Children of mothers with epilepsy exposed to antiepileptic drugs during pregnancy

Long-term neurocognitive and behavioral functioning from a family perspective

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EURAP & Development: Study protocol of a Dutch prospective observational study into fetal antiepileptic drug exposure and long-term neurocognitive, behavioral and family outcomes

This chapter is based on: Huber-Mollema, Y., van Iterson, L., Oort, F. J., Lindhout, D., & Rodenburg, R. (2018). EURAP & Development: Study Protocol of a Dutch Prospective Observational Study into Fetal Antiepileptic Drug Exposure and Long-term Neurocognitive, Behavioral and Family Outcomes. doi: 10.31234/osf.io/b8dyj

Abstract

Background: Children exposed to antiepileptic drugs (AEDs) *in utero* are at higher risk for congenital malformations. Less is known about the long-term association with neurocognition and behavior. Research into family factors related to long-term developmental outcomes of children of women with epilepsy is also rare. We present a protocol to investigate the neurocognitive and behavioral development in children of mothers with epilepsy from a family perspective.

Methods: This is a prospective observational longitudinal study, of children exposed *in utero* to monotherapy carbamazepine, lamotrigine, valproate or levetiracetam whose mother were previously included in the European Registry of Antiepileptic Drugs and Pregnancy (EURAP-NL) database. Children are tested at age six or seven years (T1) and at eight or nine years (T2). Children, mothers and fathers are asked to undergo neuropsychological assessments and to complete questionnaires on behavioral functioning and distinct family factors.

Discussion: This study contributes to future counseling of women with epilepsy who have children or wishes to start a family. Strengths are the inclusion of levetiracetam, the longitudinal design, and alongside neurocognition, the inclusion of differential behavioral and family outcome measures. Anticipated limitations are discussed.

Trial registration: Dutch Trial register: NTR4800. Registered 22 September 2014.

Introduction

Epilepsy is a common neurological disorder occurring in 0.4-1.0% of the population[1]. Prenatal exposure to antiepileptic drugs (AEDs) is also common: 0.3-0.5% of all pregnant women have epilepsy and most use AEDs[2]. Women with epilepsy wanting to get pregnant or already pregnant have to make difficult decisions regarding use of AEDs. Seizures can cause greater harm to the mother and the fetus compared to the potential adverse effects of medication on embryonic development. Most are advised to continue using AEDs during pregnancy[3]. About 0.4% of all newborns have been exposed to AEDs *in utero*[4].

The use of AEDs increases the risk of birth defects, such as heart defects, cleft lip or palate, dysmorphic disorders, defects in the limbs, defects in the genitals and urinary tract, and neural tube defects[5–7]. It is not fully known which AEDs play a role, but the risk seems especially related to valproate (VPA), higher doses and polytherapy[7].

In utero exposure to AEDs is also associated with difficulties in cognitive and behavioral functioning. A correlation between prenatal VPA exposure and a lower verbal IQ (VIQ) has been found[8–16]. Delays in speech and motor development, conduct disorder, ADHD, and school problems have also been associated with prenatal exposure[9,17–20]. VPA exposure also appears to be related to an increased risk of autism spectrum disorders (ASD), as up to 11% of children were diagnosed with autism or Asperger syndrome[19,21].

Certain cognitive and behavioral developmental outcomes such as language development, memory, executive functioning, and child psychiatric problems, including ASD, can only be assessed later in childhood. Previous assessments of children of mothers with epilepsy were often inadequate as studies used retrospective designs or small samples. High quality prospective research is warranted to assess the safety of AED use during pregnancy regarding developmental outcomes. Therefore, the central project commission (EURAP CPC) developed a neurocognitive extension protocol (NCEP) to follow prospectively neurocognitive development of children exposed *in utero*[22]. The NCEP includes an extensive neuropsychological screening, with VIQ at the age of six years as main outcome measure[22].

As it is unknown whether effects of AEDs used during pregnancy are persistent or whether children catch up later, it's important to investigate long-term development prospectively. A systematic screening for attention deficit disorder, autism, and other behavioral problems, will provide better insight of behavioral development. It is not known how mothers with epilepsy experience the upbringing of their children, whether

they feel competent to care, whether they experience parenting stress, and whether they receive social support. These topics need addressing as parenting and family factors could also contribute to developmental problems in children from special populations[23–25]. As *in utero* AED exposure seems a risk factor for child development, parenting and other family factors should be also examined as they may buffer against developmental problems or may help parents to cope better with child behavior[26]. Thus, further data on parenting as either a risk or a protective factor in the development of exposed children could contribute to fine-tuning treatment and guidance for these children and their families.

The aim of the Dutch EURAP & Development study is to extend the NCEP further: firstly through a longitudinal design with two measurement points at six or seven years and at eight or nine years of age, secondly, by including behavioral and family outcomes in addition to neurocognitive outcomes and lastly by also including children prenatally exposed to levetiracetam (LEV) as monotherapy, in addition to those exposed to monotherapy VPA, carbamazepine (CBZ) or lamotrigine (LTG).

Long-term neurocognitive and behavioral functioning after prenatal exposure

An increasing attention for the long-term neurocognitive and behavioral functioning of children exposed to AEDs *in utero* has developed since the NCEP started and prospective studies have reported[27–29]. A summary of these is provided in Table 4. Studies vary by children's age and measures. Cognition appeared to be the main focus, with intelligence (IQ) or the developmental quotient (DQ) in younger children as primary measures. Most data is on children exposed to VPA, with only a few studies on the exposure to newer AEDs such as LEV[14,30–32].

Valproate exposed children

VPA exposure is most strongly associated with long-term cognitive and behavioral functioning. Compared to healthy children, children of mothers with epilepsy without prenatal exposure, exposure to other AEDs or standardized norms, infants and toddlers have been shown to have a developmental delay[14,18,30,32–35], and lower IQ scores in school age[5,10,13,31,36–40]. Verbal functioning seems to be particularly affected[10,13,41] and, to a lesser extent, attention and memory functions[9,42]. Children seem at risk for learning problems and have more frequent additional educational needs[17].

Children seem more likely to show poor adaptive functioning in daily life[43] and are at an increased risk for neurodevelopmental disorders such as attention-deficit

hyperactivity disorder (ADHD) and ASD[44,45]. Elevated scores on the Child Autism Rating Scale (CARS)[46] suggest a dose-related effect[47]. Other studies have also found dose effects, with higher doses associated with more problems[13,31,36,37,48]. Some studies did not find significant neurocognitive or behavioral problems after prenatal VPA exposure[9,49–51]. These different outcomes may be due to lower doses or small sample sizes.

Carbamazepine exposed children

Most studies did not find differences in cognitive functioning compared to controls[5,9,10,37,52–54]. Other studies, however, reported increased rates of developmental delay[18,32,55–57]. A recent meta-analysis showed that differences were associated with study methodologies[27]. No dose effect has been found for cognitive outcome measures[27].

