancy can predispose children to febrile seizures. However, fetal growth retardation can be caused by genetic as well as environmental factors. Genetic variants also might explain the associations found. We adjusted for several fac-

FIGURE 1. Fetal growth rate of children with and without febrile seizures.



Differences in fetal growth (in standard deviation scores (SDS)) per pregnancy week are shown for children with and controls without febrile seizures. The reference (change in standard deviation scores per week of controls) is 0. Repeated regression models were used to account for the dependency between measurements in the same subject. Models are unadjusted.

tors known to influence growth (ethnicity, gender, and maternal height, BMI and educational level); unfortunately, data on the head size of the parents were not available.

We were interested specifically in the growth characteristics of the head as a possible marker of brain development. In the third trimester, children in the lowest tertiles of fetal head circumference and biparietal diameter also seemed to be at increased risk of febrile seizures. However, the differences with the higher tertiles were smaller and for head circumference, no longer statistically significant. This can be explained by the fact that the brain is relatively spared in mild fetal growth retardation. Adverse exposures during pregnancy first lead to reduced growth of peripheral tissues, which is manifested as reduced femur length and abdominal circumference[19]. Only more-severe cases of fetal growth retardation lead to reduced fetal head growth. Even without apparent growth restriction, small structural and functional changes might occur in the brain as response to adverse fetal exposures. These subtle adaptations might be difficult to detect with ultrasound measurements.

We observed that small TCDs were associated with increased risk of febrile seizures. TCD might be a more direct indicator of brain development than head circumference. The association was stronger in the second trimester than in the third trimester. This was in contrast to the other measures of fetal growth, for which especially small values in late pregnancy were associated with an increased risk of febrile seizures, which emphasizes the importance of reduced growth. These findings are consistent with the idea that the cerebellum is the least affected in growth restriction[30]. The mechanisms through which a smaller fetal cerebellum in the second trimester might predispose children to febrile seizures are not easily explained. It might be only a proxy

indicator of other structural or functional changes in the brain. Additional research is needed, focusing on fetal brain development adaptations as mechanism leading to febrile seizures.

The effect sizes for the associations between small TCDs and biparietal diameters and the risk of febrile seizures were larger for complex febrile seizures than for simple febrile seizures. This suggests that factors that influence brain development negatively might be involved especially in the pathogenesis of complex febrile seizures. The numbers were small, however, and we should be careful interpreting these findings.

We hypothesized that smoking might be involved in the pathway of fetal growth restriction and increased susceptibility to febrile seizures. Smoking during pregnancy was reported to be associated with the risk of febrile seizures, and it is well known that maternal smoking during pregnancy leads to reduced fetal growth. In addition, maternal smoking has been suggested to be associated with small structural and functional changes of the brain[20 31-32] and with neurobehavioural and cognitive disturbances[33-34]. The effect estimates for the associations between fetal growth characteristics and the risk of febrile seizures, however, were only slightly changed by data on maternal active or passive smoking during pregnancy. This suggests that fetal smoke exposure does not explain this association. Smoking still may be associated independently with febrile seizures.

The number of episodes of fever in early life also might explain part of the associations between fetal growth and the risks of febrile seizures. Children with growth retardation might be more prone to infectious diseases, which are a prerequisite for febrile seizures. However, adjustment of the analyses for the number of episodes of fever did not affect the effect estimates materially.

Some methodological considerations need to be discussed. A strength of our study is the population-based cohort with a large number of subjects studied from early pregnancy, with extensive ultrasound measurements performed during pregnancy. Data on febrile seizures were collected on a yearly basis and therefore were less dependent of parental recall. Our study also has some limitations. Information on paroxysmal events was not available for all participants. Subgroup analysis showed that nonresponse was selective; participants who did not return their questionnaires more often were of other than Dutch origin, had lower educational levels, and more often had continued smoking during pregnancy. Therefore, our results should be extrapolated only cautiously to this group. Because it is unlikely that the selection mechanisms were dependent on both determinants and outcomes, this probably did not affect the associations found. Finally, no validated screening instrument for febrile seizures exists. Our screening questions were based on questionnaires used previously for seizure disorders, with adjustment for this young age group and extension with some questions that seemed relevant[35-37].

Our results suggest that fetal growth retardation is associated with an increased risk of febrile seizures in the first 2 years of life. This was most evident for estimated fetal weight, femur length and TCD. Adverse environmental exposures as well as genetic factors might be responsible for this growth retardation.

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TABLE S4. Associations of third trimester fetal growth characteristics with the risk of simple febrile seizures

	Risk of febrile seizures OR (95% CI)		Risk of febrile seizures OR (95% CI)
Estimated fetal weight		Head circumference	
Lowest tertile	2.62 (1.22-5.66)	Lowest tertile	1.48 (0.69-3.15)
Mid-tertile	1.42 (0.62-3.25)	Mid-tertile	1.31 (0.63-2.75)
Highest tertile	1.00 (reference)	Highest tertile	1.00(reference)
Abdominal circumference		Biparietal diameter	
Lowest tertile	2.22 (1.04-4.70)	Lowest tertile	2.02 (0.96-4.25)
Mid-tertile	1.31 (0.63-2.75)	Mid-tertile	1.15 (0.52-2.530
Highest tertile	1.00 (reference)	Highest tertile	1.00(reference)
Femur length		Transverse cerebellar diameter	
Lowest tertile	2.57 (1.08-4.70)	Lowest tertile	1.43 (0.69-2.94)
Mid-tertile	1.23 (0.51-2.46)	Mid-tertile	0.86 (0.38-1.93)
Highest tertile	1.00 (reference)	Highest tertile	1.00 (reference)

Values represent odds ratios (95% confidence interval) for febrile seizures for each tertile of the fetal growth characteristics compared to children in the highest tertile. Multiple logistic regression models were adjusted for fetal gender and ethnicity and maternal body mass index, height and educational level.

TABLE S5. Associations of third trimester fetal growth characteristics with the risk of complex febrile seizures

	Risk of febrile seizures OR (95% CI)		Risk of febrile seizures OR (95% CI)
Estimated fetal weight		Head circumference	
Lowest tertile	2.09 (0.48-9.16)	Lowest tertile	1.16 (0.29-4.69)
Mid-tertile	0.66 (0.11-4.02)	Mid-tertile	0.31 (0.03-2.81)
Highest tertile	1.00 (reference)	Highest tertile	1.00(reference)
Abdominal circumference		Biparietal diameter	
Lowest tertile	1.01 (0.24-4.18)	Lowest tertile	5.65 (0.60-53.69)
Mid-tertile	0.49 (0.09-2.70)	Mid-tertile	4.42 (0.49-40.19)
Highest tertile	1.00 (reference)	Highest tertile	1.00(reference)
Femur length		Transverse cerebellar diameter	
Lowest tertile	2.87 (0.53-15.61)	Lowest tertile	5.08 (0.59-43.61)
Mid-tertile	1.82 (0.30-11.17)	Mid-tertile	4.05 (0.45-36.49)
Highest tertile	1.00 (reference)	Highest tertile	1.00 (reference)

Values represent odds ratios (95% confidence interval) for febrile seizures for each tertile of the fetal growth characteristics compared to children in the highest tertile. Multiple logistic regression models were adjusted for fetal gender and ethnicity and maternal body mass index, height and educational level.

TABLE S6. Associations of general second and third trimester fetal growth characteristics with the risk of febrile seizures, after adjusting for maternal smoking in pregnancy.

	Risk of febrile seizures Odds ratio (95% confidence interval)	
	Second trimester	Third trimester
Estimated fetal weight		
Lowest tertile	1.04 (0.56-1.95)	2.56 (1.32-4.94)
Mid-tertile	1.18 (0.64-2.18)	1.20 (0.58-2.48)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.498*	*0.008*
Abdominal circumference		
Lowest tertile	1.13 (0.59-2.16)	2.00 (1.06-3.78)
Mid-tertile	1.50 (0.81-2.77)	1.10 (0.55-2.20)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.816*	*0.031*
Femur length		
Lowest tertile	1.28 (0.67-2.42)	2.22 (1.15-4.30)
Mid-tertile	1.41 (0.76-2.63)	1.29 (0.65-2.55)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.388*	*0.011*

Values represent odds ratios (95% confidence interval) for febrile seizures for each tertile of the fetal growth characteristics compared to children in the highest tertile. Multiple logistic regression models were adjusted for fetal gender and ethnicity and maternal body mass index, height and educational level and smoking in pregnancy.

TABLE S7. Associations of second and third trimester fetal growth characteristics of the head and the risk of febrile seizures, after adjusting for maternal smoking in pregnancy.

	Risk of febrile seizures Odds ratio (95% confidence interval)	
	Second trimester	Third trimester
Head circumference		
Lowest tertile	1.04 (0.56-1.95)	1.41 (0.74-2.66)
Mid-tertile	0.94 (0.51-1.73)	1.05 (0.54-2.01)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.812*	*0.086*
Biparietal diameter		
Lowest tertile	1.36 (0.65-2.83)	1.94 (1.00-3.75)
Mid-tertile	1.58 (0.78-3.19)	1.22 (0.61-2.41)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.415*	*0.089*
Transverse cerebellar diameter		
Lowest tertile	2.88 (1.31-6.30)	1.67 (0.87-3.21)
Mid-tertile	2.40 (1.10-5.33)	1.08 (0.53-2.21)
Highest tertile	1.00 (reference)	1.00 (reference)
p-trend	*0.008*	*0.008*

Values represent odds ratios (95% confidence interval) for febrile seizures for each tertile of the fetal growth characteristics compared to children in the highest tertile. Multiple logistic regression models were adjusted for fetal gender and ethnicity and maternal body mass index, height and educational level and smoking in pregnancy.

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Chapter 3.3

Maternal folic acid supplement use in early pregnancy and the risk of febrile seizures

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Chapter 3.4

Frequent fever episodes and the risk of febrile seizures

ABSTRACT

The aim of this study was to examine the association between the number of fever episodes and the risk of febrile seizures. This study was embedded in a population-based prospective cohort study from early foetal life onwards. Information about the occurrence of febrile seizures and fever episodes was collected by questionnaires at the ages of 12, 24 and 36 months. Analyses were based on 3033 subjects. The risk of febrile seizures was compared between children with frequent fever episodes (>2 per year), and children with only 1 or 2 fever episodes per year. The frequency of fever episodes was not associated with the risk of febrile seizures in the age range of 6-12 months. In the second and third year of life, having more than 2 fever episodes was associated with an increased risk of febrile seizures (odds ratios 2.02 [95% confidence interval 1.13-3.62] and 2.29 [95% confidence interval 1.00-5.24], respectively). In the age range between 6 and 36 months, we observed a significant trend between the frequency of fever episodes (<2, 3-4 or >4 per year) and the risk of febrile seizures (p-value for trend < 0.001). The association between the number of fever episodes and the occurrence of febrile seizures was stronger for children with recurrent febrile seizures. Concluding, frequent fever episodes are associated with an increased risk of febrile seizures in the second and third years of life. Further studies are needed to identify the mechanisms underlying this association.

INTRODUCTION

Febrile seizures are the most common type of seizures in childhood, affecting 2-5% of all children between 3 months and 5 years of age. The highest incidence rates have been observed during the first two years of life[1-6]. A fever episode is a prerequisite for the occurrence of a febrile seizure. Although almost all children have fever episodes during the first years of life, only 2-5% develops febrile seizures. The aetiology of this susceptibility for febrile seizures remains largely unknown. Genetic factors as well as early environmental factors seem to play a role[7]. The common pathway is presumed to be a reduction in the seizure threshold of the developing brain.

It has also been suggested that children with febrile seizures experience more fever episodes than children of the same age without febrile seizures[8-11]. Especially febrile seizure recurrence has been associated with more frequent fever episodes. The same might be true for the occurrence of a first febrile seizure. If so, environmental and genetic factors could be associated with the occurrence of febrile seizures in an indirect way too, by influencing the number of infectious diseases besides influencing the seizure threshold.

In this study we examined the association between the number of fever episodes and the occurrence of first and recurrent febrile seizures. We hypothesized that if in susceptible children the threshold to react with a seizure to a fever episode would be low, they likely would experience a febrile seizure already during one of their first fever episodes. The number of fever episodes then would not be of major importance. We further hypothesized that this seizure threshold might not be the same for children with different ages at first seizure presentation.

METHODS

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early foetal life until young adulthood. This study is conducted in Rotterdam, the second largest city in The Netherlands, and is designed to identify early environmental and genetic determinants of growth, development and health in foetal life, childhood and adulthood. The study has been described previously in detail [12-13]. Enrolment was aimed in early pregnancy but allowed until birth of the child. Delivery dates were from April 2002 to January 2006. Assessments during pregnancy included questionnaires, physical examinations and foetal ultrasound examinations. Postnatal information on growth and development of the participating children was obtained by questionnaires and from information obtained routinely in young children in Dutch child health centres. This study has been approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from the legal representatives of all participants.

Febrile seizures assessment

Information about the occurrence of febrile seizures was collected by questionnaires at the ages of 12, 24 and 36 months. Each of these questionnaires comprised direct questions regarding epilepsy and febrile seizures. In addition the primary caregivers were asked about symptoms that could have been caused by a seizure. If one or more of these questions were answered positive, an extended follow-up questionnaire concerning this episode was sent to collect more detailed information. In this follow-up questionnaire the caregivers were also asked to describe the event in their own words. When a physician was consulted, the medical record of this visit and results of supplementary investigations were obtained. Febrile seizures were defined as a condition in childhood characterized by seizures occurring during an acute febrile episode but without evidence of intracranial infections or other defined causes [14]. Based on the available information, events were classified as febrile seizure or other event independently by the first and last author. Febrile seizures were subdivided in febrile seizure, physician confirmed (physician consulted because of the event and diagnosis "febrile seizure" confirmed), probable febrile seizure (physician consulted because of the event and diagnosis "probable febrile seizure" according to this physician, or history characteristic for a febrile seizure according to the additional questionnaire) and possible febrile seizure (physician consulted because of the event and diagnosis "possible febrile seizure" according to this physician, or history that could point to a seizure but not characteristic). A history characteristic for a febrile seizure was defined as an event during a feverish illness, 1-15 minutes in duration, with loss of consciousness, stiffening and/or involuntary movements, and a period of unresponsiveness or drowsiness afterwards. Direct consensus was present in 95%; in the other 5%, discussion led to agreement in most. If consensus could not be reached, the event was classified as "unknown". Because of the degree of uncertainty also febrile seizures with the annotation "possible" were reclassified in the category "unknown" and excluded from further analyses.

Assessment of fever episodes

At the child ages of 12, 24 and 36 months, the caregivers were asked to complete questions focused on whether their child had had a fever episode in the previous 6 (12-months questionnaire) or 12 (24 and 36 months questionnaire) months. If so, they were asked how often their child had had a fever episode ("never", "1-2 times", "3-4 times", "5 times of more"). We defined "frequent febrile episodes" as more than two fever episodes in one of the study periods (6-12, 12-24, 24-36 months).

Covariates

Date of birth, birth weight and gender were obtained from midwife and hospital registries. Information about maternal educational level and the ethnicity and medical history of both parents was obtained by questionnaires at enrolment in the study. Maternal smoking habits were assessed by questionnaires in each trimester and categorized into "no smoking during pregnancy" (never smoked, quit smoking before pregnancy or in the first trimester) and "smoking during pregnancy" (continued smoking after the pregnancy was known).

Population for analyses

In total, 7295 participants were included for postnatal follow-up (**Figure S1**). Twins were excluded. In total 527 mothers participated with 2 children in the study and 12 mothers with 3 children. For each mother randomly one child was selected and included in the analyses. Of the remaining 6565 participants, the 12, 24 and 36 months questionnaires were sent to 6123 (93%), 6409 (98%) and 6239 (95%) participants respectively. The response rates for these questionnaires varied between 72 and 76%. Of the participants whose caregivers returned the questionnaires, at least one fever episode was reported in 3483 (80%), 3958 (84%) and 2920 (68%) participants respectively in the 12, 24 and 36 months questionnaires. To ensure that all participants at least had had the opportunity to have a febrile seizure, only these children were included in the analysis. We excluded participants who were screen-positive but whose caregivers did not return the follow-up questionnaire. In total, analyses on the 6-12, 12-24 and 24-36 months period were based on 3397, 3827 and 2859 participants respectively.

Of all participants, 5403 were sent the 12, 24 as well as the 36 months questionnaire. Of these, 3270 returned all questionnaires. We excluded participants whose caregivers did not report a fever in one of the first three years of life, or who were screen-positive but whose caregivers did not return the follow-up questionnaire. Analyses on the first three years of life together were based on 3033 participants whose caregivers reported a febrile seizure or whose caregivers answered all questionnaires and reported a fever episode at least once in these years.

Data-analyses

To examine whether non-response was selective we compared baseline characteristics of participants with and without information on febrile seizures using chi-square statistics for categorical variables, independent t-tests for continuous variables with a normal distribution, and Mann-Whitney U tests for continuous variables that were not normally distributed. Non-responders were defined as participants whose caregivers did not return all questionnaires in the first three years of life. Subsequently we compared baseline characteristics of children with and without febrile seizures in the same way.

We examined the association between the frequency of fever episodes and the risk of febrile seizures using logistic regression models. First we performed this analysis for the 6-12, 12-24 and 24-36 months period separately. All children with febrile seizures in the period of analysis were included as cases, independent whether it concerned a first or recurrent febrile seizure. We adjusted for variables known to be associated with febrile seizure or that were significantly associated with febrile seizures at the 0.10 level in univariable analyses.