It seems that CBZ poses less of a risk for development compared with VPA. Children seem comparable to non-exposed on Full Scale IQ (FSIQ)[37]. Whether certain particular child characteristics or behavioral functioning are susceptible to CBZ exposure needs further studies[28].

Lamotrigine exposed children

Many women of childbearing age use LTG[58], but less research has been done into the long-term effects of prenatal exposure. LTG seems to have little or no effect on cognitive and behavioral development. Available reports do not suggest issues in the neurodevelopment of infants[32,34,57]. However, a higher risk was found for parenteral reports of impaired fine motor skills at age six months, and lower language skills at age 36 months[35]. Deficits have been found in nonverbal abilities, with lower scores on tasks of fine motor skills in early development compared to controls[34], but after controlling for confounders (e.g. maternal IQ), this was not significant.

Studies in school-age children showed no difference in IQ compared to controls[37,50]. No abnormal language development was found[41]. In comparison to VPA and CBZ, preschoolers exposed to LTG did not significantly differ from CBZ on cognitive functioning, and had less cognitive problems than VPA exposed preschoolers[12,34,57]. This was also true for school-aged children[13,36,59]. A risk for specific neurocognitive skills such as motor and sensory integration skills may exist for higher LTG dose[50]. Other studies did not find any dose effect[12,13,37]. Children seem to have less behavioral problems and better adaptive functioning compared to VPA at six years of age[48]. Compared to controls, no differences were found on behavior and attention measures[50]. No risk for neurodevelopmental disorders was seen[44]. Parents, however, reported increased

concerns about autistic traits at 36 months[60]. No increased educational support was seen[37].

Levetiracetam exposed children

Only a few studies have investigated the long-term effects of prenatal LEV exposure showing no impairments in neurodevelopment and IQ in infants, toddlers, and school-aged children[14,30–32]. In comparison with children exposed to VPA, higher levels of early and preschool development were found, indicating less problems. No effect of dose was found.

Confounding factors

There are many other factors that may contribute to cognitive and behavioral development of exposed children. Controlling for potential confounders is crucial. Confounders have seldom been included[61]. Factors that may influence developmental outcomes are diverse and interrelated, and include aspects of maternal epilepsy and pregnancy, as well as child characteristics and features of the child's family environment[61]. Possible confounders are maternal IQ, socio-economic status, maternal age at birth, gestational age, maternal use of tobacco or alcohol, maternal preconception folate use and breastfeeding[62].

Frequent convulsions during pregnancy have been found to be associated with reduced child cognitive functioning[5], but this has not been replicated[10,13]. Given the association between type of epilepsy and the choice of AED, the issue of confounding by indication persists: are relationships between long-term child development and AED exposure actually inherent to the type of maternal epilepsy? Of importance also is AED doses taken during pregnancy. Dose related deleterious effects have been found for VPA[7,13].

Family factors

As parenting stress, parental psychiatric problems, parenting and family functioning can act as mediating factors between earlier fetal exposure, the current epilepsy and the development of the child, we consider it important that these family factors are included in the research into children of mothers with epilepsy[63].

Aim of this study

The purpose of the study is to address the following questions: 1. What is the nature and severity of cognitive and behavioral problems in children at ages six or seven and at follow-up at ages eight or nine? 2. Are there differences between the four AEDs in monotherapy and is there a dose effect? 3. What is the course of child developmental problems at ages eight or nine when compared to when children were six or seven? 4. Which additional epilepsy and family factors contribute to developmental problems in these children?

Methods

Study design and participants

This is a prospective longitudinal observational study, with assessors blinded to the AED exposures. Participants are mother-child pairs identified from the European Registry of Antiepileptic Drugs and Pregnancy database in the Netherlands (EURAP-NL). EURAP registers the prevalence of major congenital malformations following prenatal exposure to AEDs[7,64]. Women with epilepsy are enrolled in EURAP-NL through referral by their health professional or by self-referral. Recruitment is national and preferably occurs within the first sixteen weeks of pregnancy facilitating prospective collection of information about epilepsy, seizures, health, and well-being during the pregnancy and other potential risk factors[64].

In order to compare different types of AEDs, a child is only invited if its mother had been on monotherapy. Children receive a complete neuropsychological examination and parents complete behavioral and family factor questionnaires at T1 (six or seven years) and at T2 (eight or nine years). Mothers and fathers complete a short-form intelligence test at T1 [65,66]. The study was approved by the medical ethics committee of the Academic Medical Center (AMC: NL 45505.018.13) and registered with the Dutch trial register (www.trialregister.nl: NTR4800) prior to enrollment of the first participant.

Inclusion criteria

Mother – child pairs must meet the following eligibility criteria: (1) enrolled in the EURAP-NL database with pregnancy ascertained and risk factors assessed prenatally, after delivery, or up until three years of age (possible exposure through breast feeding), (2) with the child born between 2007-2011, (3) prenatally exposed to CBZ, LTG, VPA,

or LEV monotherapy during the entire pregnancy, (4) and aged between six years, 0 months and seven years, 11 months, at T1 and between eight years, 0 months and nine years, 11 months at T2, with two years (minimum 22 months and maximum 30 months) between the first and second neurocognitive assessment.

All pregnancies have also been submitted to the central EURAP registry in Milan. Every effort will be made to enroll all consecutive mother-child pairs. Information about reasons for not participating are recorded and analyzed to minimize possible selection bias. Before the start of the study, and each subsequent year, addresses are checked in the municipal administration.

Exclusion criteria

Participants are excluded if: (1) the mother is unable to take care of the child (e.g., due to severity of epilepsy), (2) the child has a known chromosomal/genetic syndrome or prematurity (gestational age less than 37 weeks), or (3) there are factors other than AED exposure which significantly modify child development, such that reliable assessment is not possible.

Sample size

The sample size was calculated to enable us to find differences in change between children of mothers who use different AEDs. With a medium expected effect size of f (V) = 0.25 (e.g., a 0.5 SD difference between the most and least changing groups and a 0.5 autocorrelation[67]), a total sample size of 179 suffices for a 80% chance of finding a group by time interaction effect at a 5% level of significance, whereas a sample size of 231 suffices for a 90% chance to find a medium sized effect. Other analyses require smaller sample sizes.

A total of 517 children enrolled in EURAP-NL and born between 2007 and 2011 is invited (Table 1). Assuming that half will agree to join the study, we expect to include about 260 children and their parents. Based on earlier experiences, we assume that parents are interested in, but may also be concerned about, the development of their child, and in general willing to participate.