Next we examined the associations between frequent fever episodes and single or recurrent febrile seizures in the first three years of life together. For this purpose we compared participants whose caregivers reported frequent (3-4) or very frequent (more than 4) fever episodes in one of these years, with participants whose caregivers reported a maximum number of 2 fever episodes per year. We performed tests for trend by introducing the number of fever episodes (0-2, 3-4 and >4 per year) as a continuous variable into the models. For this analysis only the complete cases (n=3033) were used. We first performed this analysis including children with single as well as children with recurrent febrile seizures as cases. Next we also performed this analysis for children with single (n=66) and children with recurrent (n=30) febrile seizures separately. Fever episodes were counted until the occurrence of a (recurrent) febrile seizure or until the age of three years.

Missing values were estimated with multiple imputation, by means of which 5 imputed datasets were created and analyzed and their estimated values averaged. Confidence intervals for the averaged estimates reflect uncertainty both about the value of the odds ratios and about the imputed values[15]. Statistical analyses were performed using the Statistical Package of Social Sciences version 17.0 for Windows (SPSS Inc, IBM, Chicago, IL, USA).

RESULTS

Table 1 shows the baseline characteristics of participants with and without febrile seizures in the first 3 years of life. Mothers and fathers of children with febrile seizures more often reported febrile seizures themselves than parents of children without febrile seizures, differences were only statistically significant in case of the fathers. No other characteristics differed between children with and without febrile seizures. In total 21 participants reported a febrile seizure in the first, 53 in the second and 29 in the third year of life. In the first three years of life together, 96 children experienced a febrile seizure, of which the caregivers of 30 (30%) reported recurrent seizures.

We did not find an association between the number of fever episodes and febrile seizures in the age range of 6-12 months (odds ratio (OR) 1.11 [95% confidence interval (CI) 0.37-3.31]). Children with frequent fever episodes in the second or third year of life had an increased risk of developing febrile seizures in these years (OR 2.02 [95% CI 1.13-3.62] and OR 2.29 [95% CI 1.00-5.24] respectively) (**Table 2**). We adjusted for family-history and parity. As adjusting for

TABLE 1. Baseline characteristics of participants with and without febrile seizures

	Participants with febrile seizures N=96	Participants without febrile seizures n=2937	P-value
Maternal characteristics			
Age, years (SD)	31.1 (4.8)	31.7 (4.5)	0.545
Educational level, % (n)			0.483
Low	6.3 (6)	3.9 (113)	
Middle	32.6 (31)	35.1 (1007)	
High	61.1 (58)	60.9 (1747)	
Parity, first child, % (n)	71.0 (66)	62.6 (1802)	0.100
Smoking during pregnancy, % (n)	15.0 (12)	12.5 (315)	0.507
Febrile seizures mother, % (n)			0.186
Yes	4.5 (4)	2.9 (77)	
No	93.3 (83)	90.4 (2368)	
don't know	2.2 (2)	6.7 (175)	
Febrile seizures father, % (n)			0.038
Yes	7.2 (5)	2.4 (54)	
No	85.5 (59)	91.2 (2065)	
don't know	7.2 (5)	6.4 (146)	
Child characteristics			
Gender, male, % (n)	51.0 (49)	49.5 (1454)	0.767
Ethnicity, European, % (n)	71.9 (69)	78.9 (2291)	0.100
Birth weight (gram, SD)	3439 (578)	3479 (548)	0.219
Preterm birth (< 37 weeks gestational age)	4.2 (4)	3.9 (115)	0.901

N=3033, participants who answered all questionnaires and who experienced a fever at least once or who were diagnosed with a febrile seizure at least once

P-values were calculated using t-tests for continuous variables and Chi-square statistics for categorical variables.

Data were missing for febrile seizure in the mother (n= 324); febrile seizures in the father (n= 699); continued maternal smoking pregnancy (n=433); parity (n=61); maternal educational level (n= 71)

other factors known to be associated with febrile seizures from literature (birth weight, prematurity and continued smoking in pregnancy) or associated with febrile seizures at the 0.10 level in univariable analysis (ethnicity) did not change the effect estimates by >5%, they were not included in the model.

TABLE 2. Frequent febrile episodes (> 2) in the first, second and third year of life, and the risk of febrile seizures

	Risk of febrile seizures Odds ratio (95% confidence interval)		
	6-12 months	12-24 months	24-36 months
Model A	1.06 (0.35-3.15)	2.03 (1.14-3.63)	2.06 (0.91-4.69)
Model B	1.11 (0.37-3.31)	2.02 (1.13-3.62)	2.29 (1.00-5.24)

Model A: unadjusted
Model B: adjusted for febrile seizures in the parents and parity
For each period of analysis, all children with febrile seizures were included as cases, independent whether it concerned a first or recurrent febrile seizure

TABLE 3. Risk of single or recurrrent febrile seizures for participants with frequent fever episodes compared to participants with a maximum number of 2 fever episodes per year.

	Risk of febrile seizures Odds ratio (95% confidence interval)		
Maximum number of fever episodes per year	Febrile seizures, all N=96	Single seizure N=66	Recurrent seizures n=30
0-2	1.0 (reference)	1.0 (reference)	1.0 (reference)
3-4	1.55 (0.97-2.49)	1.16 (0.65-2.09)	3.05 (1.31-7.06)
>5	3.10 (1.73-5.55)	2.01 (0.93-4.34)	7.20 (2.85-18.25)
p-trend	< 0.001	0.112	< 0.001

Adjusted for history of febrile seizures in the parents and parity
Fever episodes were counted until the occurrence of a (recurrent) febrile seizure or until the age of three years.

Cumulative over the first three years of life, the risk of developing febrile seizures for participants with 3-4 fever episodes in one of these years was 1.55 [95% CI 0.97-2.49]. The risk for participants with more than 4 fever episodes in one of these years was 3.10 [95% CI 1.73-5.55] (**Table 3**). The associations between frequent fever episodes and the risk of febrile seizures was stronger for children with recurrent than for children with single seizures. For children with single febrile seizures the trend was no longer statistically significant.

Non-response analyses showed that mothers who did not return all questionnaires more often were of another than European origin, lower educated, and more often continued smoking during pregnancy. Their children were more often born preterm and had a lower birth weight.

DISCUSSION

We found a linear association between the number of fever episodes and the risk of febrile seizures in the second and third year of life, but not in the first year of life. The association between the number of fever episodes and the risk of febrile seizures was most evident for children with recurrent seizures.

Febrile seizures are a heterogeneous condition with an as yet unclear pathophysiological and genetic basis. Several studies have examined possible determinants of febrile seizures. Almost all have demonstrated that febrile seizures occur at a higher than expected rate in first- and second-degree relatives of children with febrile seizures, supporting a genetic factor[6 16-17]. However this only explains a part of the risk. Other factors found to be associated with febrile seizures include reduced foetal growth[18], low birth weight[16], premature birth[16-17], continued maternal smoking during pregnancy[6 19-21] and complications in pregnancy[17 22]. However, results concerning these factors are inconsistent. It is presumed that these genetic and early environmental factors increase the susceptibility for febrile seizures by lowering the seizure threshold.

Previous studies showed that the number of fever episodes is a risk factor independently associated with febrile seizure recurrence. However these studies were performed in children known to be at risk for febrile seizures[9]. Also some studies suggested an association between the number of fever episodes and the risk of febrile seizures in general[8 11]. Huang et al. found the number of fever episodes to be an independent risk factor for febrile seizures[8]. The occurrence of febrile seizures as well as the number of fever episodes in that study was obtained retrospectively at the age of three. Forsgren et. al found "fever or tiredness of unknown cause" and "severe infections" in the past six months to be associated with febrile seizures next to a positive family history[11]. Others reported that breastfeeding was associated with a lower[23] and full day care attendance with a higher incidence of febrile seizures[24]. However these results have not been confirmed by other studies.

In our population about 3% of the children experienced a febrile seizure in the first three years of life. This percentage is comparable to findings of other studies[1-5]. We found no association between the number of fever episodes and the risk of febrile seizures in the first year of life, but a linear association in the second and third year of life.

We hypothesized that if the tendency to react with a seizure to a fever episode would be high, it already would become manifest during one of the first fever episodes. A high number of fever episodes then would not be associated with the occurrence of a first febrile seizure. If the seizure threshold would only be slightly diminished, the majority of fever episodes might not be accompanied with a febrile seizure and the chance to have a febrile seizure would increase with the number of fever episodes. Children with a febrile seizure in the first year of life seem to differ in this aspect from children with a febrile seizure later in life. The fact that they already experience a febrile seizure in the first year of life might indeed point to a lower threshold for

febrile seizures. Other indications from literature exist that children with febrile seizures early in life might differ from children with febrile seizures later in life. These children seem to have a positive family-history more often[2] and have a higher risk of febrile seizure recurrence. Concerning other possible risk factors for febrile seizures we did find an association between continued smoking during pregnancy and febrile seizures in the first year of life in earlier studies, but not with febrile seizures later in life[18 25].

We found a high number of fever episodes to be associated with an increased risk of febrile seizures in the second and third year of life. As fever episodes are the most frequent in early childhood this might partially explain the peak incidence of febrile seizures in the first two years of life, next to the presumed highest susceptibility of the brain for seizures in early childhood. The association between the number of fever episodes and the risk of febrile seizures was only significant for children with recurrent febrile seizures. It still was significant when fever episodes were only counted until the occurrence of their first febrile seizure (data not shown). This suggests children with recurrent febrile seizures more often experience frequent fever episodes, already before their first febrile seizure. Probably, as many of these children will continue to experience frequent fever episodes, this will increase their risk of a recurrent febrile seizure.

A fever episode is a prerequisite for a febrile seizure. It might not only be the increased brain temperature itself that causes the seizure. Direct effects of endogenous pyrogens such as interleukine-1(IL-1) on the seizure threshold seem to be important[26-27]. These pyrogens are released in reaction to an infectious disease and are presumed to give rise to an increased body temperature as well as independently to an increased neuronal excitability. This is supported by studies that showed that antipyretic therapy was not protective for recurrences of febrile seizures whereas GABAergic drugs do prevent the seizures[26 28]. It may also explain why the same rise in temperature does not always result in febrile seizures in susceptible children. The functioning of the immune system thus seems to be involved in the occurrence of febrile seizures. Our finding that children with febrile seizures experience more fever episodes than children of the same age without febrile seizures could also point to a role of the functioning of the immune system. Susceptibility to infections as an individual determinant of the occurrence of fever episodes might be involved.

Some methodological considerations have to be discussed. The strength of our study is the population-based cohort with a large number of subjects studied from early pregnancy. Data collection on febrile seizures and fever episodes was on a yearly basis and therefore less dependent on parental recall. Our study also has some limitations. Participants included in our study more often were high educated than might be expected in the general population, and in their children the proportion of premature birth was lower and the mean birth weight higher. Information on febrile seizures was not available in all participants. Although it is unlikely that the selection mechanisms were dependent on both determinant and outcome, this may have affected the associations found, and it will have affected the statistical power. Also no validated screening instrument for febrile seizures exists. Our screening questions were based

on questionnaires used in the past for seizure disorders, adjusted to this young age group, and extended with some relevant questions[29-31]. Concerning the fever episodes, we did not have the exact number of fever episodes nor the exact moment of occurrence as we asked the number in a categorical way over the past (half) year. We also did not ask what level of fever had occurred. Finally, it is possible that after a child has experienced a febrile seizure, the parents will be more alert as regards later fever episodes. Therefore, the abundance of fever episodes reported in these children could partially be explained by recall bias. However, we found that in participants with febrile seizures, fever episodes were already reported more often in the year before their first febrile seizure (data not shown). This suggests a real difference in the occurrence of infectious diseases.

In conclusion, we found that frequent fever episodes are associated with an increased risk of febrile seizures in the second and third year of life. This association is stronger for children with recurrent febrile seizures compared to children with single febrile seizures. This finding may point to susceptibility for febrile seizures dependent on the number of febrile episodes, and not only on a lowered seizure threshold per se.

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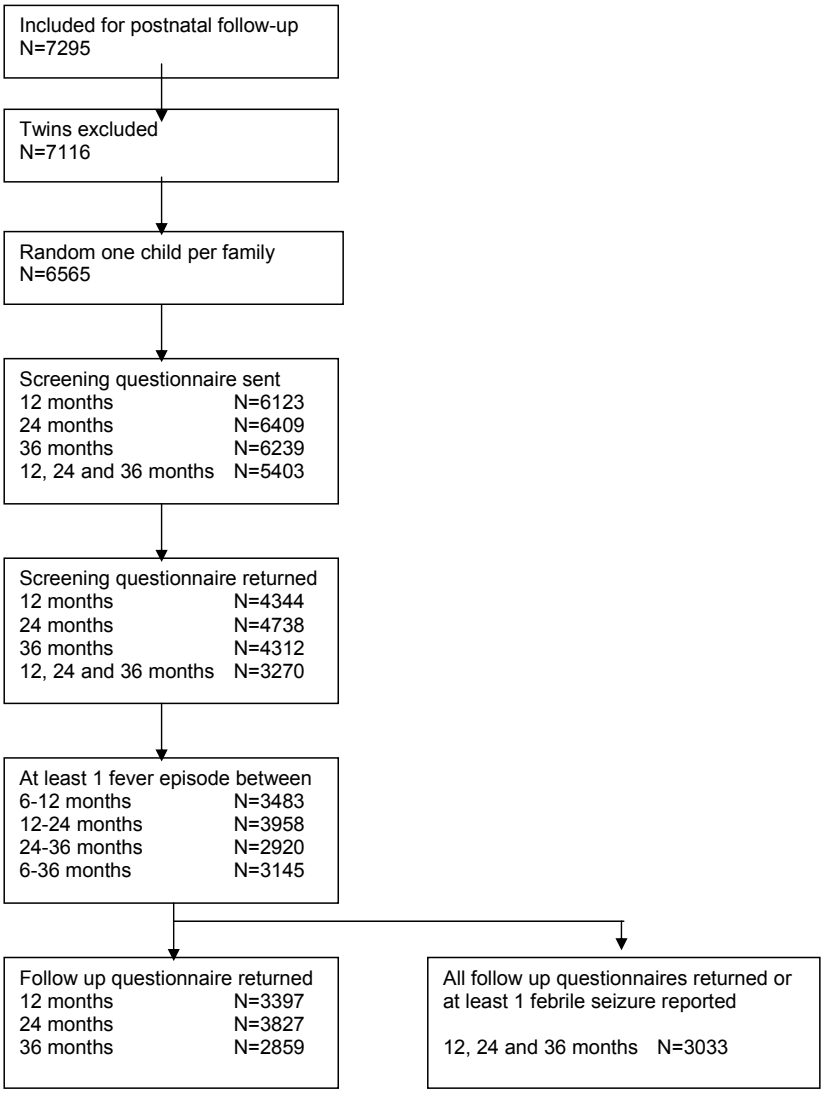
FIGURE S1. Flow diagram of the study population



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Chapter 3.5

Febrile seizures and behavioural and cognitive outcomes in pre-school children

ABSTRACT

General developmental outcome is known to be good in school-aged children who experienced febrile seizures. We aimed to examine cognitive and behavioural outcomes in pre-school children with febrile seizures, including language, and executive functioning outcomes. This study was carried out in the Generation R Study, a population-based cohort study in Rotterdam from early fetal life onwards. Information about the occurrence of febrile seizures was collected by questionnaires at the ages of 1, 2 and 3 years. At the age of 3 years, behaviour and emotion was assessed using the Child Behavior Checklist (CBCL). Information on expressive language development was obtained by the Language Development Survey (LDS) at the age of 2.5 years. To assess executive functioning, parents completed the Behaviour Rating Inventory of Executive Function – Preschool Version (BRIEF-P) at the age of 4 years. Final analyses were based on 3476 children. No associations were found between febrile seizures and the risk of behavioural problems or executive functioning. In contrast to single febrile seizures, recurrent febrile seizures were significantly associated with an increased risk of delayed vocabulary development (odds ratio 3.27, [95% confidence interval 1.33-8.12]). Our results suggest that febrile seizures are not associated with problem behaviour or executive functioning in preschool children, but children with recurrent febrile seizures might be at risk for delayed language development.

INTRODUCTION

Febrile seizures are common in young children, with a cumulative incidence of 2 to 5% in the first 5 years of life. The highest incidence has been reported in the first two years of life. The etiology has remained unclear, although genetic and environmental mechanisms are known to be involved[1].

The behavioural and cognitive outcomes of children who had febrile seizures have been subject of many studies. Most population-based cohort-studies did not find clear differences in developmental outcomes between children with and without febrile seizures, and suggest that febrile seizures are an essentially benign disorder with a good prognosis[2-5]. Most of these studies assessed general intelligence, academic progress and behavioural outcome in school-aged children. However, other aspects of cognitive function or behaviour still might be adversely affected in children with febrile seizures. Also at a young age differences in cognitive function or development might be apparent that later disappear. Besides this, certain subgroups of children with febrile seizures may have a less favourable prognosis. Several studies reported that children with recurrent or prolonged febrile seizures perform worse on neuropsychological tests compared to healthy controls or children with single, simple febrile seizures[6-8]. Other studies suggested an adverse outcome for children with a first febrile seizure before their first birthday[3 5 9].

The current study examined whether a history of febrile seizures during the first 3 years of life is associated with verbal and nonverbal cognitive and/or behavioural functioning in preschool children in a population-based cohort among 3476 subjects. Measures included language development, executive functioning, behaviour and emotion. We also studied these outcomes in children with recurrent febrile seizures and in children with a first febrile seizure in infancy. We hypothesized that outcome might be less favourable in these groups.

METHOD

Design

The present study was carried out within the Generation R Study, a population-based cohort study from early fetal life onwards in Rotterdam, the Netherlands. The Generation R Study has been described in detail before[10]. Participant recruitment started in April 2002 and baseline data collection was completed January 2006. Follow-up assessments in parents and children included questionnaires, physical examinations and ultrasound examinations. This study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. Written informed consent was obtained from all parents.