Procedure

Participants who meet the inclusion criteria receive an invitation letter around the time of the child's sixth birthday. Parents may use a reply card, email or the website (www.sein.nl/eurap) to indicate whether or not they want to participate. Families who

Table 1. *Number of mother-child pairs in EURAP-NL database born from 2007-2011 and total expected number of children to be included*

Year	CBZ	LTG	VPA	LEV	Total of potential children	Expected inclusion 50%
2007	34	38	16	7	95	47
2008	23	29	16	11	79	39
2009	29	39	16	16	100	50
2010	40	47	16	17	120	60
2011	20	57	12	34	123	61
					Study population 517	Sample size 257

do not respond receive a reminder after one month. If no reply has been received after three months, families are contacted by telephone to ask whether they are willing to participate. Parents who do not wish to participate are asked to complete the survey part of the study by completing online questionnaires. If the child has had a psychological examination within the last year, we ask parents for the reports (e.g., IQ test). For families willing to participate, an appointment is made at one of our test sites for the first assessment with, ideally, both parents and the child. If the father is unable to attend, he is asked to complete the online questionnaires at home.

The study is carried out within one day, from 9:30 in the morning until approximately 15:00 hours (Daily schedule, Table 2). A fixed test sequence is used for children and parents (Figure 2 and 3). To minimize the study load for the family, mother, father, and child have their assessments simultaneously. To minimize bias, the parent interview about the child is at the end of the day. The parents and the child are examined by assessors in nearby rooms. Assessors are child (neuro)psychologists who are authorized to conduct clinical testing in children, and who are trained and monitored according to the test protocol. If the child does not want to be examined without the presence of the parent, changes in the protocol are made to accommodate to this. Any change in procedure is noted in the case record form; the child's assessment is recorded on video for possible clinical consultation.

At T1 there are two assessors and at T2 one assessor, because at T2 only the child has an assessment. Prior to the assessment, parents sign a written informed-consent form for the child and themselves. Parents are enabled to claim traveling expenses and receive a voucher of 50 euros as a reward for participation. After participating in both T1 and T2 parents receive a report with feedback from the child's assessment. If

necessary, parents receive further explanation, advice, or a referral (i.e., to their family doctor, neurologist or child psychologist).

Table 2. *Daily schedule Dutch EURAP & Development study*

T1	**Parent(s)**	**Child**
9:30	Arrival / introduction, informed consent	
10:00-12:00	Mother: short intelligence test and vocabulary task Father: questionnaires and vocabulary task	First part test assessment
12:00-13:00	Lunch break	
13:00-14:30	Father: short intelligence test Mother: questionnaires Mother and father: interview about child	Second part test assessment
14:30/15:00	Close of day	
T2	**Parent (s)**	**Child**
9:30	Arrival / introduction, informed consent	
10:00-12:00	Questionnaires	First part test assessment
12:00-13:00	Lunch break	
13:00-14:00		Second part test assessment
14:00-14:30	Parent interview (meanwhile child will play/draw)	
14:30	Close of day	

Study settings

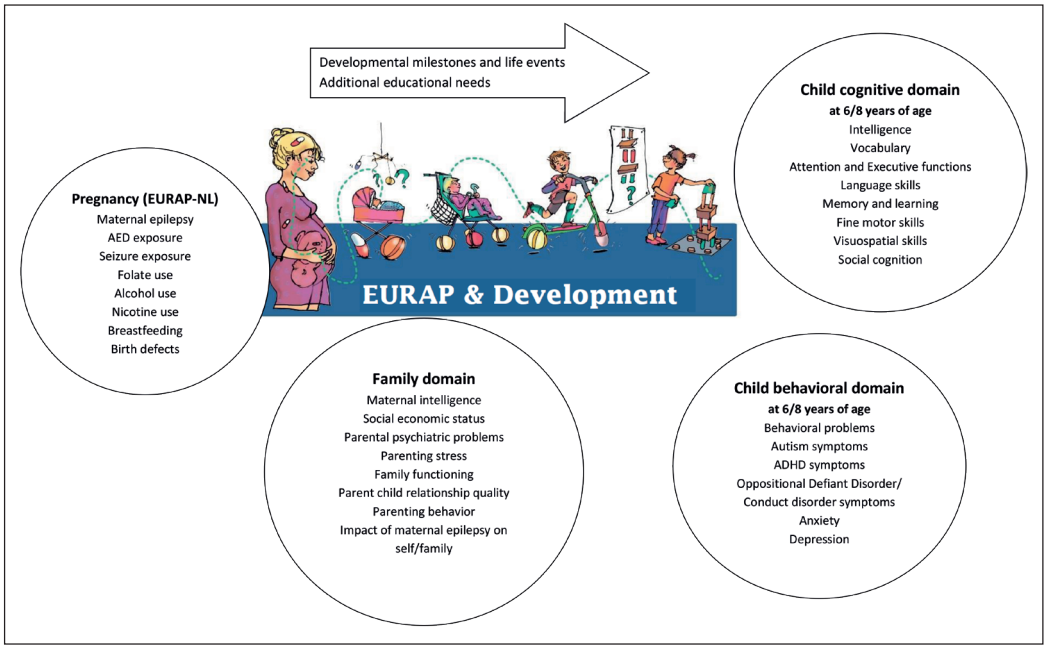
Participants live all across the Netherlands, and therefore the study is conducted in different locations. If travel to one of the study locations is not possible, the examination takes place at home. The study locations are at: Heemstede (epilepsy center SEIN), Amsterdam (University of Amsterdam), Rotterdam and Zwolle (outpatient clinics SEIN) and Heeze (epilepsy center Kempenhaeghe).

Measures

The study examines different domains of development from a bio-ecological perspective[68]: (1) child neurocognition, (2) child behavior, and (3) family factors (Figure 1). Primary study parameters are: (1) Verbal IQ (VIQ), Performance IQ (PIQ), Full Scale IQ (FSIQ) and processing speed index (PSI), attention and executive functioning, language skills, verbal fluency and vocabulary, visuospatial skills, fine motor skills, memory and learning, and social cognition (theory of mind and affect recognition); (2) Child behavioral problems and psychiatric symptoms, including ADHD and autism. Secondary outcome measures (3) are parenting stress, parental psychiatric symptoms, impact of maternal epilepsy on self and family, quality of parent child relationship, parenting and

family functioning. Table 3 presents an overview of the measures and the time points of study assessments.

Figure 1. *Dutch EURAP & Development study domains*



Note: EURAP: European Registry of Antiepileptic Drugs and Pregnancy, AED: antiepileptic drug.