Febrile seizure assessment

At the ages of 1, 2 and 3 years, the parents received a questionnaire on the occurrence of febrile seizures. Parents were asked if their child had experienced a febrile seizure or epileptic fit. In addition they were asked about several symptoms that could have been caused by a seizure. If the answer to one or more of these questions was "yes", then parents were asked to fill in an extended questionnaire about this event. Any medical records resulting from additional physician visits were also obtained. Febrile seizures were defined as "an event in infancy or childhood, usually between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or other defined cause. Seizures with fever in children who have suffered a previous nonfebrile seizure are excluded"[11]. According to this definition, seizures with fever in children with known neurological disabilities were not considered as febrile seizures. Based on the information available, the first and last author independently classified the events as a febrile seizure or another event. In some cases, insufficient information was available to classify the event or consensus could not be reached. These events were classified as "unknown" and excluded from further analyses. Recurrent febrile seizures were defined as more than one febrile seizure.

Behavioural and emotional problems

At the age of 3 years, parents were asked about possible behavioural and emotional problems in their children in mailed questionnaires. For this purpose the Dutch translation of the Child Behavior Checklist for ages 1.5 – 5 years (CBCL /1½-5) was used[12]. The CBCL /1½-5 uses 99 questions to obtain ratings of behavioural and emotional problems by parents of 1½-to 5-year-old children and is validated on a general population sample. These 99 items can be scored on seven syndrome scales: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems and Aggressive Behavior. The CBCL also uses two broadband scales, designated as Internalizing and Externalizing, which include the first four scales and the last two scales respectively. Finally the Total Problems score is the sum of all items. More problems result in higher scores on the CBCL scales. Good reliability and validity have been reported for the English and Dutch CBCL /1½-5[12]. Within Generation R the CBCL was filled in by the primary care-giver, in more than 90% the mother of the child. Since the resulting scores did not satisfy the assumption of normality, test results were dichotomized as has been described in previous studies[13]. We defined a non-optimal score in our population as the highest 20 percent of problem item scores.

Expressive language functioning

Language skills were assessed by mailed questionnaires. At the age of 1.5 years this was done using the Dutch version of the MacArthur Short Form Vocabulary Checklist (MCDI), which is appropriate for measuring the word production and comprehension of children aged 16 to 30 months[14]. Parents reported on the production of a set of 112 words. To identify expressive language delay at 1.5 years the expressive vocabulary raw scores were converted into age and gender specific percentile scores based on the whole Generation R sample. Expressive language delay was defined as scores below the 10th percentile, in line with a previous definition of expressive language delay based on the MCDI[15 16].

At the age of 2.5 years, parents completed a Dutch translation of the Language Development Survey. The LDS is a 310-word vocabulary checklist, with words arranged within 14 semantic categories (e.g. animals, foods etc.). Parents have to identify the words the child uses spontaneously. The total vocabulary sum scores were converted in age and gender specific percentile scores based on the complete Generation R sample. The parents are asked also if the child has begun to combine phrases. Expressive language delay at 2.5 years was defined as word production scores below the 10th percentile, or not being able to use word combinations, in line with previous studies on language delay[17]. The LDS has been generated using community-based samples in the United States and has been shown to be a valid and reliable instrument to assess expressive language development in children under age 3 in diverse populations[12 18-19].

Executive function

Executive functioning, as evidenced in daily life, was assessed by having the parents complete the Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) in mailed questionnaires at the age of 4 years[20]. The BRIEF-P is the only standardized executive functioning scale designed specifically for use with preschoolers. It yields five non-overlapping theoretically and empirically derived clinical scales, each of which reflects a specific aspect of executive functioning: Inhibit, Shift, Emotional Control, Working Memory and Plan/Organize. These clinical scales yield three composite indexes: the Inhibitory Self- Control Index (ISCI), Flexibility Index (FI), and Emergent Metacognition Index (EMI). The overall composite index is the Global Executive Composite (GEC). Results are reported as T-scores standardized for sex and age; higher scores indicate greater degrees of dysfunction. Scores > 65 on the BRIEF are considered to be potentially clinically significant[20]. The normative sample, although based on the general population, contained relatively high proportions of upper and middle class families

Covariates

Questionnaires at enrollment in the Generation R study included items on maternal age and education, and on ethnicity and medical history of both parents. Midwife and hospital registers provided information on the date of birth, as well as birth weight and gender of the child. We assessed maternal psychopathology at 36 months postpartum with the Brief Symptom Inventory. We used the depression/ anxiety score as an indicator of psychopathological problems[21].

Study population

In total, 7295 participants were enrolled for the postnatal phase of the study (**Figure S1**). Twins (n=179) were excluded. In total, 527 mothers participated with 2 and 12 mothers with 3 children in the study. Results did not change after random inclusion of only one of these siblings and because of this we decided to include them all in the analyses. Children without information on febrile seizures (n=3640) were excluded. The remaining 3476 participants were eligible for the present study. Of these, information on behavioural outcome (CBCL) was available in 3425 (98.5%) and on executive functioning (BRIEF-p) in 3203 (92.1%) participants. Concerning language functioning, word production (MCDI) at the age of 1.5 years was available in 3334 (95.9%) participants. The vocabulary score of the LDS was available in 2877 (82.8%) participants and the information on word combinations in 2445 (70.3%).

Statistical methods

To examine whether non-response was selective we compared baseline characteristics of participants with and without information on febrile seizures using chi-square statistics for categorical variables, independent t-tests for continuous variables with a normal distribution and Mann-Whitney U tests for continuous variables that were not normally distributed. In the same way characteristics of participants with and without febrile seizures were compared with similar models.

Logistic regression models were used to examine whether febrile seizures are associated with internalizing and externalizing behavioural problems as assessed with the CBCL at 3 years of age. We adjusted for covariates known to influence child behaviour from literature: maternal age, educational level and psychopathology; sex and ethnicity of the child. We also adjusted for parity as this was associated with febrile seizures in univariate analyses and changed the effect sizes of the associations by ≥ 5%. Using similar models we examined whether febrile seizures were associated with expressive language delay at the age of 1.5 years and 2.5 years. Ethnicity, socio-economic status, maternal age, low birth weight and gender have been identified as factors influencing early language development in previous studies and were considered as possible confounders. Low birth weight, maternal age and ethnicity did not change the

effect measures found by ≥ 5% and as such were not included in the final model. We again additionally adjusted for parity as this was associated with febrile seizures in univariate analyses and changed the effect sizes of the associations found. Finally we examined the association between febrile seizures and the standardized scores on the BRIEF-P. Differences of mean T-scores between participants with and without febrile seizures were calculated, adjusted for ethnicity and educational level of the mother as these might influence executive functioning and the association found[20].

Missing values of covariates were multiple imputed, by means of which five imputed datasets were created. Each dataset was analyzed separately and the results were pooled using the method of Rubin[22]. Confidence intervals reflect the uncertainty about the imputed values.

The Statistical Package of Social Sciences version 17.0 for Windows (SPSS Inc, Chicago, IL, USA) was used to perform the statistical analyses.

RESULTS

Of the 3476 participants included in the analyses, 96 had experienced a febrile seizure until the age of 2.5 and 108 until the age of 3 years. Thirty-three children had had recurrent febrile seizures and 25 had a first febrile seizure before their first birthday. **Table 1** shows that mothers of children with febrile seizures more frequently were more often not from Dutch origin and more often were primiparous ($p<0.05$). Parents of children with febrile seizures more often reported a history of febrile seizures themselves. No other differences were found.

Primary caregivers of children with febrile seizures tended to report more sleep problems in their children. Increased vigilance of the parents might have played a role. Besides this, febrile seizures were not significantly associated with an increased risk of problem behaviour at the age of 3 years (**Table 2**). Also the subgroup of participants with a first febrile seizure before the age of 12 months did not have more problem behaviour than children without febrile seizures (data not shown). **Table 3** show that we did not find a significant association between single febrile seizures and expressive language functioning at the age of 2.5 years. However, recurrent febrile seizures were associated with expressive language delay at the age of 2.5 years (odds ratio 3.06, [95% confidence interval 1.23-7.58]). In the same group of children there was no apparent expressive language delay at the age of 18 months (odds ratio 0.98, [95% CI 0.40-2.43]). We also did not find a significant association between febrile seizures in the first year of life and expressive language delay at 18 months (data not shown). Only 6 children already had recurrent febrile seizures before the age of 18 months, this group was too small to justify separate analyses.

We did not find differences in executive functioning between children with and without febrile seizures (**Table S1**), even if only the subgroups of children with recurrent febrile seizures, or with a first febrile seizure before their first birthday were included.

TABLE 1. Subject characteristics of participants with febrile seizures

	No febrile seizure N=3368	Febrile seizure N=108	p-value
Maternal characteristics			
Age, years (SD)	31.7 (4.4)	31.5 (4.8)	0.649
Ethnicity, european N(%)	2602 (78.2)	73 (67.6)	0.009
Educational level			0.343
Primary	134 (4.1)	7 (6.5)	
Secondary	1126 (34.2)	32 (39.9)	
High	2033 (61.7)	68 (63.6)	
Primipara N (%)	2006 (60.8)	74 (71.2)	0.032
Smoking during pregnancy N (%)	353 (12.3)	12 (14.0)	0.636
GSI score mother	0.15 (0-0.57)	0.11 (0-0.53)	0.212
Febrile seizure mother N (%)			0.043
Yes	84 (2.8)	6 (6.1)	
No	2722 (90.9)	91 (91.9)	
Don't know	187 (6.2)	2 (2.0)	
Febrile seizures father N (%)			0.012
Yes	62 (2.4)	6 (7.6)	
No	2377 (91.5)	67 (84.8)	
Don't know	160 (6.2)	6 (7.6)	
Child characteristics			
Gender, male N (%)	1663 (49.4)	60 (55.6)	0.206
Ethnicity (Caucasian) N (%)	2665 (79.9)	82 (75.9)	0.307
Birthweight, grams (SD)	3483 (540)	3428 (584)	0.304
Birthweight < 2500 grams	3.9 (132)	5.6 (6)	0.392
Gest age birth, weeks (SD)	40.0 (1.6)	39.9 (1.7)	0.729
Preterm birth (<37 weeks) N(%)	134 (4.0)	6 (5.6)	0.412

Missings on ethnicity mother 39 (1.1%), educational level 76 (2.2%), parity 70 (2.0%), smoking during pregnancy 509 (14.6%), GSI score mother 69 (2.0%), febrile seizures mother 384 (11.0%), febrile seizures father 798 (23.0%), ethnicity child 34 (1.0%).

DISCUSSION

We found no differences in behavioural problems or executive functioning between children with and without a history of febrile seizures. Children with recurrent febrile seizures seemed to be at increased risk of expressive language delay.

The issue of whether febrile seizures are associated with brain damage or dysfunction has been subject to many epidemiological and experimental studies. Earlier epidemiological studies reported a significant risk of intellectual and behavioural problems among children with

TABLE 2. Febrile seizures and the risk of behavioural problems at the age of 36 months (CBCL)

	Risk of behavioural problems OR (95% CI)			
	Internalising problems	Externalising problems	Sleep problems	Total problems
Febrile seizures, all (n=108)	0.73 (0.40-1.32)	0.88 (0.51-1.51)	1.67 (1.04-2.68)	1.05 (0.62-1.78)
Single febrile seizures (n=75)	0.86 (0.43-1.71)	0.75 (0.38-1.50)	1.52 (0.84-2.75)	1.18 (0.63-2.21)
Recurrent febrile seizures (n=33)	0.52 (0.17-1.59)	1.23 (0.35-2.98)	2.06 (0.93-4.58)	0.84 (0.32-2.20)

Values represent odds ratios from logistic regression models adjusted for maternal age, educational level, parity, anxiety/ depression index and child sex and ethnicity

TABLE 3. Febrile seizures in the first 2.5 years of life and the risk of delayed expressive language development at the age of 1.5 years (MacArthur) and 2.5 years (LDS)

	Risk of delayed vocabulary development at 18 months OR (95% CI)	Risk of delayed vocabulary development at 30 months OR (95% CI)	Risk of delayed phrase development at 30 months OR (95% CI)
Febrile seizures, all (n=96)	0.95 (0.57-1.59)	1.19 (0.53-1.95)	1.07 (0.57- 2.03)
Single febrile seizures (n=65)	0.94 (0.51-1.74)	0.52 (0.33- 1.48)	0.78 (0.70-5.15)
Recurrent febrile seizures (n=31)	0.98 (0.40-2.43)	3.27 (1.33-8.12)	1.90 (0.70- 5.15)

Values represent odds ratios from logistic regression models adjusted for maternal educational level, income and parity. Missing data on vocabulary development at 1.5 years n= 142 (4.1%), missing data on vocabulary development at 2.5 years n=599 (17.2%), missing data on phrase development n=1031 (29.7%).

febrile seizures[8 23]. Most of these studies were hospital-based and because of this, selection towards more severe cases may have occurred. Also some studies included children with known neurological disabilities. Two large national birth cohort studies assessed developmental outcomes in children with a history of febrile seizures. A large prospective population-based study in the United States reported febrile seizures not to be associated with a reduction in IQ or early academic performance at the age of 7[24]. The Child Health and Education Study followed a large cohort of children born in the same week in 1970 in the United Kingdom. At the age of 5 and 10 years no differences in academic progress, intelligence and behaviour were found between children with or without a history of febrile seizures[5]. Chang et al. even reported higher scores on tests of intelligence and academic achievement in Chinese school-children with a history of febrile seizures. In a second study on learning and memory aspects, again children with a history of febrile seizures performed better[2-3].

Considering that the current study also involved a population-based cohort, in contrast to a clinical population, the results of our study are very much in line with the USA and UK recent studies. Together, these large population-based studies, that focused on different age-groups and different aspects of cognitive functioning, are strongly indicative of a good developmental outcome for most children with febrile seizures.

However, both the British, the Chinese, and also a Danish study reported a less favourable outcome in children with a first febrile seizure in the first year of life[9]. Also recurrent and prolonged febrile seizures have been associated with a less benign outcome[6-8]. It is also well known that epilepsy can be associated with neuropsychological impairment. Several studies already identified cognitive impairments at epilepsy onset, or shortly after diagnosis, even in children with idiopathic epilepsy.[25]. Taken together, some evidence exists that at least in part of the children with seizures brain injury or dysfunction can be involved.

We studied language development, executive functioning and behaviour in pre-school children with febrile convulsions in a population-based cohort. Most children begin to use words and rapidly extend their vocabulary between 1 and 3 years of age, the same age most febrile seizures manifest. We hypothesized the occurrence of (recurrent) febrile seizures might be associated with delayed language development. Also executive functioning has been described to be disturbed in a rat model of febrile seizures and was added because of this. We also studied these outcomes separately in subsets of children with febrile seizures that might be more vulnerable for an adverse outcome: those with early seizure onset or with recurrent febrile seizures. The size of the group of children with prolonged febrile seizures was too small to justify separate analyses.

In accordance to the majority of population-based studies, we did not find any significant differences in behavioural disturbances or executive functioning in children with febrile seizures. Moreover, no associations were found between recurrent febrile seizures or early seizure onset and problem behaviour or impaired executive functioning later in childhood. In contrast to single febrile seizures, we did find recurrent febrile seizures to be associated with an increased risk of expressive language delay at the age of 2.5 years. These children did not show expressive language delay yet at the age of 1,5 years. As far as we are aware of, language functioning has not been examined before in association with febrile seizures. A few earlier studies reported poorer linguistic ability in school-aged children with a history of febrile seizures[23]. Our findings should be replicated before definitive conclusions can be drawn.

Strengths of this population-based birth cohort-study include the large number of participants that are followed prospectively. Data on febrile seizures were collected every year to increase parental recall. Limitations are that information on paroxysmal events, language and executive functioning, and behaviour was missing in part of the participants. Subgroup analysis showed that non-response was selective. Mothers of children without information on febrile seizures were more often not from Dutch origin and lower educated. In children without information on febrile seizures, behavioural problems, language delay and problems with executive functioning were reported more often (**Table S2**). It seems unlikely that the associations studied would be different in this group of participants, but the possibility of selection bias cannot be ruled out completely. Concerning our outcome measures, the non-response was highest for the LDS, so results concerning language development are based on a smaller amount of cases. No validated screening instrument for febrile seizures exists. We based our

screening questions on previously used screening questionnaires for seizure disorders. These questions were adjusted to young children and some clinically relevant questions were added. In accordance with the definition of febrile seizures, we excluded children with intracranial infections or other defined causes. However, it can not be completely excluded that in some children a more subtle underlying pathology was involved that we were not aware of. In some children the febrile seizure may have been a first manifestation of an underlying genetically determined seizure disorder. We did not take anti-epileptic drug treatment into account. However, within the Netherlands, anti-epileptic drugs on a daily basis are only very rarely described for febrile seizures, even if they are recurrent. Therefore it is not likely that these children were treated with anti-epileptic drugs

In conclusion, in line with previous studies our results suggest that febrile seizures are not associated with poor behavioural or cognitive outcome in young children. Experiencing recurrent febrile seizures, however, might adversely affect expressive language development. Further studies for replication and long term follow–up of these results are needed.