Table 3. *Dutch EURAP & Development Study constructs with concomitant child- and parent-measures*

Construct	Measure	Time points	
		T1	T2
Child assessment			
Intelligence (verbal, performance, full scale and processing speed)	WISC-III-NL (9 subtests)	X	X
Attention and executive functioning, Language skills, Memory and learning, Fine motor skills, Visuospatial skills and Social cognition	NEPSY-II-NL (18 plus 2 delayed tasks)	X	X
Vocabulary	PPVT-III-NL	X	
Verbal fluency	Lindeboom	X	X
Visual attention	Tea-CH	X	X
Auditory synthesis	TvK	X	
Phoneme deletion	DST	X	X
Autism	CARS2-HF	X	X

Table 3. Continued

Construct	Measure	Time points	
		T1	T2
Parent Assessment			
Intelligence	WAIS-III-NL	X	
Vocabulary	PPVT-III-NL	X	
Questionnaires			
Demographics, health and education child and parents	General information	X	X
Development of child from birth until 6	Development history	X	
Child behavioral problems	CBCL, SEV	X	X
Autism	CARS2-QPC	X	X
Adult behavioral problems	ASR	X	
Impact of maternal epilepsy on self/family	IPES	X	X
Quality of life of mother with epilepsy	Qlife	X	X
Parenting stress	OBVL	X	X
Family functioning	VGFO	X	X
Parenting	VSOG	X	X
Family events	VMG	X	X
Quality of parent child relationship	OKIV-R	X	X

Note. WISC-III-NL: Wechsler intelligence scale for children - third edition[70], NEPSY-II-NL: developmental neuropsychological assessment - second edition[71], PPVT-III-NL: peabody picture vocabulary test - third edition[72], Lindeboom: verbal fluency task[73], Tea-ch: Test of everyday attention for children[74], TvK: taaltest voor kinderen [“language test for children”][75], DST: dyslexie screening test [“dyslexia screening test”][76], CARS2-HF: Childhood autism rating scale – second edition - higher functioning version[46], WAIS-III-NL: Wechsler adult intelligence scale – third edition[77], CBCL: Child Behavior Checklist[78], SEV*: Sociaal Emotionele Vragenlijst [“Social Emotional Questionnaire”][79], CARS2-QPC: childhood autism rating scale, parent questionnaire[46], ASR: Adult self-report[80], IPES: adapted version from ‘Impact of Pediatric Epilepsy on the Family’[81], Qlife: Quality of life[82], OBVL*: Opvoedingsbelasting Vragenlijst [“Parenting Stress Questionnaire”] [83], VGFO*: Vragenlijst Gezinsfunctioneren [Family Functioning Questionnnaire”][84], VSOG*: Vragenlijst Ouderlijk Gedrag [“ Parenting Behavior Questionnaire ”][85], VMG*: Vragenlijst Meegemaakte Gebeurtenissen [“Life Events Questionnaire”][85], OKIV-R: Ouder-Kind Interactie Vragenlijst Revised [“The Parent-Child Interaction Questionnaire-Revised PACHIQ-R”][86]. * These questionnaires are only available in Dutch.

Figure 2. *Test sequence child assessment Dutch EURAP & Development study T1*

max. 75 min	WISC-III-NL	PC	5-10 min	Picture Completion
	WISC-III-NL	IN	5 min	Information
	WISC-III-NL	OA	10-15 min	Object Assembly
	WISC-III-NL	SI	5-10 min	Similarities
	WISC-III-NL	BD	10 min	Block Design
	WISC-III-NL	CO	10 min	Comprehension
	WISC-III-NL	CD	5 min	Coding (A)
	WISC-III-NL	SS	5 min	Symbol Search (A)
	WISC-III-NL	DS	5 min	Digit Span
5 min	small water break			
45 min	NEPSY-II-NL	SN	5 min	Speeded Naming
	NEPSY-II-NL	MF	5 min	Memory for Faces [after 15-25 min MFD!]
	NEPSY-II-NL	*ST*	*2-3 min*	*Statue* ***(only for 6 year olds)***
	NEPSY-II-NL	AA+RS	10 min	Auditory Attention and Response Set (all ages)
	NEPSY-II-NL	VP	3 min	Visuomotor Precision
	Lindeboom		2 min	version B [depending on time first MFD]
	NEPSY-II-NL	MFD	2 min	Memory for Faces Delayed
	NEPSY-II-NL	CI	5 min	Comprehension of Instructions
	NEPSY-II-NL	TM	10-15 min	Theory of Mind
60 min	Lunchbreak			
90-100 min	NEPSY-II-NL	IN	6-10 min	Inhibition
	NEPSY-II-NL	AR	4-6 min	Affect Recognition
	NEPSY-II-NL	NM	6 min	Narrative Memory
	NEPSY-II-NL	MN	10 min	Memory for Names [after 25-35 min MND!]
	NEPSY-II-NL	AW	5-7 min	Arrows
	NEPSY-II-NL	FT	5 min	Fingertip Tapping
	NEPSY-II-NL	IH	5 min	Imitating Hand Positions
	NEPSY-II-NL	DC	5 min	Design Copying
	NEPSY-II-NL	WG	3-4 min	Word Generation (extra)
	NEPSY-II-NL	DF	4 min	Design Fluency (extra)
	NEPSY-II-NL	MND	2 min	Memory for Names Delayed
	NEPSY-II-NL	*AS*	*8 min*	*Animal Sorting (extra)* ***[only for 7+ years old]***
	PPVT-III-NL		10-15 min	Peabody Picture Vocabulary Test

Extra:

Visual Sky Search	("Ruimteschepen" task from Tea-Ch) - version A	5-10 min
Auditory synthesis	(part of language test "Taaltest voor kinderen")	3-5 min
Phoneme Deletion task	("Klanksplitsing" from Dyslexia screening test) >> from 6;6 years!	3-5 min

Note. The sequence of subtests taken may have an impact on the test results, e.g., because of initial shyness of the child at the beginning of the day, or fatigue occurring during the course of the day. Therefore, the sequence of subtests was hold the same for all children. This may also help to repeat our study.

Figure 3. *Test sequence child assessment Dutch EURAP & Development study T2*

	WISC-III-NL	PC	5-10 min	Picture Completion
	WISC-III-NL	IN	5 min	Information
	WISC-III-NL	OA	10-15 min	Object Assembly
	WISC-III-NL	SI	5-10 min	Similarities
max.	WISC-III-NL	BD	10 min	Block Design
60	WISC-III-NL	CO	10 min	Comprehension
min	WISC-III-NL	CD	5 min	Coding (B)
	WISC-III-NL	SS	5 min	Symbol Search (B))
5 min	small water break			
	NEPSY-II-NL	SN	5 min	Speeded Naming
	NEPSY-II-NL	MF	5 min	Memory for Faces [after 15-25 min MFD!]
	NEPSY-II-NL	AS	8 min	Animal Sorting
45-60	NEPSY-II-NL	AA+RS	10 min	Auditory Attention and Response Set
min	Lindeboom		2 min	version A [depending on time first MFD]
	NEPSY-II-NL	MFD	2 min	Memory for Faces Delayed
	NEPSY-II-NL	VP	3 min	Visuomotor Precision
	NEPSY-II-NL	CI	5 min	Comprehension of Instructions
	NEPSY-II-NL	TM	10-15 min	Theory of Mind
(extra)	Phoneme Deletion task ("Klanksplitsing" from Dyslexia screening test)			3-5 min
60 min	Lunchbreak			
	NEPSY-II-NL	IN	10 min	Inhibition
	NEPSY-II-NL	AR	4-6 min	Affect Recognition
	NEPSY-II-NL	NM	6 min	Narrative Memory
	NEPSY-II-NL	MN	10 min	Memory for Names [after 25-35 min MND!]
60	NEPSY-II-NL	FT	5 min	Fingertip Tapping
min	NEPSY-II-NL	IH	5 min	Imitating Hand Positions
	Tea-CH	5-10 min		Visual Sky Search ("Ruimteschepen") - version B
	NEPSY-II-NL	WG	3-4 min	Word Generation
	NEPSY-II-NL	DF	4 min	Design Fluency
	NEPSY-II-NL	DC	5 min	Design Copying (extra)
	NEPSY-II-NL	MND	2 min	Memory for Names Delayed

Statistical analyses

The nature and severity of cognitive and behavioral problems in children at ages six or seven (T1) and at follow-up at ages eight or nine (T2) are investigated through descriptive analyses, and by comparing the mean scores of prenatally exposed children with normative mean scores. This gives a comprehensive description of the neurocognitive and behavioral development of prenatally exposed children.

Regression analysis will be used to investigate whether there are significant differences between the children from the four AED groups at T1 as well as T2, and whether there is a dose effect, while taking into account potential confounders. In order to select confounding factors, we first check the relationships of confounders with medication as well as with the outcome variables. Variables included as potential confounders are type of maternal epilepsy, occurrence of tonic-clonic seizures during pregnancy, use of folic acid, alcohol and nicotine exposure during the first trimester and during the second and third trimesters, breastfeeding, maternal age at birth, maternal IQ, paternal IQ, socioeconomic status (based on parental education), gestational age, gender, age at assessment, congenital malformations and time of inclusion in EURAP-NL database. Variables showing a relationship ($p < 0.15$) with both medication and outcome measures, or variables that are expected to influence child development (e.g., maternal IQ) are entered one by one, each in a separate multiple regression analysis that also includes AED-exposure type (with the VPA-exposed group as the reference group) and standardized dose (taking the percentage relative to the median according to the formula [dose 1st trimester – median AED dose / median AED dose] x 100%).

To examine the course of child developmental problems at ages eight or nine when compared to children aged six or seven, multilevel multiple regression analyses are conducted with repeated measures 'nested' within children. Factors such as epilepsy, parenting, family factors that may contribute to developmental problems are included in the models to investigate interaction effects.

Discussion

We hope to obtain insights in neurocognitive, behavioral and family functioning of children who were exposed to AEDs in pregnancy. Findings may help future parents to minimize developmental problems or to cope better with child behavior [26]. We anticipate that strengths are the extensive developmental, neurocognitive and behavioral measurements of both children and parents, with standardized tests and trained assessors blinded to AED exposure. This study extends the NCEP protocol by including children exposed to LEV, which is increasingly prescribed for pregnant women with epilepsy. LEV seems to be associated with fewer malformations after birth[69], but the long-term neurocognitive and behavioral outcomes should also be investigated[30,31].

The follow up on children at eight or nine years allows us to investigate whether their development will improve or deteriorate over time. To date, no studies are available on the long-term outcome for these AEDs in relation to epilepsy and family factors. Examining children at an older age allows us to examine areas of neurocognitive functioning, such as executive functioning, which emerge only later in development. Previous studies have included children up to six years only, or were cross-sectional, using a wider age range[9,13,15,31,37,42,51].

An anticipated limitation is that the presence of early developmental concerns in children may lead to a bias in the participation in the study. Families of children who experienced problems at a younger age and who may already have been diagnosed may not want to participate. The opposite may also be conceivable, that parents who experience problems with their child are more likely to participate.

Our study is expected to contribute to clinical practice, offering new information to treating neurologists and other health care professionals to help fine-tuning the counselling of women with epilepsy, before, during, and after pregnancy. The study may not only be of help with the choice of a suitable AED but may also reveal which topics associated with the upbringing of the child should be discussed. Professionals counselling mothers with epilepsy may use the outcomes to ask about family life, parenting, and child development. As such, mothers with epilepsy can be continuously given appropriate support and referral if needed. We hope that this will contribute to the quality of life in mothers with epilepsy, their children, and their families. Finally, by publishing this study protocol, we intend to provide other researchers and healthcare professionals with the tools to set up future studies into child developmental outcome in the context of having been exposed to AEDs and growing up with a mother with epilepsy.

Table 4. *Studies on long-term associations between child development and prenatal exposure to antiepileptic drugs*