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TABLE S1. Association between febrile seizures and executive functioning at the age of 4 years

	T-scores, mean (SD)	Difference with mean T-scores of children without febrile seizures (95% confidence interval)	
		Model1	Model 2
Inhibition	46.1 (9.2)	0.59 (-1.74-1.86)	0.11 (-1.67-1.89)
Shift	47.3 (8.3)	-0,23 (-1.98-1.53)	-0,27 (-2.02-1.49)
Emotional control	47.6 (10.1)	-0.31 (-2.39-1.76)	-0.35 (-2.43-1.72)
Working memory	46.6 (9.1)	-0.19 (-2.11-1.73)	-0.14 (-2.03-1.76)
Plan/Organize	45.1 (8.4)	-0.16 (-2.02-1.71)	-0.16 (-2.01-1.68)
Global executive composite	46.1 (9.2)	-0.17 (-2.08-1.75)	-0.15 (-2.05-1.75)

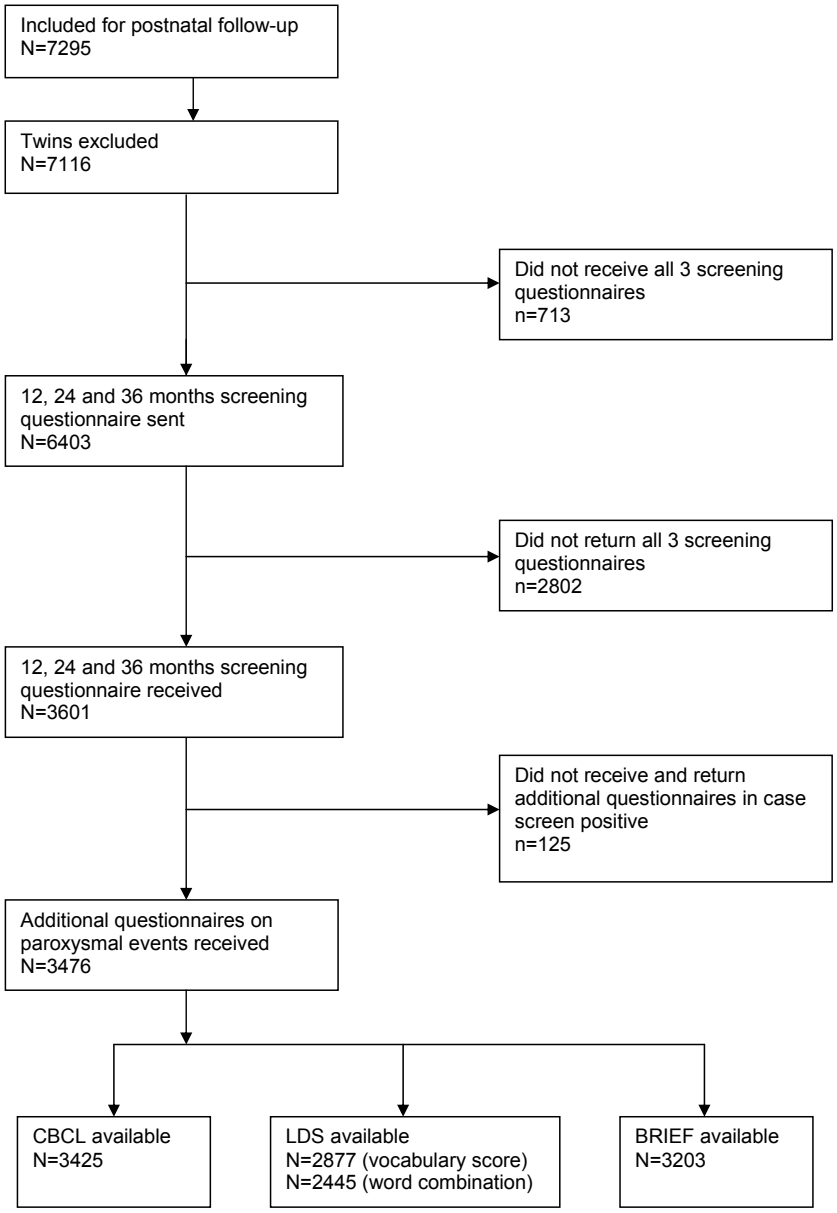
Model 1: unadjusted
Model 2: adjusted for ethnicity and educational level mother

TABLE S2. Subject characteristics and cognitive problems in participants with and without information on febrile seizures

	Response N=3476	Non-response N=3640	p-value
Maternal characteristics			
Age, years (SD)	31.7 (4.4)	29.4 (5.5)	< 0.001
Ethnicity, European %(n)	77.8 (2672)	49.4 (1570)	< 0.001
Educational level %(n)			< 0.001
Primary	4.1 (40)	14.3 (440)	
Secundary	34.1 (1157)	51.1 (1575)	
High	61.8 (2099)	34.6 (1067)	
Primipara % (n)	61.0 (2076)	50.7 (1766)	< 0.001
Child characteristics			
Birthweight, grams (SD)	3482 (547)	3383 (553)	< 0.001
Apgar score 5 minutes < 7	0.8 (26)	1.3 (46)	0.026
LDS % (n) > 80th percentile study population			
Delayed phrase	18.3 (448)	24.9 (257)	<0.001
Delayed vocabulary	13.8 (396)	17.9 (236)	0.001
CBCL % (n) > 80th percentile study-population			
Internalising sum score	19.4 (664)	28.8 (402)	<0.001
Externalising sum score	20.5 (702)	25.4 (354)	<0.001
Sum overall	20.0 (685)	27.9 (388)	<0.001
BRIEF-T mean t-score (SD)			
Inhibition	47.2 (8.7)	48.5 (9.0)	< 0.001
Shift	48.1 (8.5)	48.3 (8.5)	0.484
Emotional control	47.9 (10.0)	48.6 (10.8)	0.027
Working memory	46.8 (9.3)	48.2 (10.3)	< 0.001
Plan/Organize	45.3 (9.0)	47.0 (10.0)	< 0.001
Global executive composite	46.2 (9.2)	47.6 (10.2)	< 0.001

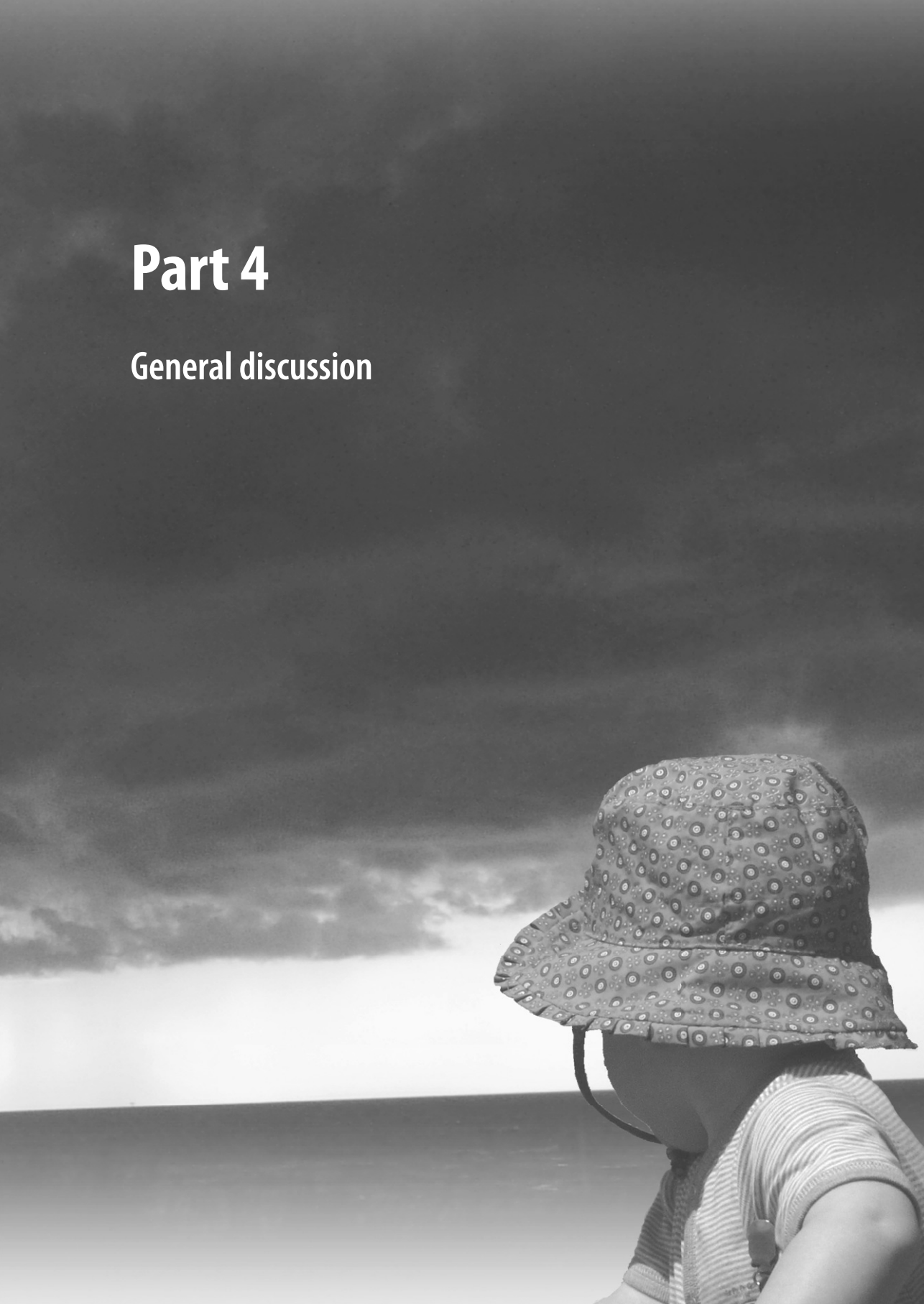
Missing data (especially in the non-response group): ethnicity n=505 (7.1%); educational level n=638 (9.0%); parity n=233 (3.3%); apgar score n=316 (4.4%); delayed phrase development n=3641 (51.2%); delayed vocabulary development n=2919 (41.0%); CBCL internalizing sumscore n=2300 (32.2%); externalizing sumscore n=2297 (32.3%); sum overall n=2298 (32.2%); BRIEF T global executive composite n= 4766 (67.0%)

FIGURE S1. Flow diagram of the study population



Part 4

General discussion



GENERAL DISCUSSION

Research in this thesis is focused on paroxysmal events and febrile seizures in early childhood. In the first part we report the results of a study on paroxysmal epileptic and non-epileptic events in infancy in the general population. The second part focuses on febrile seizures, the most common epileptic paroxysmal event in young children. In this chapter the main findings will be summarized and their significance discussed, as well as possible implications for clinical practice. Also methodological issues and suggestions for further research will be addressed.

Summary of the main findings

In **part 2**, we present the results of a study on the incidence of paroxysmal events, as well as their possible risk factors, in the general population, in the first year of life. Paroxysmal events were defined as disorders characterized by suddenly-occurring mostly short-lasting events, with altered consciousness, altered behaviour, involuntary movements, altered muscle tone and/or a changed breathing pattern, alternating with periods during which the symptoms did not occur. We found an incidence of paroxysmal events of 8.9-12.9 % in the first year of life. The largest group of these events are innocent, physiologic events, especially in the first 6 months of life. Epileptic seizures only form a small minority of these events. Preterm birth, low birth weight and low Apgar scores were associated with paroxysmal disorders in the first year of life. Physiologic events were reported more often in first-born children. Children with a small head circumference at 30 weeks gestational age, that were born preterm or whose mothers continued smoking during pregnancy had a higher incidence of febrile seizures in the first year of life.

Part 3 focuses on febrile seizures. Several studies on possible risk factors and on outcome of febrile seizures are presented. In **chapter 3.1** the results of a study on the validity of parentally reported febrile seizures are reported. The reply to the question: "Did your child have a febrile seizure?" was compared with the classification of the paroxysmal event by a paediatric neurologist, as based on an extended questionnaire on the event and, when available, the medical record. The sensitivity of a positive reply to the question "Did your child have a febrile seizure?" was 92% and the specificity 72%. The negative predictive value was high (98%). The positive predictive value was only 41%. This means that this question is sufficiently appropriate as a screening instrument for febrile seizures, as case-identification will be nearly complete. However, a second stage of evaluation is necessary to identify true cases. Among the false-positives, an isolated fever, shivering during a fever episode and vasovagal collapse were the most frequent diagnoses.

In **chapter 3.2** we showed that fetal growth retardation in the second half of pregnancy is associated with an increased risk of febrile seizures. Adverse environmental exposures as well

as genetic factors might be responsible for this growth retardation. Associations were stronger for general growth characteristics than for head or brain growth characteristics. Among the growth characteristics of the head and the brain, associations were strongest with second trimester transverse cerebellar diameter. The mechanisms by which a smaller fetal cerebellum might predispose to febrile seizures are not known. It might be only a proxy of other structural or functional changes in the brain. Further research is needed, focused on fetal brain developmental adaptations as mechanism leading to febrile seizures.

In **chapter 3.3** we describe the associations between inadequate folic acid supplement use and the risk of febrile seizures. Information on folic acid use was collected in early pregnancy by questionnaires. We categorized folic acid supplement use in 'preconceptional use', 'start during the first trimester of pregnancy' or 'no use during embryogenesis'. No folic acid supplement use tended to be associated with an increased risk of febrile seizures in the offspring. The association of inadequate folic acid supplementation and the risk of febrile seizures was most evident for febrile seizures during the first year of life. As this is the first study that explored this association, further research is necessary to replicate these findings and to identify underlying mechanisms.

In **chapter 3.4** we showed that frequent fever episodes are associated with an increased risk of febrile seizures. Frequent fever episodes were defined as more than 2 fever episodes per year. We found a linear association between the number of fever episodes and the risk of febrile seizures in the second and third year of life, but not in the first year of life. The association between the number of fever episodes and febrile seizures was stronger among children with recurrent than with single seizures. The number of fever episodes a child experiences is in its own turn dependent on environmental as well as genetic factors. When a child presents with a febrile seizure, next to asking whether febrile seizures are running in the family, it might also be informative to ask whether the child experienced many fever episodes.

Chapter 3.5 focuses on the developmental outcomes of children who had a febrile seizure. Febrile seizures are generally considered to be a benign condition with an excellent outcome. However, some indications exist that in children with febrile seizures before their first birthday or children with prolonged or recurrent febrile seizures, developmental outcomes are less favourable. Previous studies on this topic only examined school-aged children. We studied developmental outcomes at a younger age as possible adverse effects might be more evident shortly after the seizure. However, in line with these previous studies, we did not find differences in behaviour, executive functioning or expressive language development in children with febrile seizures. This was also the case for children with febrile seizures in the first year of life. In contrast with single febrile seizures, we did find recurrent febrile seizures to be associated with an increased risk of expressive language delay.

DISCUSSION

1. Paroxysmal events in infancy

Paediatricians and paediatric neurologists are regularly confronted with children with paroxysmal occurring symptoms, such as altered consciousness, altered behaviour, involuntary movements, altered muscle tone or a changed breathing pattern. These symptoms can be very alarming to the parents. When a child presents with a paroxysmal event, it may indicate an epileptic seizure. However, also other disorders can present with paroxysmal symptoms and may mimic epileptic seizures[3 141-142]. We found paroxysmal events to be common in the general population in infancy. However, epileptic seizures only constitute a small part. This should be taken into account when judging an infant with a paroxysmal event and planning diagnostic strategies. This is especially the case as an erroneous diagnosis of epilepsy can have negative consequences both because of unnecessarily prescribed medication with possible adverse effects, and because of the negative implications this diagnosis might have for daily life[143-144].

2. Febrile seizures

Febrile seizures are the most common type of seizures in childhood. Although in general considered as harmless, they are often very alarming to parents and lead frequently to hospital admissions[10 18 20 23]. With a prevalence of 2-5%, febrile seizures are a major disease burden on an individual scale and for society as a whole[10 17-20 23 36]. Besides this, the incidence of epilepsy seems to be increased in children with febrile seizures[25 65-68], and subgroups of children with febrile seizures might have less favourable cognitive and behavioural outcomes[77 79 82]. Nevertheless the pathogenesis is largely unknown. Increasing knowledge on febrile seizures might change our approach of children with febrile seizures in daily practice and possibly lead to development of new prevention strategies. It also implies that we can better counsel the parents. Besides this, it might help generating hypothesis on other seizure disorders, that although less frequent, have a stronger impact on daily life of the involved as well as on the health care system.

ETIOLOGY

Genes

Risk factors for febrile seizures have been subject of many epidemiological studies (**Table 1**). In literature, most evidence exists for a genetic predisposition leading to febrile seizures. Family studies have shown that relatives of probands with febrile seizures have a higher risk of having

febrile seizures themselves (**Table 1**). Besides this, in twin studies higher concordance rates for febrile seizures for monozygotic than for dizygotic twins were shown[42].

Most cases of febrile seizures probably are genetically complex disorders influenced by variation in several common susceptibility genes[42]. Common genetic variants might be involved in neurotransmission and inhibition, and as such influencing neuronal excitability. However, in the past years, findings from both clinical and experimental studies have shown that also components of the immune response are directly involved in the pathogenesis of febrile seizures[31]. Cytokines, especially the pro-inflammatory cytokine interleukin-1, are presumed to induce an increased neuronal excitability, independent of giving rise to an increased body temperature. In subjects with febrile seizures, an increased immune or cytokine response has been reported[29-30 145-146]. The genetic predisposition for febrile seizures might thus also concern genes that influence the functioning of the immune system. Moreover, children with certain genetic alterations in the interleukin system appeared to be more susceptible to febrile seizures[32 147-148]. Our finding that the number of fever episodes is an independent determinant of febrile seizures can be seen as another indicator of the involvement of the immune system. The number of fever episodes that a child experiences is partially dependent on environmental factors. Also the functioning of the immune system is involved. The genetically based functioning of the immune system thus might influence the susceptibility for febrile seizures directly and indirectly, by affecting the course and number of infections or fever episodes.

In conclusion, next to common genetic variants involving neuronal excitability, also variants involving the functioning of the immune system may influence the susceptibility for febrile seizures. Moreover, both of them have been reported to be associated with the risk of febrile seizures[49]. However, this mostly concerned results of small studies that could not be replicated by others. Until now no consistent and convincing susceptibility genes have emerged that affect the majority of febrile seizures[48-49]

Family history

Most studies with information on the family-history of febrile seizures, found an association between a positive family history and an increased risk of febrile seizures (**Table 1**). Therefore, it is remarkable that in our studies, we found no or only a slightly increased prevalence of a parental history of febrile seizures in children with febrile seizures. Several explanations might be relevant.