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
Infants											
1	Videman et al. (2016) *Finland*	Prospective	56 exposed 59 non-exposed	Monotherapy (40): CBZ (9), OXC (10), VPA (5), LTG (8), LEV (7) Polytherapy (16)	7 months	DQ (GMDS) clinical neurological status (HINE)		Visual attention (attention orienting and attentional bias for faces)			CBZ, OXC, and VPA, but not LTG or LEV, were each associated with impaired early language abilities compared to control children. The general speed of visuospatial orienting or attentional bias for faces did not differ between AED-exposed and control children.
2	Wide et al. (2000) *Sweden*	Prospective	81 exposed 81 non-exposed	Monotherapy (65): including CBZ (35), PHT (21) Polytherapy (16)	9 months	Griffiths' test					Drug exposure did not influence Griffiths' score. No significant difference between the exposed and the non-exposed children.
3	Veiby et al. (2013) *Norway* [Norwegian Mother and Child Cohort Study: MoBa]	Prospective	503 CME, with 223 exposed to AED; 471 children had a father with epilepsy and 77770 reference group	Monotherapy (182): LTG (71), CBZ (48), VPA (27) Polytherapy (41)	6 months	Ages and Stages Questionnaire; BSID (motor and communication skills, social skills and language skills)			Temperament (Infant Characteristics Questionnaire); Autistic traits (Checklist for Autism in Toddlers); ADHD/conduct problems from CBCL/ DSM-IV; Social Communication Questionnaire		Children of mothers using AEDs had higher risk of impaired fine motor skills than reference group; similar risks for monotherapy LTG, CBZ and VPA. Polytherapy highest risks - significant effects on fine motor and social skills. Other developmental measures within normal range. Continuous breastfeeding associated with less impaired development than breastfeeding < 6 months. CME who did not use AEDs and children of fathers with epilepsy - normal development.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
4	Thomas et al. (2008) *India*	Prospective	395 CME with 363 exposed 32 non-exposed	Monotherapy (246): CBZ (101); VPA (71); PB (41); PHT (29) Polytherapy (122)	1-1,5 years (*M* age 15.3 months)	Motor and mental development (Indian BSID)					Mean MeDQ 89.1 and mean MoDQ 90.7, was impaired (<84) for 37.6% and 33.5% children respectively. Maternal age, type of epilepsy, seizure frequency, or use of folic acid did not correlate. Maternal education was significantly correlated with MoDQ, but not with MeDQ. Non-exposed had higher scores than exposed. Polytherapy significantly lower DQ than monotherapy. Multiple regression analysis showed that polytherapy was stronger predictor of lower DQ than dose. Compared with CBZ monotherapy, VPA monotherapy was associated with significantly lower scores, but the differences between other AEDs were not significant.
5	Bromley et al. (2010) *UK*	Prospective	194 CME with 167 exposed and 27 non-exposed and 230 control	Polytherapy (30) monotherapy (137): CBZ (48); VPA (42); LTG (34); PHT (7)	2-24 months (*M* age 10 months)	GMDS					VPA significantly increased risk of delayed early development compared to control children. 29% of children exposed to VPA fell below average (<84) with a relative risk of 3.6. CBZ or LTG did not differ significantly from control children. Dose-dependent relationship was found for VPA, with daily doses >900 mg being associated with statistically poorer scores. No other AED showed a significant relationship with dose.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
6	Shallcross et al. (2011) *UK*	Prospective	95 exposed 97 non-exposed	LEV (51); VPA (44)	3-24 months; (*M* age 14 months)	GMDS					LEV exposed children had higher scores compared to VPA exposed children. LEV did not differ from control children. 8% of LEV exposed with DQ <84, compared to 40% of children exposed to VPA. After controlling for maternal epilepsy and demographic factors, exposure to LEV was not associated with outcome.
7	Veiby et al. (2013) *Norway* [Norwegian Mother and Child Cohort Study: MoBa]	Prospective	726 CME, with 333 exposed to AED; 653 children with a father with epilepsy and 107597 control group	Monotherapy : LTG (104), CBZ (69), VPA (40), LEV (17) Polytherapy (62)	18 months 36 months	Questionnaire motor, language and social development			Questionnaires with symptoms of ASD and ADHD		Mothers of exposed children reported more concerns about their child's development and had more referrals to a specialist. Compared to children of parents without epilepsy, exposed children had with 18 months an increased risk of abnormal scores for gross motor skills (7.1% vs. 2.9%) and autistic traits (3.5% vs. 0.9%). At 36 months, the exposed children had increased risk of abnormal gross motor skills (7.5% vs.3.3%), sentence skills (11.2% vs. 4.8%), and autistic traits (6.0% vs. 1.5%). LTG exposed children had higher risk for adverse scores on autistic traits and language at 36 months. CBZ exposure was associated with impaired fine motor and personal social skills at 18 months and aggressive symptoms at 36 months. VPA exposure was associated with adverse gross motor skills at 18 months and language at 36 months. Children born to WWE not using AEDs had no increased risks. Children of fathers with epilepsy generally - within the normal range.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
Toddlers											
8	Meador et al. (2009) *North America /UK* [NEAD study]	Prospective	258 exposed CME	Monotherapy: CBZ (73); LTG (84); PHT (48); VPA (53)	2-3 years		BSID-II; DAS				VPA significantly lower IQ than those exposed to other AEDs. After adjustment for maternal IQ, maternal age, dose, gestational age at birth, and maternal preconception use of folate, the mean IQ was 101 for LTG, 99 for PHT, 98 for CBZ, and 92 for VPA. The association between VPA and IQ was dose dependent. Child IQ was significantly related to maternal IQ for CBZ, LTG, and PHT but not with VPA.
9	Scolnik et al. (1994) *Canada*	Prospective	70 exposed 70 non-exposed	CBZ (36); PHT (34)	18-36 months	BSID / McCarthy		Language (Reynell)			PHT global IQ 10 points lower than controls and more often IQ < 84. Language development similar trend, with children exposed to PHT scoring significantly lower than controls. CBZ did not differ from controls.
10	Rovet et al. (1995) *Canada*	Prospective	58 exposed 58 non-eposed	Monotherapy CBZ (29);PHT (29)	7-85 months (*M* age 30 months; 3 years)	BSID / McCarthy		Language (Reynell)	Temperament		PHT affected younger age and particularly language development, CBZ only showed effects past age 3. Regression analyses found maternal IQ and type of epilepsy as significant predictors of language. No effect of predictors on intelligence. Findings suggest effects due to AED regardless of seizure activity and more favorable outcome in treatment with CBZ than PHT. There were no differences on any of the temperament scales.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
11	Meador et al. (2011) *North America /UK* [NEAD study]	Prospective	216 exposed CME	Monotherapy: CBZ (59); LTG (70); PHT (39); VPA (43)	3 years (36-45 months)		DAS	Preschool language scale; PPVT-IV; Beery			Verbal abilities lower than non-verbal in all exposed children. Folate use associated with higher verbal outcomes. VPA associated with poorer cognitive outcomes and negatively associated with dose for both verbal and non-verbal domains. CBZ dose associated with verbal performance. No dose effects for LTG and PHT.
12	Cohen et al. (2011) *North America /UK* [NEAD study]	Prospective	229 exposed CME	Monotherapy: CBZ (61); LTG (76); PHT (40); VPA (46)	3 years (36-45 months)	BSID-II			ABAS-II; BASC	Parental stress (PSI)	Adjusted mean scores for the four AED groups were in the low average to average range for motor, adaptive, and emotional/behavioral functioning. Dose-related performance decline in motor functioning for both VPA and CBZ and performance decline in adaptive functioning for VPA. Parents endorsed a significant decline in social skills for VPA that was dose related. VPA exposed children at higher risk for future diagnosis of ADHD. No significant group differences on Parenting Stress Index.
13	Cummings et al. (2011) *Northern Ireland /UK*	Observational cohort study	186 exposed CME; 44 control	LTG (35); VPA (58); CBZ (49)	9-60 months (*M* age CME 3 years; control 4 years)	BSID; GMDS					39.6% of VPA, 20.4% of CBZ and 2.9% of LTG exposed had mild (≥1, <2 SD below the mean) or significant developmental delay (score ≥2 SD below the mean), compared to 4.5% of control children. Multivariable analysis demonstrated exposure to VPA (OR 26.1) and CBZ (OR 7.7) but not LTG had a significant detrimental effect on neurodevelopment.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
14	Shallcross et al. (2014) *UK*	Prospective	228 CME with 97 exposed and 131 control	LEV (53); VPA (44)	3 - 4,5 years (*M* age 3,5 years)	GMDS		Reynell Language Development Scale			After controlling for confounding variables, children exposed to LEV did not differ from unexposed control children. VPA scored, on average, 15.8 points below children exposed to LEV on measures of gross motor skills, 6.4 points below on comprehension language abilities, and 9.5 points below on expressive language abilities. No dose effect was detected for either LEV or VPA. Maternal seizures during pregnancy were predictive of poorer developmental outcomes.
15	Ornoy & Cohen, 1996	Prospective (national teratogen information service)	47 exposed 47 non-exposed	CBZ (47)	6 months – 6 years	Bayley developmental scales for children up to 2.5 years of age, or McCarthy's developmental scales for children above 3 years.					6 of the 47 children exposed to monotherapy CBZ had typical facial features of 'carbamazepine syndrome'. Cognitive scores of exposed children significantly lower than non-exposed. All six children with CBZ syndrome had DQ or IQ below 90. No differences between the two groups in physical growth, rate of major anomalies or motor scores.
School age children											
16	Kasradze et al. (2017) *Georgia* [EURAP]	Prospective	50 exposed 50 non-exposed	VPA (18); CBZ (16); Other AED: 3 LTG; 3 PB;1 LEV	36-72 months (*M* age 4 years)	Developmental milestones	WPSI-4				Exposure to VPA was associated with lowest cognitive performance regarding FSIQ and verbal comprehension (VCI). Maternal IQ, and child's age at first phrases were independent factors negatively associated with the cognitive development of children.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
17	McVearry et al. (2009) *North America [substudy of NEAD]*	Prospective	42 exposed CME	Monotherapy CBZ (16); LTG (17); VPA (9)	*M* age 4.2 years			Cognitive fluency (TCAM)			Both for cognitive fluency and originality, main effect was found for exposure to AEDs. For fluency and originality, the group mean for VPA was significantly different from LTG and CBZ. No significant difference found between LTG and CBZ.
18	Meador et al. (2012) *North America /UK* [NEAD study]	Prospective	209 exposed CME	Monotherapy CBZ (53); LTG (72); PHT (40); VPA (38)	4,5 years (51-61 months)		DAS				IQ of VPA was lower compared to other AEDs and negatively associated with dose. Adjusted means were CBZ 106, LTG 106, PHT 105, VPA 96. Maternal IQ correlated with child IQ for children exposed to the other AEDs, but not VPA. Age 4.5 IQ correlated with age 2 BSID and age 3 IQ. Frequency of marked intellectual impairment diminished with age except for VPA (10% with IQ < 70). Verbal abilities were impaired for all 4 AED groups compared to nonverbal skills.
19	Kjaer et al. (2013) *Denmark*	Follow-up study	81 exposed CME, 208 non-exposed CME and 828 control	*Not enough power to analyze between different AEDs*	4 – 5 years				SDQ		Prenatal AED exposure may increase risk of behavioral problems even after adjustment for potential confounders and maternal epilepsy. Children prenatally exposed to AEDs more often abnormal total SDQ score as compared with children of women without epilepsy and compared with CME not on AEDs during pregnancy.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
20	Wide et al. (2002) *Sweden*	Prospective	67 exposed 66 non-exposed	CBZ (35); PHT (16)	4,5 – 5 years	Griffiths'test					No significant difference between the two groups of children. PHT showed a significant but subtle reduction in the scores for locomotor development compared to the unexposed children. No such difference for the children exposed to CBZ.
21	Natarajan (2016) *India*	Prospective	55 exposed 55 non-exposed	Monotherapy: PHT (10; CBZ (5); VPA (10); Polytherapy (30)	3-10 years	Vineland social maturity scale	Binet Kamat scale				Compared to non-exposed children monotherapy VPA and polytherapy had significantly more neurodevelopmental delay. Polytherapy and VPA exposed had low IQ scores 79.4 and 82.8, respectively. PHT IQ score of 94.2 and CBZ 95.2. Exposed children had lower scores in language, vocabulary, sentence building, similarities and differences, analogies sentence repetition and conceptual thinking. No significant difference on visuomotor tasks, auditory perception, and social skills between exposed and non-exposed children.
22	Vanoverloop et al. (1992)	Retrospective	20 exposed 98 non-exposed	PHT monotherapy and polytherapy with PB	4-8 years		WPPSI/ WISC-R	Visual motor integration (VMI); Gramatic closure and Auditory Association (language)	Spontaneous activity (play)		No children with below average IQ. PHT-exposed children significantly lower scores for both PIQ, FSIQ, Visual Motor Integration Test and time in quadrant, as well as several subtests.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
23	Rihtman et al. (2013) *Israel*	Prospective	72 exposed 52 unexposed	VPA (30) LTG (42)	3-6.11 years (*M* age 50-60 months)		SB5	Fine and gross motor (DCDQ; M-FUN), Visual motor integration (BEERY) Sensory processing (SP), Executive function (BRIEF)	Conners'rating scale (behavioral problems and attention problems)		In both comparison between AED vs control and VPA-LTG vs control, control children performed better in all areas. No significant differences were found between VPA and LTG. But more differences were found between VPA and control than LTG and control. Compared to control group VPA exposed children scored lower on motor and sensory tasks, and according to parent report higher on behavior / attention problems. LTG exposed children had lower scores on motor and sensory tasks when compared to control children, but did not have behavior / attention problems. Notable were relatively low doses, with mean daily dose of 546.3 mg for VPA.
24	Bromley et al. (2016) *UK [overlap in sample with Shallcross et al., 2011, 2014]*	Prospective	130 exposed 55 non-exposed	Monotherapy: LEV (42); TPM (27); VPA (47); GBT (14)	5-9 years		WISC-IV/ WPSI-III	NEPSY	BASC		Prenatal exposure to LEV and TPM were not associated with reductions in child cognitive abilities, and adverse outcomes were not associated with increasing dose. Increasing dose of VPA was associated with poorer FSIQ, verbal and nonverbal abilities. Doses of 800 mg VPA was significantly associated with a 10.6-point reduction in FSIQ, 11.2-point reduction in verbal abilities, and 11.1-point reduction in nonverbal abilities. VPA was also associated with poorer outcomes on expressive naming index as well as behavioral variables of withdrawal, adaptability, and daily living skills but not on other measures of language, memory, attention and executive functioning, or behavioral outcomes.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