First, it should be mentioned that in our studies numbers are small. We studied between 30 and 110 children with febrile seizures per study. There were also missing data on the parental history of febrile seizures. Several participants did not answer the question whether they had febrile seizures as a child, or they answered that they did not know. The resulting percentages of parents with febrile seizures were small and there might not have been enough power to show significant differences between participants with or without febrile seizures, especially in the studies with the lowest numbers of cases. Second, because of the young age at which

TABLE 1. Risk factors for febrile seizures

	Ross	Verity	Cassano	Nelson	Forsgren	Bethune	Berg	Greenwood	Huang	Vestergaard
Family history		+	+	+	+	+	+	+	+	+
Parity				-	-			-	-	+
Smoking	-		+	±			+	-	-	±**
Maternal educational level / SES	-	-		+	+		-	-	-	-
Pre-eclampsia		-			+*			+	-	-
Hospital admissions mother		-		±				+		
Factors delivery	-	***		-	-		-	-	-	
Prematurity					+		-	-	-	+
Birthweight	-	+				+	-	+	-	+
Day care attendance					+****	+	-		-	
Febrile episodes					+				+	
Breastfeeding								+		
Delayed development prior to seizure					-	+	-		+*	

Study's on febrile seizures (first author (country, year), type, cases/controls): Ross (UK, 1980), cohort study (National Child development Study(NCDS)), 332/ 15.496; Verity (UK, 1985), cohort study (Child Health and Education Study, began as NCDS), 303/13135; Cassano (US, 1990), case-control, 163/309; Nelson & Ellenberg (US, 1990), cohort study (National Collaborative Perinatal Project), 1706/55000; Forsgren (Sweden, 1991), case-control, 110/220; Bethune (Canada, 1993), case-control, 75/300; Berg (New York, 1995), case-control, 69/99; Greenwood (UK, 1998), cohort study (British Birth Survey), 378/ 16.163; Huang(Taiwan, 1999), cohort study, 256/10460; Vestergaard (Denmark, 2002), cohort study, (2 populations of 10.224 and 21.218 children; febrile seizures rescpectively between 8-12 and 3-4%).
; ± only trend; * no longer in multivariate analyses; **only when smoking > 10-15 cigarettes a day; *** only breech presentation; ****children who spent most of their time in day by day care institutions and who lived in appartments

febrile seizures occur, it concerns information on many years in the past that the parents will not be able to remember themselves and misclassification will probably have occurred. An advantage of our study was that information on the history of febrile seizures was collected during pregnancy. Misclassification therefore was not dependent on the febrile seizure-status of the child. It will probably have attenuated the results. In many other studies information on the family history was obtained after the child had experienced a febrile seizure what might lead to recall bias and stronger associations. Third, we only used information on a history of febrile seizures in the parents. Previous studies showed the strongest associations between febrile seizures and a history of febrile seizures in siblings. In our study, most children at the time of collecting data did not yet have siblings, or their siblings had not yet reached the susceptible age for febrile seizures.

Environment

Although genetic factors are involved in the susceptibility for febrile seizures, they only explain part of the increased risk. Moreover, as families often share environmental factors as well, a positive family-history does not necessarily reflect a genetic background. Findings from previous studies on risk factors for febrile seizures already suggested that environmental factors are involved as well[36-37 53-55 116]. This is supported further by our findings that fetal growth retardation, inadequate folic acid supplement use and the number of fever episodes are associated with an increased risk of febrile seizures.

During pregnancy, rapid growth and development of the central nervous system take place. Adverse influences in the prenatal period can influence this process in a negative way. Examples of this are the consequences of maternal smoking or alcohol use during pregnancy[97 149]. It can be hypothesized that the resulting brain damage or dysfunction might also result in a lower threshold for febrile seizures.

As many adverse environmental influences during pregnancy result in fetal growth retardation, this might be a sensitive marker of sub-optimal circumstances during pregnancy. Our finding that fetal growth retardation is associated with an increased risk of febrile seizures supports the hypothesis that early environmental factors are involved in the susceptibility of febrile seizures. We found the associations to be stronger for body than for head and brain growth characteristics. This might reflect that head and brain growth are relatively spared in mild growth retardation[97]. However, still small structural or functional changes might result. These might be difficult to detect with ultrasound measurements.

Within the head and brain characteristics, we found the strongest association with transverse cerebellar diameter. Generally, the cerebellum is not considered to be an area of the brain where epileptic activity arises. A small transverse cerebellar diameter might only serve as a proxy of other structural or functional changes in the brain. At the other side experimental evidence exists of an inhibitory role of the cerebellum on the cortex in seizure generation. Also

in this context it should be mentioned that for a long time now a relationship between chronic epilepsy and cerebellar atrophy has been recognized. The etiology of cerebellar damage in temporal lobe epilepsy and other epilepsy syndromes continues to be subject of debate. Next to hypoxic-ischemic injury due to prolonged seizures or adverse effects of antiepileptic drugs, theories also include perinatal or developmental injury[150]. Further research is needed, focused on fetal brain developmental adaptations as mechanism leading to febrile seizures and the possible role of the cerebellum.

One of the environmental factors known to influence foetal growth negatively is maternal folate deficiency[151]. Folic acid is an essential micronutrient. During pregnancy folic acid demand increases because of rapid foetal and placental growth[152]. Folate deficiency was first linked to the formation of neural tube defects by the observation that pregnant women who took medication that interfered with or antagonized folate metabolism (carbamazepin, valproate) had a greater number of children with spina bifida[108-109]. Subsequently also other congenital abnormalities, as well as behaviour and temperament problems in the offspring were reported to be associated with folate deficiency, or inadequate folic acid supplementation in pregnant women[111 152] Besides this, a number of inborn errors of folic acid metabolism exist that are associated with the occurrence of seizures[112]. These findings suggest that folic acid can modulate mechanisms for growth and development in the central nervous system. This led to recommendations on folic acid supplement use during pregnancy[152-154]. We observed that inadequate folic acid supplement use was associated with an increased risk of febrile seizures.

Although an association between folate deficiency and central nervous system development and functioning has been recognized now for a long time, the underlying mechanisms are not exactly known. Folate is a critical cofactor in methyl metabolism[155]. Methylation is essential for synthesis of membrane phospholipids, myelin basic protein and neurotransmitters. Folate is also essential for DNA methylation. Genomic DNA methylation status has been found to correlate directly with folate status[156]. DNA methylation is of major importance in establishing proper gene expression in embryogenesis. Experiments in Yellow Avy agouti mice for example have shown that supplementing the diet of pregnant dams with methyl donors results in silencing of the agouti gene due to DNA methylation. This in turn results in offspring with a different brown coat colour, and a lower tendency for obesity, cancer and diabetes. Folate deficiency thus might be involved in central nervous system development, and possibly the susceptibility for febrile seizures, both directly and indirectly by epigenetic mechanisms. Environmental and genetic factors in this way come together.

We further found the number of fever episodes to be a determinant of the risk of febrile seizures. The number of fever episodes that a child experiences at the one side is dependent on the susceptibility for infectious diseases, as influenced by the partially genetically based functioning of the immune system. At the other side, environmental factors play a role. Examples of environmental factors reported to be involved in the number of gastro-intestinal or respiratory tract infections children experience are day-care attendance, exposure to passive smoking and

breast feeding[157-158]. Day-care attendance and breast feeding both have also been found to be associated with the risk of febrile seizures, albeit only in one or two studies[39 55 116].

Outcome

A lot has been speculated on whether febrile seizures damage the brain. This might manifest by structural or functional changes of the brain, or clinically by the subsequent development of unprovoked seizures or an adverse cognitive or behavioural outcome. Findings from experimental and observational studies have shown that at least some febrile seizures are capable of producing at least transient brain injury or dysfunction[139 159-161].

Experimental studies in a rat-model of febrile seizures have shown an increased risk of subsequent unprovoked seizures after prolonged hyperthermia-induced seizures[162]. Also in a rat model, cognitive dysfunction involving the hippocampus and prefrontal cortical networks was reported especially after prolonged experimental febrile seizures[139].

Epidemiological studies found the risk of epilepsy to be increased in children with febrile seizures[25 65 67-68]. Also in incidence-cohorts of children with newly diagnosed epilepsy, an increased prevalence of antecedent febrile seizures is reported of 13-18% [69-73]. An association between febrile seizures and epilepsy, however, does not necessarily mean that febrile seizures increase the risk of developing epilepsy; they might also have been the first manifestation of an underlying seizure disorder. Retrospective studies have linked temporal lobe epilepsy to a history of prolonged febrile seizures[74]. One of the structural hallmarks in patients with mesial temporal lobe epilepsy and a history of prolonged febrile seizures is a specific pattern of cell loss in the hippocampus; mesial temporal sclerosis[74 163]. It has been widely hypothesized that febrile seizures cause mesial temporal sclerosis and that the development of temporal lobe epilepsy is a consequence of this mesial temporal sclerosis[164 165]. Some neuro-imaging studies have demonstrated oedema of the hippocampus in children, shortly after experiencing prolonged febrile seizures, resolving again within a few days[159-160]. In some of these children later a reduction in hippocampal volume was shown, or an increase in hippocampal volume asymmetry[159]. Though pre-existing hippocampal abnormalities could not be excluded, these findings suggest that some febrile seizures are capable of inducing structural changes.

Several prospective cohort studies did not find differences in cognitive and behavioural outcome between children with and without febrile seizures[22 51 76-78]. In our study we also found no association between a history of febrile seizures during the first 3 years of life, and cognitive or behavioural functioning in preschool children. However, indications exist that certain subgroups of children might have a less favourable outcome. This concerns children with complex febrile seizures, febrile seizures before their first birthday and children with recurrent febrile seizures[77 79-80 82]. In our study, we did not observe that febrile seizures during the first year of life do affect outcome adversely. However recurrent febrile seizures were associated with an increased risk of expressive language delay. To our knowledge, language development

has not been studied before in children with febrile seizures. Also only few studies are available on the cognitive functioning of preschool children with epilepsy. In a study of Rantanen et al, intellectual functioning of preschool children with uncomplicated epilepsy was within normal range, but differed significantly from that of healthy controls. Statistically significant differences emerged in verbal IQ and full scale IQ, but not in performal IQ. The children with uncomplicated epilepsy also had minor difficulties in verbal short-term memory compared to healthy controls. These results suggest that uncomplicated epilepsy in preschool children might interfere with verbal functions[166]. Another possibility is an underlying substrate giving rise to seizures as well as to language dysfunction. However, we were the first to show this association and findings should be replicated before definite conclusions are possible.

In conclusion, it appears that most febrile seizures are benign disorders with an excellent outcome. However, certain subgroups of febrile seizures, that is prolonged or focal febrile seizures, recurrent febrile seizures and febrile seizures in the first year of life might affect neurodevelopment outcome at later adversely.

Febrile seizures, a heterogeneous disorder

In conclusion, a variety of genetic and environmental factors, as well as the interaction between these, seems to be involved in the individual susceptibility for febrile seizures. The individual combination of risks factors might not only determine the susceptibility for febrile seizures on itself, but also the clinical presentation. We found several indications that, concerning pathogenesis, febrile seizures in the first year of life might differ from febrile seizures occurring later in life. Maternal smoking in pregnancy was found to be associated with febrile seizures in the first year of life, but this could not be replicated when children with febrile seizures in the second or third year of life were included. Also inadequate folic acid supplement use seemed to be associated especially with an increased risk of febrile seizures in the first year of life. The number of fever episodes was associated with the risk of febrile seizures in the second and third year of life but not in the first year of life. This suggests that the relative importance of different risk factors involved in the pathogenesis of febrile seizures might differ, dependent on the age of first seizure presentation. Hypothetically, the presence of (several) genetic susceptibility genes and/ or environmental risk factors might result in a lower threshold for febrile seizures. As a result, the child experiences a febrile seizure already during one of its first fever episodes and as such early in life. Also in this group, more children with febrile seizures in the spectrum of genetically determined epilepsies might be represented. Without (some or all of) these risk factors, the susceptibility for febrile seizures might be lower, and the number of fever episodes becomes more important in determining the chance of having a febrile seizure.

Some studies found outcome to be less favourable in children with febrile seizures in infancy, compared to children with a first febrile seizure after their first birthday[77 82]. We could not confirm this in our study. Possibly the number of cases was too low to detect a small effect. Besides this,

we did not study all aspects of cognition and behaviour. The adverse outcome in children with early febrile seizures as found in other studies, might reflect an injurious effect of early febrile seizures on brain function or development. The possibility of a common underlying factor that predisposes to febrile seizures as well as to cognitive dysfunction should also be considered. In this perspective it is worth mentioning that children with epilepsy frequently present with learning difficulties that when asked further were already present before the first seizure.

METHODOLOGICAL CONSIDERATIONS

In the previous chapters, strengths and limitations have been discussed for the individual studies in this thesis. Now more general methodological issues will be addressed pertaining to the study as a whole. Subsequently we will discuss the study design, the methods of case-ascertainment, bias by selection, misclassification and confounding and missing values.

Study design

Febrile seizures have been subject of many epidemiological studies. Some of these studies are case-control studies[37 39-40], the last decades also several large cohort studies reported their results[18 36]. In case-control studies most often children admitted to the hospital because of a febrile seizure were compared with children admitted for other reasons. The advantage of this study design is that it is an efficient way of collecting cases, especially in less frequent disorders as febrile seizures. The study can be done in a relatively short period of time, and the number of subjects to be examined can be kept relatively small. Detailed clinical information is available and the diagnosis is likely to be accurate. A disadvantage is that hospital-based series might only comprise the more severe cases. Another disadvantage in etiologic studies can be their retrospective nature. If exposure-information is obtained by interviews, case-control studies depend on correct reporting of a risk factor that may be many years in the past. Moreover, the information reported might be influenced by the occurrence of the disease under study. For example, parents of a child who experienced a febrile seizure might be more inclined to investigate the family history concerning seizure-disorders than parents of a child without a febrile seizure.

In cohort studies, groups of unaffected children are followed for a period of time to see who develops the disease of interest. Cohort studies better reflect the general population and the spectrum of disease severity and frequency. A cohort can be studied from birth or even pregnancy, allowing prospective evaluation of febrile seizure occurrence and possible risk factors. The disadvantage of this design is that it can be time-consuming, labour intensive and, as a consequence, expensive. Especially in case of a less frequent disorder such as febrile seizures, a large number of subjects has to be followed for a long time to identify a sufficient number

of cases. The diagnosis of febrile seizures also might be less accurate than in a hospital based setting. And as participants have to stay in the study for a longer time, this type of studies might be more prone to selection bias due to loss to follow-up.

All our studies were embedded in the Generation R study, a prospective cohort study. A clear advantage is that it is population-based and contains a large number of subjects, of which the majority was studied from the first trimester of pregnancy onwards. Extensive data-collection was already from early pregnancy, allowing identification of determinants in the earliest phase of life and unbiased data-collection – long before the occurrence of febrile seizures. In this way, several risk factors could be studied, and adjustments could be made for many possible confounders. Data collection on febrile seizures was on a yearly basis and therefore less dependent on parental recall. However, there are also several limitations concerning case-ascertainment, bias by selection, misclassification, confounding and missing data that will be discussed below.

Case-ascertainment

The diagnosis of febrile seizures depends on careful history taking from an eye-witness. When the seizure is over, no clinical signs remain to support the diagnosis and supplementary investigation is not helpful. An EEG recorded afterwards is frequently normal and besides this, 2-5% of children without seizures do show epileptiform discharges on EEG.

Case identification in large populations can be done by interviewing and examining all participants. Although in this way cases are most likely to be accurately diagnosed, it is time-consuming and expensive. Another possibility is surveillance of hospital admissions and medical records. However, this still can be time-consuming and cases who are not admitted to the hospital or do not consult a physician can be missed. An efficient and inexpensive alternative is provided by a questionnaire survey. We used this method for our study. For a less frequent disorder as febrile seizures this seems the most effective procedure. The completeness of case-ascertainment depends on the validity of the questionnaire used. To the best of our knowledge, a validated questionnaire on febrile seizures does not exist. Most studies that used screening questions to identify febrile seizure-cases do not report on the validity. Previously, some studies reported on the validity of screening questionnaires for the ascertainment of epilepsy, mostly in adults[84 86 167]. In these studies high sensitivity and specificity were reported, at the cost of a high false-positive rate. This means case-identification is nearly complete, however a second stage of evaluation is unavoidable to discriminate true form false-positives. In accordance with this we also used a two-step procedure. The questionnaires that were routinely sent to all participants included 8 screening questions on paroxysmal events. If one or more of these questions were answered positive, final classification of the event was based on an extended follow-up questionnaire concerning this episode and when available a medical record.

Our screening questions comprised direct questions on febrile seizures as well as questions on symptoms that might have been caused by a seizure. By using these screening questions,

we found a high incidence of non-epileptic paroxysmal events, most of which consisted of innocent physiologic events. This suggests that the threshold to report events was low. Therefore, it is likely that distressing events like febrile seizures will have been reported. This is also supported by the fact that we found an incidence of febrile seizures of 2.8% in the first 3 years of life which is comparable to findings of other studies, including two Dutch studies[10 18 20 23 168]. In conclusion, though some children with febrile seizures might have been missed, this probably will not concern a large amount of cases.

We hypothesized that asking whether a child had a febrile seizure might be sufficient to detect febrile seizure cases. We assessed the validity of parentally reported febrile seizures, as compared to a physician-made diagnosis. We found that the question "Did your child have a febrile seizure?" has a high sensitivity and moderate specificity in children with paroxysmal events. Asking the parents whether their child had a febrile seizure satisfies to detect nearly all febrile seizure cases. The positive predictive value however is low, urging the need for a second stage of evaluation of screen-positive cases.

Selection bias

Not all participants eligible for the Generation R Study were included in the study. Of all eligible children at birth, 61% participate in Generation R[83]. The percentages of mothers from ethnic minorities and lower socio-economic status and the percentages of mothers or children with medical complications are lower among the participants than expected from the population figures in Rotterdam. This means selection towards a more healthy population of a higher socio-economic class. A major part of the information within the Generation R study was obtained by questionnaires. Due to logistic problems (changed addresses, changed telephone numbers, technical problems with the database) not all participants received all questionnaires. Besides this a substantial part of the participants did not return all questionnaires. Participants who did not return their questionnaires were more often not from Dutch origin, younger of age and lower educated and they had less healthy life style habits. Their children more often were born premature with lower birth weights. Thus, the willingness to participate in the Generation R Study as well as the loss to follow up was selectively related to several determinants and probably also will be related to some outcomes. This selection influences statistical power and generalization of the results. Besides this, selection bias occurs when the relation between exposure and disease is different for those who participate and those who are theoretically eligible for study, including those who do not participate. The associations observed in the study in that case represent a mix of factors determining participation, as well as factors determining disease[169].

Our studies on paroxysmal events and febrile seizures also suffered from selective non-response on postal questionnaires. To be diagnosed as a febrile seizure the parents had to complete the screening questionnaire as well as the additional questionnaire. To serve as a

control we selected the participants who were screen-negative in all screening questionnaires. Next to guaranteeing that controls truly did not have a febrile seizure in the first years of life, in this way both cases and controls consisted of participants who were inclined to return the questionnaires. In this way we tried to prevent large differences between cases and controls only based on differences in attrition. In accordance with most earlier reports, we now found no clear differences in socio-economic status, as indicated by maternal educational level, between participants with and without febrile seizures in most of our studies[10 35 40 55 170].

Selection bias may have occurred in our studies if non-response was associated with the determinant as well as with the outcome under study. It seems unlikely that the febrile-seizure status of a child would influence the response on the questionnaires, but this cannot be excluded. It is possible, however, that lower educated mothers, especially of other than Dutch origin, might experience more difficulties in answering the additional questionnaire and in this way are underrepresented in the febrile-seizure group. This would attenuate the effect measures found. This appears to have occurred in our study on folic acid supplement use in pregnancy and the risk of febrile seizures.

Information bias

Bias in evaluating an effect can also occur from errors in obtaining the information that you want to compare in the subjects under study. As mentioned before, a major part of the information used in our studies was obtained by questionnaires. Self-reported information might be liable to errors as participants might not understand the questions, they might not recall the information asked, or they might be inclined to give socially desirable answers. This may result in misclassification of determinants or outcome-measures. Classification error that depends on the values of other variables (exposure or disease) is referred to as differential misclassification and classification error that does not depend on the values of other variables as non-differential. Whereas non-differential misclassification in general will attenuate results, differential misclassification can either exaggerate or underestimate an association[169].

Non-differential misclassification occurs to some extent in every study, for example due to typing errors etc. In this thesis differential misclassification of the determinant may have occurred in our study on the association between the number of fever episodes and the risk of febrile seizures. Information on the number of fever episodes was collected retrospectively after the possible occurrence of a febrile seizure. Parents whose child experienced a febrile seizure might be more alert with regard to further fever episodes and might better recall or report them than parents of children without febrile seizures. However, we found fever episodes already to be reported more frequently in children with febrile seizures in the year before their first febrile seizure took place, supporting a real association.

Confounding

In confounding the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect. An extraneous factor can only be a confounder when it is associated with both the exposure and the disease under study. However, not all factors satisfying this definition really act as a confounder. The distortion introduced by a confounding factor can lead to overestimation or underestimation of an effect, depending on the direction of the associations that the confounding factor has with exposure and disease[169]. Confounding can be controlled for by adjusting in regression models. The major advantage of Generation R is the availability of a lot of information on possible confounders. We selected possible confounders based on previous literature and on conceptual grounds. Potential confounders were retained in the regression models if they changed the effect measures found by more than 5%. Besides this, some potential confounders were included on subject-matter grounds even if they did not meet the quantitative criteria for inclusion. Residual confounding can never be completely excluded in observational studies. There is always the possibility of confounding variables that you are not aware of or that were not measured. We also were limited in the number of covariates included in our models because of the relatively small number of participants with febrile seizures. In this thesis concerns on residual confounding for example exist in our study on folic acid supplement use in pregnancy and the risk of febrile seizures (**chapter 3.3**). Folic acid supplement use is strongly associated with several socio-economic factors and life style habits. Though we tried to control for this, residual confounding cannot be excluded. For example, detailed information on the dietary pattern, including the intake of folic acid by the diet as well as possible other important nutrients, were lacking.

Missing values

Missing data can be missing completely at random, at random or not at random. Missing completely at random means that the probability that an observation is missing is not dependent of the value of the observation nor the value of any other variable under study. Data are missing at random when their absence is related to variables in the study, but not to the outcome under study. Missing not at random takes place when absence of data is related to both the determinant and outcome under study. The most common approach to deal with missing values is to simply omit those cases with missing data and to run the analyses on what remains. Under the assumption that the data are missing completely at random, this leads to unbiased parameter estimates. However, in most of our studies data probably were missing at random. Missing data for example are more frequent in participants with a lower educational level or other than Dutch origin. Besides this, omitting cases with missing values results in a substantial decrease of sample size and subsequently a decrease of statistical power. For this reason in later studies

(**chapter 3.3, 3.4 and 3.5**) we decided to use multiple imputation to deal with missing values of covariates. Existing data were used to generate imputed values, and in this way 5 imputed datasets were created. Each dataset was analyzed separately and the results were pooled using the method of Rubin[113]

FUTURE RESEARCH

Further research is necessary to confirm our findings, to study their underlying mechanisms and to investigate new hypotheses. Some suggestions for further research are summarized below.

Fetal growth

We found fetal growth to be associated with the risk of febrile seizures. Further research is needed on the mechanisms by which fetal growth retardation is associated with an increased risk of febrile seizures. We hypothesize that suboptimal circumstances during pregnancy that lead to reduced fetal growth also can adversely influence brain development, including structural or functional changes of the brain that might lower the threshold for febrile seizures. With ultrasound investigations, small associations between fetal growth characteristics of the head and the risk of febrile seizures were found. With more advanced imaging techniques, as structural and functional magnetic resonance imaging, more detailed information on the specific effects of adverse environmental influences during pregnancy on different regions of the brain could be obtained. Specific attention should be paid to the hippocampus as this region seems to be involved in febrile seizure generation[162]. Notably we found a small transverse cerebellar diameter to be associated with an increased risk of febrile seizures; the cerebellum and its role in seizure generation also should be subject of further research.

Structural or functional changes of the brain might especially predispose to complex or recurrent febrile seizures. Numbers in our study were relatively small. In larger studies, it would be possible to verify our results, and to examine the associations of fetal growth retardation with complex versus simple febrile seizures, recurrent versus single febrile seizures and early versus late onset of febrile seizures.

Folic acid

Our finding that folic acid is associated with the risk of febrile seizures is intriguing. However, we were the first to study this and the number of children with febrile seizures in our study was rather small. Besides this, folic acid use is strongly associated with many other life style habits and residual confounding is difficult to exclude. Our findings in the first place should be replicated for confirmation, preferable in large cohort-studies with sufficient data on possible

confounders. Also findings would be stronger if folate biomarkers in the periconceptional period would be available. We now used questionnaires to obtain data on folic acid supplement use during pregnancy. Information bias and giving desirable answers might render this information less accurate. Besides this, folate intake by normal dietary intake was not taken into account.

In some countries folic acid fortification of the food supply was mandated. It would be interesting to examine whether in these countries the incidence of febrile seizures has declined after the introduction of folic-acid fortified foods.

Next to folic acid use, also other nutritional factors during pregnancy might affect fetal brain development and as such be associated with susceptibility for (febrile) seizures; for example maternal intake of vitamins or fatty acids. In analogy with folate deficiency, direct mechanisms as well as epigenetic modifications, including DNA methylation, might be involved. This provides another area of further research.

Genetics

Genetic factors clearly are involved in the pathogenesis of febrile seizures. Probably most cases of febrile seizures are genetically complex disorders influenced by variation in several susceptibility genes as well as environmental factors. Until now no consistent and convincing susceptibility genes have emerged that affect the majority of febrile seizures[48-49]. Genome wide association studies in large populations might provide the opportunity to examine possible febrile seizure genes. At the moment a GWAS is planned in Generation R, in cooperation with several large population-based European, American and Australian cohort studies.

Epilepsy

It is not known whether febrile seizures and epilepsy are two manifestations of the same underlying disorder or if they should be considered as two totally distinct entities in the majority of cases. Especially in the first situation, risk factors associated with one might also predispose to the other. Fetal growth retardation and folate deficiency might also be associated with the risk of epilepsy. It will be a challenge to study this in a prospective manner, as the incidence of epilepsy is lower than that of febrile seizures and epilepsy is an even more heterogeneous disorder than febrile seizures with many different possible causes that should be taken into account. Possibly with a longer follow up, a sufficient number of cases with epilepsy will be identified within the Generation R cohort to be able to perform these analyses.

GENERAL CONCLUSIONS

1. Paroxysmal events are common in infancy. They are associated with preterm birth and a poor condition at birth. Epileptic seizures only constitute a small part. This should be taken into account when judging an infant with a paroxysmal event and planning diagnostic strategies

2. Simply asking young parents whether their child had a febrile seizure is not sufficient to diagnose a febrile seizure. Although almost all true febrile seizures will be reported, many non-epileptic paroxysmal events will be misclassified as febrile seizures.

3. Fetal growth retardation and the inadequate use of folic acid supplements are associated with an increased risk of febrile seizures. This underlines the importance of healthy life style habits and the adequate use of folic acid supplements during pregnancy.

4. Frequent fever episodes are associated with an increased risk of febrile seizures in the second and third year of life. Next to the family-history concerning febrile seizures, also the history concerning fever episodes could help to identify children with an increased risk of febrile seizures.

5. Parents of children with febrile seizures can be reassured that in general febrile seizures are a benign disorder with a favourable outcome. Recurrent febrile seizures may lead to slower language development, but further studies are needed.

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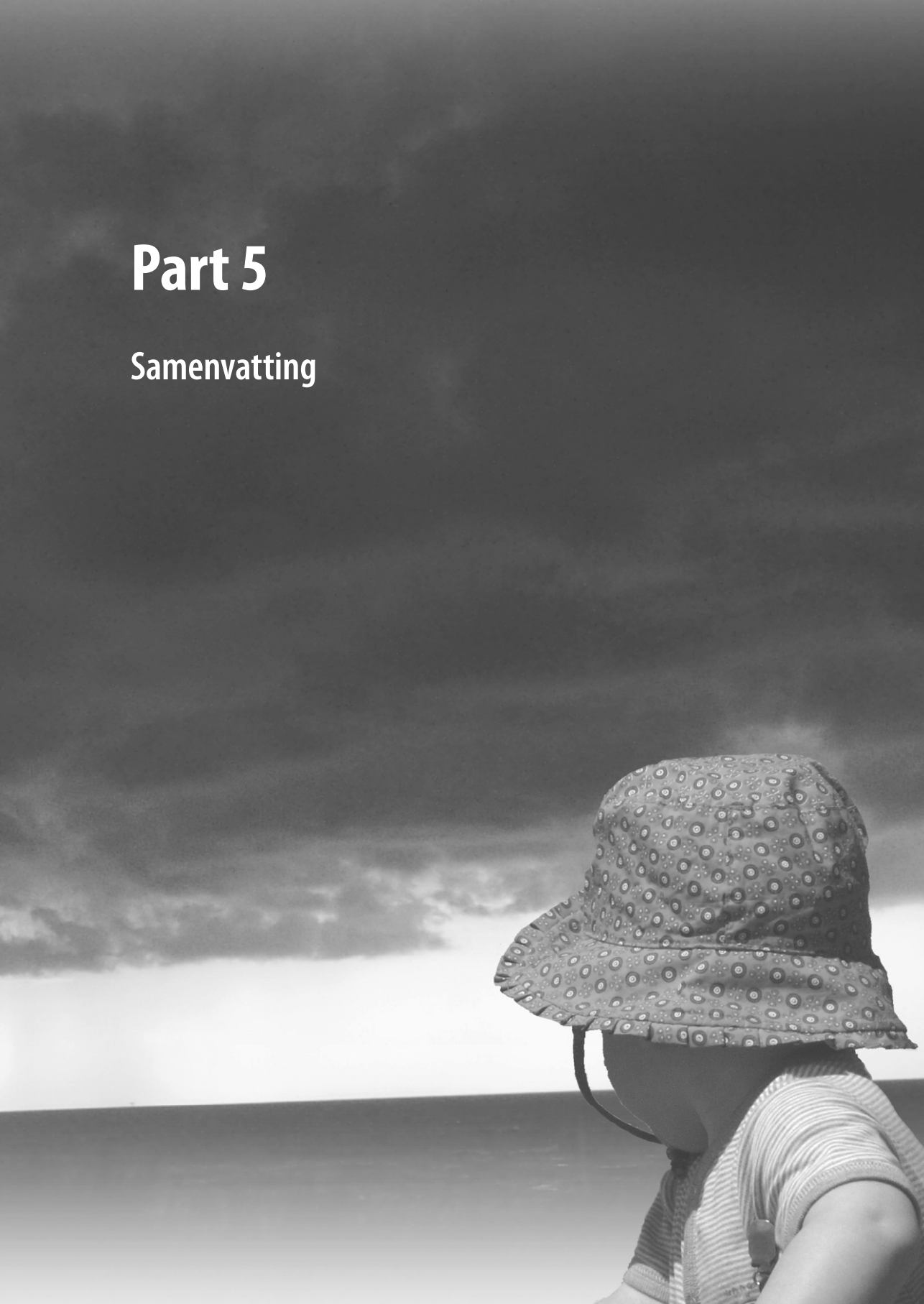
Part 5

Samenvatting



Dit proefschrift gaat over epileptische en niet-epileptische plots optredende gebeurtenissen bij jonge kinderen. Epileptische aanvallen worden gekenmerkt door plotseling optredende motorische, sensorische, autonome of psychische verschijnselen. Zij komen relatief vaak voor in de eerste levensjaren. Er zijn verschillende andere aandoeningen op de kinderleeftijd die zich eveneens kunnen manifesteren met plotseling optredende verschijnselen, en die van epileptische aanvallen moeten worden onderscheiden. Er zijn weinig gegevens over hoe vaak dergelijke plotselinge gebeurtenissen in de algemene bevolking op de kinderleeftijd voorkomen en welk deel daarvan berust op epilepsie.

De meest voorkomende vorm van epileptische aanvallen op de kinderleeftijd is de koortsconvulsie. Koortsconvulsies zijn gedefinieerd als epileptische aanvallen die optreden bij kinderen tussen de 3 maanden en 6 jaar oud, tijdens een koortsepisode, zonder dat er aanwijzingen zijn voor een intracraniele infectie of een andere onderliggende oorzaak. Koortsconvulsies komen voor bij 2-5% van alle kinderen. Ondanks dat ze relatief vaak voorkomen is de oorzaak grotendeels onbekend. Zowel genetische als omgevingsfactoren lijken een rol te spelen. Wat betreft genetische factoren is een positieve familie-anamnese de meest consistent aangetoonde risico-factor voor het krijgen van een koortsconvulsie. Wat betreft omgevingsfactoren bleken prematuriteit, een laag geboorte-gewicht, complicaties tijdens de zwangerschap en roken door de moeder tijdens de zwangerschap geassocieerd met een verhoogd risico op koortsconvulsies in een aantal studies. Dit kon echter niet altijd in andere studies worden bevestigd.

Wat betreft de gevolgen van koortsconvulsies vonden in het verleden verschillende onderzoeken plaats naar gedragsproblemen en intelligentie of schoolprestaties bij kinderen die koortsconvulsies hebben doorgemaakt. Over het algemeen lijkt de uitkomst van kinderen met koortsconvulsies op de schoolleeftijd goed te zijn. Een uitzondering wordt mogelijk gevormd door kinderen met complexe of recidiverende koortsconvulsies, of met een eerste koortsconvulsie in het eerste levensjaar. Het zou echter nog steeds zo kunnen zijn dat kinderen met koortsconvulsies op bepaalde meer specifieke cognitieve domeinen minder goed presteren. Ook zouden op jongere leeftijd, korter na het doormaken van de koortsconvulsies, mogelijk wel verschillen met kinderen zonder koortsconvulsies kunnen bestaan, die op latere leeftijd niet meer aantoonbaar zijn.

Op basis van bovengenoemde wilden wij in dit proefschrift de volgende vragen beantwoorden:

1. Hoe vaak komen plotselinge epileptische en niet-epileptische gebeurtenissen voor bij jonge kinderen in de algemene bevolking, en wat zijn mogelijke risicofactoren hiervoor.
2. Zijn foetale groeivertraging, foliumzuurgebruik tijdens de zwangerschap en de frequentie van koortsepisodes in de eerste levensjaren geassocieerd met de kans op het krijgen van koortsconvulsies.

3. Zijn er op de voorschoolse leeftijd verschillen wat betreft gedragsproblemen, taalontwikkeling en executieve functies tussen kinderen met en zonder koortsconvulsies in de voorgeschiedenis.

Methode

Al onze studies werden uitgevoerd binnen het Generation R onderzoek. Dit is een prospectief bevolkingsonderzoek waarin bijna 10.000 in Rotterdam geboren kinderen worden gevolgd vanaf de zwangerschap tot in de volwassenheid. Tijdens de zwangerschap vonden foetale echo-onderzoeken en bloed-afnames en metingen bij de ouders plaats. De ouders vulden ook vragenlijsten in over onder andere hun afkomst, opleiding, medische voorgeschiedenis en het beloop van de zwangerschap. In de postnatale fase van het onderzoek werden gegevens zoals verzameld op de consultatiebureaus gebruikt, en waren er vragenlijsten over de groei, gezondheid en ontwikkeling van de kinderen. Voor de studies in dit proefschrift zijn met name gegevens uit de vragenlijsten gebruikt.

Plotselinge gebeurtenissen

Gegevens over plotselinge gebeurtenissen werden verkregen door middel van vragenlijsten. In de postnatale vragenlijsten waren hiertoe 8 screeningsvragen opgenomen (**bijlage 1**). Er werd zowel direct gevraagd naar het optreden van epilepsie en koortsconvulsies, als naar symptomen die op epileptische aanvallen zouden kunnen wijzen. Op deze wijze probeerden wij alle epileptische aanvallen te identificeren, als ook gebeurtenissen die deze kunnen nabootsen. Wanneer één of meer van deze vragen positief werd beantwoord volgde een uitgebreide vragenlijst (**bijlage 2**) over deze gebeurtenis en werden, indien een arts geraadpleegd was, de gegevens hieromtrent opgevraagd. Op basis van deze gegevens werden de gebeurtenissen geclassificeerd als koortsconvulsie of een andere plotselinge gebeurtenis. Hiervoor werden 8 elkaar uitsluitende categorieën van gebeurtenissen gebruikt (**bijlage 3**).

Belangrijkste bevindingen

In **hoofdstuk 2.1** bespreken wij de resultaten van ons onderzoek naar het voorkomen van plotseling optredende gebeurtenissen in het eerste levensjaar, in de algemene bevolking. Plotseling optredende gebeurtenissen werden gedefinieerd als episodes met een plotseling veranderd bewustzijn, een plotseling veranderd ademhalingspatroon, plotseling verstijven of verslappen of het optreden van onwillekeurige bewegingen als trillen of trekkingen. Wij vonden een incidentie van 8.9-12.9% van plotselinge optredende gebeurtenissen in het eerste levensjaar. De meeste van deze gebeurtenissen waren goedaardige, fysiologische gebeurtenissen. Slechts een minderheid van de gebeurtenissen berustte op epilepsie. Het grootste deel hiervan betrof koortsconvulsies. Prematuriteit, een laag geboorte gewicht en lage Apgar

scores waren geassocieerd met plotseling optredende gebeurtenissen in het eerste levensjaar. Fysiologische gebeurtenissen werden vaker gerapporteerd bij kinderen die het eerste kind in het gezin waren. Een kleinere hoofdomvang bij 30 weken zwangerschapsduur, vroeggeboorte en roken tijdens de zwangerschap waren geassocieerd met een verhoogd risico op koortsconvulsies in het eerste levensjaar.

Concluderend komen plotselinge gebeurtenissen veel voor bij jonge kinderen, maar vormen epileptische aanvallen hiervan maar een klein deel. Dit moet in overweging worden genomen bij het beoordelen van een kind met een plotselinge gebeurtenis en het plannen van aanvullend onderzoek.

Het volgende deel van dit proefschrift gaat over koortsconvulsies. In **hoofdstuk 3.1** presenteren wij de resultaten van onze studie naar de validiteit van door ouders gerapporteerde koortsconvulsies. Het antwoord op de vraag: "Heeft uw kind een koortsconvulsie doorgemaakt?" werd vergeleken met de classificatie van de plotselinge gebeurtenis door een kinderneuroloog, gebaseerd op de aanvullende vragenlijst betreffende deze gebeurtenis en het medische rapport indien een arts bezocht was. De sensitiviteit van een positief antwoord op bovengenoemde vraag voor koortsconvulsies was 92% en de specificiteit 72%. De negatief voorspellende waarde was hoog (98%). De positief voorspellende waarde was slechts 41%. Dit betekent dat de vraag "Heeft uw kind een koortsconvulsie doorgemaakt?" voldoet als screeningsinstrument voor koortsconvulsies, daar vrijwel alle gevallen zullen worden opgespoord. Een tweede evaluatie is echter noodzakelijk om echte koortsconvulsies van hierop lijkende gebeurtenissen te onderscheiden. Bij een fout-positief antwoord op deze vraag ging het in werkelijkheid meestal om geïsoleerde koorts, rillingen bij koorts of een vasovagale collaps.

In **hoofdstuk 3.2** bespreken wij de resultaten van ons onderzoek naar foetale groei en het optreden van koortsconvulsies. Vertraagde foetale groei in de tweede helft van de zwangerschap bleek geassocieerd te zijn met een verhoogd risico op koortsconvulsies in de eerste twee levensjaren. De associatie met lichaamsgroei bleek sterker te zijn dan die met de groei van hoofd of hersenen. Dit zou verklaard kunnen worden doordat bij het optreden van milde groeivertraging de groei van de hersenen relatief gespaard blijft. Ondanks een beperkte groeivertraging zouden er nog steeds kleine structurele of functionele afwijkingen in de hersenen kunnen optreden. Binnen de onderzochte groei-karakteristieken van hoofd en hersenen vonden wij de sterkste associatie tussen een kleine cerebellaire diameter en een verhoogd risico op koortsconvulsies. Het onderliggende mechanisme hiervan is niet duidelijk. Een kleine cerebellaire diameter zou alleen een marker kunnen zijn van structurele of functionele veranderingen elders. Nader onderzoek naar aanpassingen van de foetale hersenontwikkeling op ongunstige omstandigheden als mechanisme leidend tot koortsconvulsies is aangewezen.

In **hoofdstuk 3.3** beschrijven we de associaties tussen foliumzuur gebruik tijdens de zwangerschap en de kans op het krijgen van koortsconvulsies. Foliumzuurdeficiëntie tijdens de zwangerschap is geassocieerd met een verhoogd risico op neurale buisdefecten. Hiernaast zijn ook associaties met onder andere problemen met gedrag en temperament beschreven. Ook bestaan er enkele aangeboren stoornissen in het foliumzuur metabolisme die onder andere gepaard gaan met epilepsie. Foliumzuur lijkt dus van belang voor de ontwikkeling en het functioneren van het zenuwstelsel. Derhalve was onze hypothese dat foliumzuurdeficiëntie tijdens de zwangerschap ook geassocieerd zou kunnen zijn met een verhoogd risico op koortsconvulsies. Informatie over foliumzuurgebruik werd verkregen door middel van vragenlijsten. Foliumzuurgebruik werd gecategoriseerd als gestart voor de conceptie, gestart in het eerste trimester van de zwangerschap, of geen gebruik tijdens de embryogenese. Het niet gebruiken van foliumzuur bleek geassocieerd te zijn met een verhoogd risico op koortsconvulsies bij het nageslacht. De associatie tussen inadequaat foliumzuurgebruik en een verhoogd risico op koortsconvulsies was het grootste voor koortsconvulsies in het eerste levensjaar. Daar wij de eerste waren om de associatie tussen foliumzuurgebruik en het optreden van koortsconvulsies te bestuderen is nader onderzoek om deze bevindingen te repliceren en de onderliggende mechanismes te identificeren geïndiceerd.

Hoofdstuk 3.4 behandelt de associatie tussen het aantal koortsepisodes en de kans op het krijgen van een koortsconvulsie. Frequente koortsepisodes werd gedefinieerd als meer dan 2 koortsepisodes per jaar. Wij vonden een lineair verband tussen het aantal koortsepisodes en de kans op een koortsconvulsie in het tweede en derde levensjaar, maar niet in het eerste levensjaar. De associatie tussen het frequent optreden van koorts en een verhoogd risico op koortsconvulsie was sterker voor kinderen met recidiverende koortsconvulsies. Hoe vaak koortsepisodes voorkomen is op zijn beurt weer afhankelijk van zowel genetische als omgevingsfactoren. Wanneer een kind zich presenteert met een koortsconvulsie zou niet alleen naar de familie-anamnese betreffende koortsconvulsies gevraagd kunnen worden, maar ook naar hoe vaak het kind ziek is.

Koortsstuipen worden over het algemeen beschouwd als een goedaardige aandoening met een uitstekende prognose. Eerdere studies over dit onderwerp bestudeerden met name intelligentie en schoolprestaties bij schoolgaande kinderen. In **hoofdstuk 3.5** beschrijven wij de resultaten van ons onderzoek naar gedragsproblemen, taalontwikkeling en executieve functies bij voorschoolse kinderen. Ook op deze jonge leeftijd vonden wij in deze domeinen geen verschillen tussen kinderen met en zonder koortsconvulsies. Dit geldt ook voor kinderen met een eerste koortsconvulsie in het eerste levensjaar. Alleen kinderen met recidiverende koortsconvulsies leken iets vaker een achterstand in de expressieve taalontwikkeling te hebben. Het aantal kinderen met langdurige koortsconvulsies was te laag om deze apart te bestuderen.

Het vierde deel van dit proefschrift bevat een algemene discussie over de belangrijkste bevindingen van de verrichte studies, behandelt methodologische aspecten van de onderzoeken beschreven in dit proefschrift en geeft aanbevelingen voor toekomstig onderzoek.

Appendices

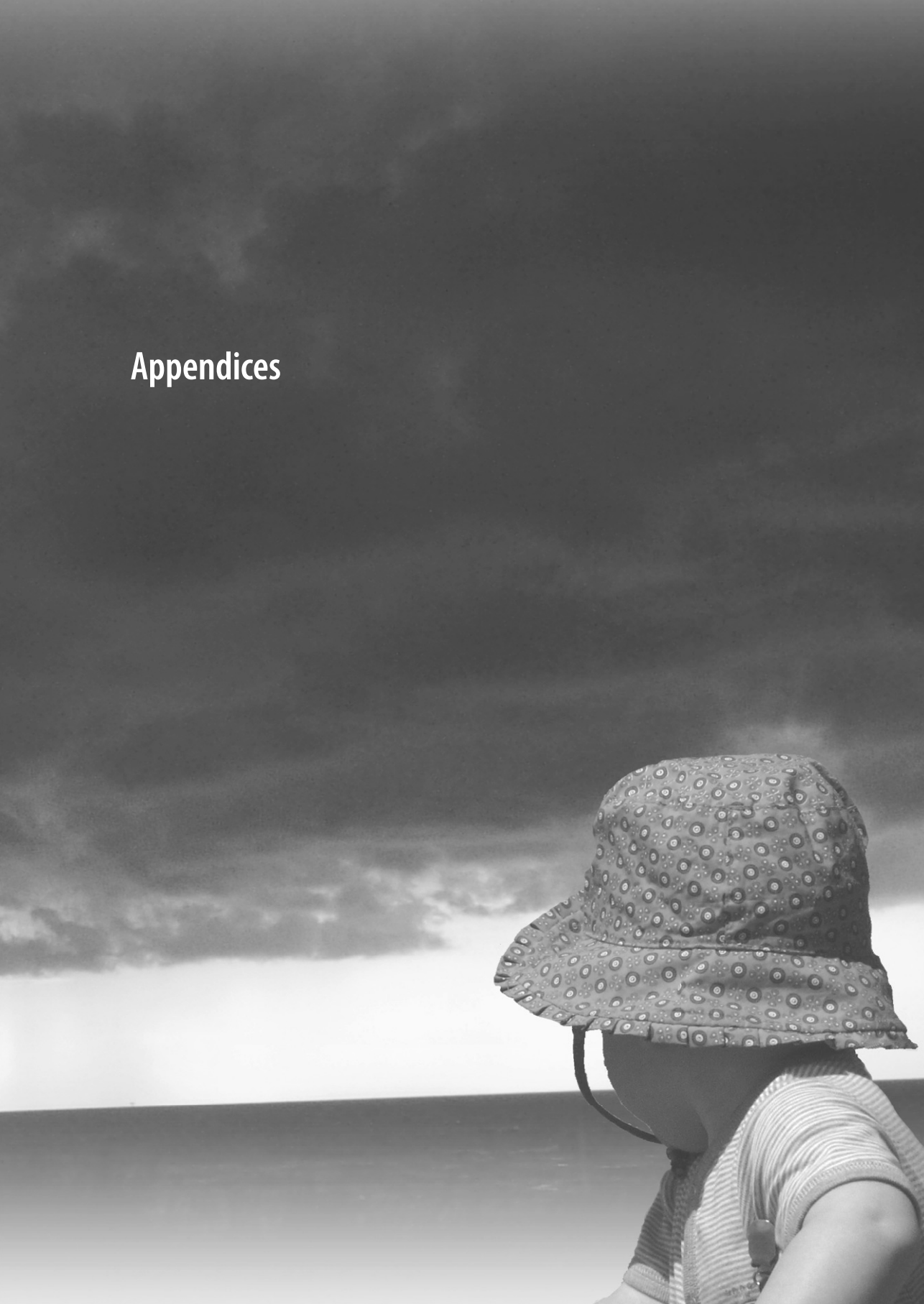


TABLE 1. Screeningsvragen

1. Heeft uw kind wel eens een aanval van epilepsie doorgemaakt? (of is bij uw kind de diagnose epilepsie gesteld)?
2. Heeft uw kind een koortsstuip/koortsconvulsie doorgemaakt?
3. Heeft uw kind wel eens plotseling het bewustzijn – geheel of gedeeltelijk –verloren waarbij het niet meer reageerde op aanspreken?
4. Heeft uw kind wel eens een periode doorgemaakt waarbij hij/zij plotseling afwezig was, waarbij u geen contact met hem/haar kon maken?
5. Heeft uw kind wel eens een aanval doorgemaakt met plotseling beginnende spiertrekkingen of trillingen of andere onvrijwillige bewegingen van het hele lichaam of een deel daarvan (armen, benen, handen, gezicht, romp, tong)?
6. Is uw kind wel eens plotseling helemaal verstijfd of verkrampt of juist helemaal verslapt geraakt?
7. Heeft uw kind wel eens een periode doorgemaakt waarbij het plots stopte met ademhalen of een veranderende ademhaling kreeg?
8. Heeft uw kind wel eens plotseling beginnende momenten van vreemd gedrag of vreemde bewegingen tijdens de slaap doorgemaakt?

1. Uw kind heeft in de afgelopen periode één of meer plotselinge gebeurtenis(sen) of aanval(len) doorgemaakt. **Kunt u in uw eigen woorden beschrijven wat u toen heeft gezien of wat er gebeurde?** (Als er meerdere verschillende gebeurtenissen of aanvallen zijn geweest kunt u die afzonderlijk beschrijven; de rest van de vragen gaan dan over de gebeurtenis die het meest is voorgekomen of als ze even vaak zijn voorgekomen, die zich het eerste heeft voorgedaan.)

2. **Hoe vaak** heeft u deze gebeurtenis of aanval bij uw kind gezien?

- ☐ Eén keer
- ☐ Twee keer
- ☐ Tussen de twee en 10 keer
- ☐ Meer dan 10 keer
- ☐ Meer dan 100 keer

3. Wanneer is de **eerste keer** geweest dat u deze gebeurtenis of aanval bij uw kind heeft gezien?

dag	maand	jaar

4a. Heeft u in verband met deze gebeurtenis(sen) of aanval(len) **een dokter** bezocht?

☐ Nee (ga door naar vraag 5)
☐ Ja

4b. Zo ja, **welke dokter(s)** heeft u bezocht?

	naam	*ziekenhuis*
☐ Huisarts		n.v.t.
☐ Kinderarts		
☐ Anders, namelijk:		

5. **Op welke moment(en)** heeft u deze gebeurtenis(sen) of aanval(len) bij uw kind gezien?

	Nee	*Ja*	*Weet niet*
a. Terwijl mijn kind wakker was	☐	☐	☐
b. Tijdens of vlak na het eten of drinken	☐	☐	☐
c. Bij het in slaap vallen	☐	☐	☐
d. Tijdens de eerste uren van de slaap ‘s nachts	☐	☐	☐
e. Tijdens de laatste uren van de slaap ‘s nachts	☐	☐	☐
f. Tijdens de slaap overdag	☐	☐	☐
g. Bij het wakker worden	☐	☐	☐

6. Wat was uw kind (meestal) **aan het doen** bij het begin van deze gebeurtenis(sen) of aanval(len)?

	Nee	*Ja*	*Weet niet*
a. Slapen	☐	☐	☐
b. Drinken of eten	☐	☐	☐
c. Rustig zitten spelen	☐	☐	☐
d. Televisie of video kijken	☐	☐	☐
e. Rennen of stoeien	☐	☐	☐

f. Anders, namelijk: _____

7a. Soms komen dit soort gebeurtenissen of aanvallen niet zomaar, maar worden ze uitgelokt door bijvoorbeeld vermoeidheid, koorts, of andere dingen. Was dit bij uw kind ook zo?

- ☐ Nee (ga door naar vraag 8)
- ☐ Ja
- ☐ Weet niet

7b. Zo ja, werd de gebeurtenis dan wel eens uitgelokt door:

	Nee	*Ja*	*Weet niet*
a. Huilen	☐	☐	☐
b. Lachen	☐	☐	☐
c. Eten of drinken	☐	☐	☐
d. Hoesten	☐	☐	☐
e. Overgeven	☐	☐	☐
f. Vermoeidheid of slaaptekort	☐	☐	☐
g. Pijn of verwondingen	☐	☐	☐
h. Stoten van het hoofd	☐	☐	☐
i. Inenting (vaccinatie) of injectie	☐	☐	☐
j. Koorts	☐	☐	☐
k. Ziekte	☐	☐	☐
l. Warmte of kou	☐	☐	☐
m. Schrikken of angst	☐	☐	☐
n. Televisie kijken of zien van lichtflitsen	☐	☐	☐
o. Horen van bepaalde geluiden	☐	☐	☐
p. Boosheid	☐	☐	☐
q. Lichamelijke activiteit	☐	☐	☐
r. Anders, namelijk:			

8a. Heeft uw kind de plotselinge gebeurtenis of aanval (ook) doorgemaakt **binnen 4 weken** na een **inenting (vaccinatie)**?

- ☐ Nee (ga door naar vraag 9)
- ☐ Ja

8b. Zo ja, **na welke** inenting (vaccinatie) heeft zich deze gebeurtenis of aanval voorgedaan?

- ☐ DKTP
- ☐ Hepatitis B
- ☐ Pneumococ
- ☐ Meningococ C
- ☐ BCG
- ☐ Dat weet ik niet

8c. **Hoeveel dagen** zaten er tussen de vaccinatie en de gebeurtenis of aanval?

☐☐ **dagen**

9. **Hoelang duurde** de gebeurtenis of aanval (meestal)?

- ☐ Korter dan 30 seconden
- ☐ 30 seconden tot 5 minuten
- ☐ 5 tot 30 minuten
- ☐ Langer dan 30 minuten
- ☐ Meerdere aanvallen achter elkaar, samen langer dan een half uur
- ☐ Dat weet ik niet

10. Heeft u één of meer van onderstaande verschijnselen bij uw kind gezien of opgemerkt bij deze gebeurtenis(sen) of aanval(len)?

	Nee	*Ja*	*Weet niet*
a. Niet kunnen bewegen	☐	☐	☐
b. Keelgeluiden maken zoals gorgelen, klokken	☐	☐	☐
c. Hevig kwijlen of niet kunnen slikken	☐	☐	☐
d. Gevoel te stikken of achterblijven van de ademhaling	☐	☐	☐
e. Angst	☐	☐	☐
f. Onrust	☐	☐	☐
g. Verdriet of huilen	☐	☐	☐
h. Schreeuwen	☐	☐	☐
i. Misselijkheid of braken	☐	☐	☐
j. Schuim op de mond	☐	☐	☐

11. Soms zijn er bij dit soort gebeurtenissen bepaalde dingen aan een kind te zien, bijvoorbeeld dat het vreemd beweegt of juist helemaal niet beweegt. **Was er bij de gebeurtenis(sen) of aanval(len) bij uw kind een of meer van de volgende dingen te zien?**

	Nee	*Ja*	*Weet niet*
a. Trillen of beven	☐	☐	☐
b. Trekkingen of schokken van 1 of beide armen, handen of benen	☐	☐	☐
c. Trekkingen of schokken in het gezicht	☐	☐	☐
d. Verkrampen of stijf worden van het hele lichaam	☐	☐	☐
e. Verkrampen of stijf worden van 1 of beide armen, handen of benen	☐	☐	☐
f. Verkrampen of stijf worden van het gezicht of de kaak	☐	☐	☐
g. Slap worden van het hele lichaam	☐	☐	☐
h. Slap worden van 1 of beide armen, handen of benen	☐	☐	☐

i.	Maken van ongerichte maaiende, schoppende of slaande bewegingen	☐	☐	☐
j.	Draaien van het hoofd naar één kant	☐	☐	☐
k.	Draaien van de ogen naar één kant	☐	☐	☐
l.	Knipperen met de ogen, grimassen	☐	☐	☐
m.	Kauwen, slikken, smakken of kwijlen	☐	☐	☐
n.	Andere bewegingen, namelijk:			

12. **Aan welk deel van het lichaam** was het te zien bij deze gebeurtenis(sen) of aanval(len)?

- ☐ Het hele lichaam
- ☐ Eén kant van het lichaam
- ☐ Begon aan één kant, later het hele lichaam
- ☐ Alleen aan het gezicht of de ogen
- ☐ Anders, namelijk:

13a. Was uw kind (meestal) **goed wakker** tijdens de gebeurtenis of aanval?

- ☐ Nee
- ☐ Ja (ga door naar vraag 14)
- ☐ Dat weet ik niet

13b. Als uw kind niet goed wakker was, hoe was het dan?

- ☐ Mijn kind sliep
- ☐ Mijn kind was bewusteloos, reageerde nergens op
- ☐ Mijn kind staarde, had de ogen open, reageerde nergens op
- ☐ De ogen waren weggedraaid, mijn kind reageerde nergens op
- ☐ Mijn kind was afwezig maar reageerde wel
- ☐ Mijn kind was verward of onrustig

13c. Als uw kind niet goed wakker was, **hoe lang** duurde het dan voordat uw kind weer goed reageerde na de gebeurtenis of aanval?

- ☐ Mijn kind was meteen weer goed wakker
- ☐ Mijn kind was binnen 5 minuten weer goed wakker
- ☐ Mijn kind was binnen een uur weer goed wakker
- ☐ Mijn kind is langer dan een uur maar korter dan een dag suffig of verward geweest
- ☐ Mijn kind is langer dan een uur maar korter dan een dag bewusteloos geweest
- ☐ Mijn kind is langer dan een dag suffig of verward geweest
- ☐ Mijn kind is langer dan een dag bewusteloos geweest
- ☐ Mijn kind is snel in slaap gevallen of heeft gewoon doorgeslapen
- ☐ Dat weet ik niet

14. Hoe was de **kleur** van uw kind (meestal) tijdens de gebeurtenis of aanval?

- ☐ Normaal
- ☐ Bleek, grauw
- ☐ Rood
- ☐ Blauw
- ☐ Dat weet ik niet

15a. Was er tijdens de gebeurtenis of aanval (meestal) een **verandering van de ademhaling**?

- ☐ Nee (ga door naar vraag 16)
- ☐ Ja
- ☐ Dat weet ik niet

15b. Als de **ademhaling anders was** dan normaal, was er dan sprake van

- ☐ Een ademstilstand of stoppen met ademhalen
- ☐ Hyperventilatie of heel snel of diep ademen
- ☐ Te weinig of onregelmatig ademen
- ☐ Anders, namelijk: _____

16. Was er bij de gebeurtenis of aanval een verandering van de **pols of hartslag** van het kind?

- ☐ Nee
- ☐ Ja
- ☐ Dat weet ik niet

17a. Soms is een kind na zo'n gebeurtenis of aanval niet direct weer de oude; waren er bij uw kind (meestal) **nog klachten na de gebeurtenis of aanval**:

- ☐ Nee (ga door naar vraag 18)
- ☐ Ja
- ☐ Dat weet ik niet

17b. Zo ja, welke klachten had uw kind nog na de gebeurtenis of aanval?

		Nee	*Ja*	*Weet niet*
a.	Misselijkheid, overgeven	☐	☐	☐
b.	Sufheid, moeheid	☐	☐	☐
c.	Pijn	☐	☐	☐
d.	Niet goed kunnen bewegen van armen of benen	☐	☐	☐
e.	Niet kunnen praten	☐	☐	☐
f.	Anders, namelijk: _____			

18. Overige **opmerkingen en suggesties**

19. Heeft u er bezwaar tegen wanneer wij zonodig contact met u opnemen voor aanvullende informatie?

☐ Ja

☐ Nee, geen bezwaar, wij zijn bereikbaar onder telefoonnummer(s)

Deze vragenlijst is ingevuld op:

dag	maand	jaar

Bedankt voor uw medewerking!

U kunt deze vragenlijst naar ons toesturen in de bijgevoegde envelop. Een postzegel is niet nodig.

TABLE 2. Classification of events

1. No paroxysmal event	Does not fulfil our definition of a paroxysmal event
2. Physiologic event	Behaviour that can be normally seen in children of this age group
3. Seizure disorder [a]	Including epilepsy, neonatal seizures, febrile seizures, other seizures
4. Apnoeic spell	Cyanotic spells or reflex anoxic spells
5. Loss of consciousness	Not caused by a seizure or a breath holding spell
6. Parasomnia	Benign neonatal myoclonus, repetitive movements, arousal disorder
7. Other	Paroxysmal events not belonging to one of the other categories
8. Unknown	Insufficient data to classify in one of the aforementioned groups

[a] definite: diagnosis confirmed by a physician; probable: diagnosis "probable seizure" according to a physician or history characteristic for a seizure; possible: diagnosis "possible seizure" according to a physician or history that could point to a seizure but not characteristic. Possible seizures were categorised in group 8 "unknown ".

Epilogue

PHD PORTFOLIO

Name of PhD student	Annemarie Visser
Erasmus MC Department	Epidemiology and Neurology
Research school	Netherlands Institute for Health Sciences
PhD period	august 2001- november 2011
Promotor	Prof.Dr. W.F.M. Arts
Supervisor	Dr. V.W.V. Jaddoe

PhD training

Erasmus Summer Programme		***ECTS credit***
ESP01	Principles of Research in Medicine	0.7
ESP04	Clinical Decision Analysis	0.7
ESP11	Methods of Public Health Research	0.7
ESP13	Epidemiology, Globalisation and Health Policy	0.7
ESP30	Public Health Research and Practice	0.7
ESP34	Topics in Evidence-based Medicine	0.7

Core Curriculum	***ECTS credit***
CC01 Study Design	4.3
CC02 Classical Methods for Data-analysis	5.7
CE02 Clinical Epidemology	5.7
EP02 Methodological Topics in Epidemiological Research	1.4
EP03 Modern Statistical Methods	4.3

Advanced Short Courses		***ECTS credit***
EWP07	Repeated Measurements in Clinical Studies	1.9
EWP08	Missing Values in Clinical Research	0.9
EWP24	Survival Analysis for Clinicians	1.9
GE03	Advances in Population-based Studies of Complex Genetic Disorders	1.4

Skills Courses		***ECTS credit***
SC04	Working with SPSS for Windows	0.15
SC05s	A first glance at SPSS for Windows	0.15

Molecular Medicine Postgraduate School

SNP's and Human Diseases

Presentations

Nov 2001	Research meeting Generation R; research proposal
Sep 2009	Poster presentation EPNS congres Harrogate, UK
Apr 2010	Research meeting Generation R
May 2011	Poster presentation EPNS congres Dubrovnik, Croatia

PUBLICATION LIST

1. **Visser AM**, ten Holter JB. Het Harlekijnsyndroom. Ned Tijdschr Geneesk 1997; 141(51): 2495-9

2. **Visser AM**, Kros JM, Tanghe HLJ, Dippel DWJ. Primaire angiïtis van het centrale zenuwstelsel. Tijdschr Neurol Neurochir 2004;105:120-125

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6. **Visser AM**, Jaddoe VWV, Arends LR, Tiemeier H, Hofman A, Moll HA, Steegers EAP, Breteler, MMB, Arts WFM. Paroxysmal disorders in infancy and their risk factors in a population-based cohort, The Generation R Study. Dev Med Child Neurol 2010;52:1014-20.

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11. Visser AM, Jaddoe VWV, Hofman A, Moll HA. Validity of parentally reported febrile seizures; The Generation R Study. *Submitted.*

ABOUT THE AUTHOR

Annemarie Visser was born on June 29th 1971 in Alkmaar, the Netherlands. She studied medicine at the Rijks Universiteit Groningen, the Netherlands. She also studied Spanish for one year at the Rijks Universiteit Groningen. She graduated from medical school in 1997. She worked as a resident at the neurology department of the St Antonius Hospital in Nieuwegein and the Onze Lieve Vrouwe Gasthuis in Amsterdam. She continued working as a neurology resident at the Erasmus Medical Center in 2000. In 2001 here she started her AGIKO training, combining her neurologic training with her PhD training at the Generation R Study. She finished her neurologic training January 2011. Since April 2011 she works as a neurologist in the Havenziekenhuis (Harbour Hospital - Institute for Tropical diseases), Rotterdam, the Netherlands.

She is married to Eelke Kemner and they have two daughters, Jip and Noortje, and a son, Quint.

DANKWOORD

Ten eerste al die duizenden ouders en kinderen die meedoen aan het Generation R onderzoek, en die steeds maar weer al die vragenlijsten invullen, bedankt! Zonder jullie waren er geen gegevens geweest over kinderen met koortsconvulsies in Rotterdam, en hadden we de vragen die in dit proefschrift aan de orde komen niet kunnen beantwoorden.

Willem Frans Arts
Bedankt voor het vertrouwen dat je in mij stelde, inmiddels meer dan 10 jaar geleden, om dit project tot een goed einde te brengen. Er moesten nogal wat hindernissen worden genomen en de plannen moesten nogal eens worden bijgesteld, maar het vertrouwen bleef. Het opende voor mij de weg naar het wetenschappelijke onderzoek, en naar de neurologie, en heeft daarmee in belangrijke mate bijgedragen aan de richting die mijn leven is opgegaan. Door je snelle en heldere reacties was de samenwerking altijd prettig. Vervolgens kon ik mede door jou bemiddeling afgelopen jaar in de Kinderhaven aan de slag, waar ik nu met zoveel plezier werk. Zelf heb jij inmiddels je klinische bezigheden neergelegd. Geniet van deze nieuwe fase in je leven. Fijn dat ik je af en toe nog kan raadplegen, en van je kennis betreffende de kinderneurologie en epilepsie gebruik kan maken.

Vincent Jaddoe
We begonnen ooit als collega-promovendi. Ik meen me te herinneren dat ik zelfs hogere cijfers haalde op de "Classical Statistical Methods". Maar met mijn AGIKO-constructie, mijn deeltijd werken en een zwangerschap hier en daar had ik de snelheid er niet zo in. Bovendien duurde het nogal voor alle Generation-R kinderen geboren waren, en voldoende oud om een koortsconvulsie door te maken. Op het gebied van de wetenschap ben je mij dus inmiddels ver voorbijgestreefd, en zo kon het gebeuren dat je zelfs mijn co-promotor werd. Bedankt voor je positieve inbreng en het erin brengen en houden van de vaart.

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Aanvankelijk was jij mijn co-promotor. Door je vertrek naar een andere universiteit is aan de samenwerking een einde gekomen. Bedankt voor je scherpe inzicht en hulp bij het opstarten van mijn onderzoeksproject.

Leescommissie
Henriette Moll, mijn dank voor je hulp bij het tot stand komen van dit proefschrift. Je was zowel betrokken bij mijn project als PI van de ziekte en ongevallen groep, als door je kennis van, en ervaring met (onderzoek naar) koortsconvulsies; je ideeën, het kritisch beoordelen van mijn manuscripten en je adviezen voor verbetering zijn het eindresultaat zeer ten goede gekomen. Ten slotte wilde je optreden als secretaris van mijn leescommissie; dankjewel!

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Grote Commissie
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Co-auteurs
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Paranimfen
Lisette en Anushka; wat fijn dat ik jullie vandaag achter mij weet! Een neurologie en een Generation R collega en vriendin van het eerste uur. En ook 2 ervaringsdeskundigen op het gebied van langdurige promotie-trajecten; jullie zijn afgelopen jaar beiden gepromoveerd, nu kan ik niet meer achterblijven!

Lisette, precies een jaar nadat jezelf promoveerde sta je hier opnieuw, nu naast mij. Wat lijkt het, nee is het lang geleden dat we samen op 6 midden rondliepen. Inmiddels zijn we beiden neuroloog. We liepen twee keer tegelijk met een dikke buik rond (ik steeds wat langer dan jij…). En we zijn op allerlei vlakken ervaringen rijker. Nu ik straks ook gepromoveerd ben kunnen we het tijdens onze nachtelijke praatsessies weer eens over andere dingen gaan hebben.

Anushka, vorig jaar mocht ik jou bijstaan als paranimf, wat fijn dat je dat nu bij mij wil doen! We begonnen ongeveer tegelijk bij Generation R. De eerste jaren gezellig samen ritsen, verifyen, bellen en onderwijl het leven doornemen. Maar toen zat de onderzoekstijd erop, maar was het boekje nog niet klaar. Een hele opgave om het afronden te combineren met een baan en kleine kinderen. Op de promoties van Generation R collega's - die meestal pas lang na ons begonnen waren en toch nu al klaar– was het altijd weer gezellig en maakten we grappen over de vraag of er nu al een datum was. Onze tijd kwam nog wel. Maar verhip – vorig jaar hoorde ik opeens dat jij echt een datum had! Toen kon ik niet achter blijven natuurlijk. We hebben heel wat afgeklaagd, en of het het allemaal waard was weet ik nog steeds niet.

Generation R

Inmiddels loop ik met tussenpozen al 10 jaar rond bij Generation R. Aanvankelijk nog op de 19e, waar we met zijn allen in een paar grote ruimtes zaten. De algemene taken bestonden toen nog uit het benaderen van potentiële deelnemers, het includeren van aanstaande ouders (in het SFG zaten we bij gebrek aan een goede ruimte in de gang, achter een kamerscherm, wat met name toestanden gaf als er weer eens een vader collabeerde bij de bloedafname). En niet te vergeten het ritsen, scannen en verifyen van de vragenlijsten.

Later verhuisden we naar het AE gebouw met keurige 2-persoonskamers, werd het mooie onderzoekscentrum in het Sophia Kinderziekenhuis in gebruik genomen, en het verwerken van de vragenlijsten uitbesteed. Het aantal promovendi en andere medewerkers groeide en groeide. Het zijn inmiddels teveel namen geworden om allemaal hier op te noemen, maar wat waren jullie belangrijk voor het werkplezier.

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Neurologie ErasmusMC

Het grootste deel van mijn onderzoekstraject heeft zich afgespeeld tijdens mijn opleiding tot neuroloog. Een onmogelijke combinatie als je beiden goed wil doen. Maar ook een hele leuke tijd met name ook door het prettige gezelschap van AGNIOS, AGIOS, AGIKOS, ANIOS en AIOS neurologie door de jaren heen, de neurologen en alle andere medewerkers van de neurologie afdeling.

Sonja

Wat leuk dat we vanavond samen feest kunnen vieren! We zijn bijna buren en deelden naast de neurologie al de C1000, maar nu dus ook nog onze promotie-datum. Ik zie je weer bij het speeltuintje, daar hebben we straks weer genoeg tijd voor…

Boekenclub

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En dan mijn drietal

Jip Madelief, mijn eigen unieke Generation R kind
(ondanks dat je soms "dan wel ergens anders gaat wonen")

Noortje "eigenwijs" **Jasmijn**
(ondanks dat je de toetsen van mama's laptop peuterde)

Quint, mijn kleine mannetje
(ondanks dat we avonden met je rond moesten lopen, terwijl mama eigenlijk moest typen)

Voor het verrijken van mijn leven. Wat relativeren jullie het belang van dit boekje. Hoeveel ik van jullie houd is niet in getallen of woorden uit te drukken.

Liefste Eelke,
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Ik hou van je ♥

Having a place to go is a home, having someone to love is a family