25	Thomas et al. (2007) *India*	Prospective	71 exposed CME, 201 non-exposed	PB; PHT; CBZ; VPA	6 years (*M* age 6.4 years)		Indian IQ test	Indian language test			FSIQ and language scores were significantly lower for CME (87.7 and 73.4) compared to control children (93.0 and 83.2). CME scored poor on all subtests of language but their impairment was confined to only some of the subtests of IQ. Maternal education and maternal IQ significantly correlated with low IQ and language scores for CME whereas type of epilepsy, seizures during pregnancy or low birth weight did not. Polytherapy and higher dose of AEDs were associated with significant impairment in outcome measures. The FSIQ or language score of CME did not vary significant according to monotherapy exposure.
26	Bromley et al. (2013) *UK*	Prospective	201 CME 214 control	Monotherapy: CBZ; LTG; VPA; Polytherapy	6 years				Neurodevelop-mental problems (e.g. diagnoses ASD/ADHD)		Neurodevelopmental disorders more frequently reported in children of WWE (7.46%) than in control group (1.87%). Increase in risk of neurodevelopmental disorders in children exposed to monotherapy VPA (12.0%; a OR 6.05) and in those exposed to polytherapy with VPA (15.0%; a OR 9.97) compared with control children. ASD was the most frequent diagnosis. No significant increase was found among children exposed to CBZ or LTG. Children of women with untreated epilepsy had no neurodevelopmental disorders.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
27	Meador et al. (2013) *North America /UK* [NEAD study]	Prospective	224 exposed CME	Monotherapy CBZ (61); LTG (74); PHT (40); VPA (49)	6 years (70-87 months, *M* age 74 months)		DAS	CMS; BRIEF; NEPSY; Beery			IQ was lower after exposure to VPA (97) than CBZ (105), LTG (108), or PHT (108). VPA did poorly on verbal and memory abilities compared with those exposed to other AEDs and on non-verbal and executive functions compared with LTG (but not CBZ or PHT). High doses of VPA were negatively associated with IQ, verbal ability, non-verbal ability, memory, and executive function, but other AEDs were not. Age-6 IQ correlated with IQs at younger ages, and IQ improved with age for infants exposed to any AED. Verbal abilities were worse than non-verbal abilities and in the LTG and VPA groups in particular.
28	Cohen et al. (2013) *North America /UK* [NEAD study]	Prospective	195 exposed CME	Monotherapy: CBZ (53); LTG (63); PHT (31); VPA (45)	6 years				ABAS-II; BASC	Parental stress (PSI)	Adjusted mean scores for all AED groups were in the low average to average range for adaptive and emotional/behavioral functioning. VPA had significantly lower adaptive functioning than LTG and PHT. With dose-related performance decline for VPA and PHT. VPA had more atypical behaviors and inattention than children exposed to LTG and PHT. Children exposed to VPA at a significantly greater risk for a diagnosis of ADHD. No significant group differences on Parenting Stress Index.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
29	Baker et al. (2015) *UK [overlap in sample with NEAD study by Meador et al., 2013]*	Prospective	198 CME with 173 exposed and 25 non-exposed and 210 control	Monotherapy: VPA (51); CBZ (50); LTG (29); other (13) and polytherapy (30)	6 years		DAS				Adjusted mean IQ 9.7 points lower for children exposed to high-dose VPA (>800 mg daily); similar significant effect for verbal, nonverbal, and spatial subscales. VPA > 800 mg had an 8-fold increased need of educational intervention relative to control children. VPA at doses <800 mg daily was not associated with reduced IQ, but was associated with impaired verbal abilities and a 6-fold increase in educational intervention. CBZ or LTG did not have a significant effect on IQ, but CBZ was associated with reduced verbal abilities and increased frequency of IQ <85. No association with increased educational intervention and no dose effect for CBZ.
30	Moore et al. (2000) *Scotland /UK*	Retrospective clinical study	57 exposed	VPA (46 with 34 monotherapy); PHT(4); CBZ(4)	0-16 years (*M* age 6.48 years)	Developmental delay			Fetal anticonvulsant syndrome; behavioral problems (symptoms/ diagnosis of ASD/ADHD)		81% reported behavioral problems, 39% with hyperactivity or poor concentration of whom 7% had a diagnosis of ADHD. 60% reported two or more autistic features, of whom four had a diagnosis of autism and two of Asperger's syndrome. 77% had learning difficulties, 81% speech delay, 60% gross motor delay, and 42% fine motor delay.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
31	Mawer et al. (2002)	Prospective	69 exposed (56 follow –up)	Monotherapy: VPA (23); CBZ (18); PHT (7); LTG (4); Polytherapy (15)	4 months – 10 years	Developmental delay, dysmorphic features and structural anomalies					Dysmorphic features in more than half of the children and developmental delay in about one-quarter. Structural anomalies were found in about one-third. Adverse features were mild but in about 10% moderate or severe. Developmental delay was associated with dysmorphic features but not with structural anomalies. Positive association between adverse outcome in all domains and VPA dose. With VPA <1000 mg adverse features were absent or mild but at higher doses moderate or severe. No significant association between adverse outcome and CBZ dose.
32	Nadebaum et al. (2011) *Australia*	Prospective	57 exposed CME	Monotherapy VPA (23); Polytherapy with VPA (15) and (19) without VPA	6-8 years (*M* age 7.4 years)		WISC-IV				All groups had elevated frequencies of Extremely Low (<70) or Borderline (70–79) FSIQ. Verbal Comprehension and Working Memory scores in all groups fell significantly below the standardized test mean, while Perceptual Reasoning and Processing Speed scores were relatively intact. Multivariate analysis of covariance analysis revealed significant main effects of VPA on Verbal Comprehension and Working Memory, and of polytherapy on Verbal Comprehension and Processing Speed. Results suggest that VPA has a dose-dependent negative impact on verbal intellectual abilities, and may also affect working memory.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
33	Nadebaum et al. (2011) *Australia*	prospective	102 exposed CME	Monotherapy: VPA (23); CBZ (34); LTG (9); polytherapy with VPA (15) and without VPA (10)	6-8 years (*M* age 7.4 years)			Language (CELF-4)			Language scores of children exposed to VPA monotherapy (91.5) or polytherapy (73.4) were significantly below the standardized test mean of 100. Children exposed to CBZ or LTG monotherapy, or polytherapy without VPA, were not significantly different from normal. First-trimester VPA dose was negatively correlated with language.
34	Gaily et al. (2004) *Finland*	Prospective	182 CME with 137 exposed, 45 non-exposed and 141 control	Monotherapy (107): CBZ (86); VPA (13) and Polytherapy (30, with VPA 17)	*M* age CME 7.0 years control:7.4 years		WPPSI-R				Mean verbal and nonverbal IQ in children exposed to CBZ monotherapy were 96 and 103 and did not differ from control children. Significantly reduced verbal IQ in children exposed to VPA (82) and polytherapy (85) compared with the other study group children and control children.
35	Adab et al. (2001) *UK*	retrospective	400 CME with 224 exposed and 176 non-exposed	Monotherapy (150); CBZ (63); VPA (56); LTG (5); PHT (22); polytherapy (74)	4-18 years (*M* age 8.95)	Additional educational needs					The OR of additional educational needs (AENs) for all exposed children compared with those unexposed was 1.49. VPA monotherapy had an OR of 3.4 by contrast with an OR of 0.26 for CBZ. Polytherapy including VPA had similarly high ORs for AENs compared with those unexposed of 2.51 versus OR of 1.51 for polytherapy without VPA.
36	Christensen et al. (2013) *Denmark*	Population based cohort study; follow-up	655615, of which 2644 exposed and 655107 non-exposed	VPA (508)	*M* age at follow-up 8.84 years (4-14 years)				ASD diagnoses		Maternal use of VPA during pregnancy was associated with a significantly increased risk of ASD and childhood autism, even after adjusting for maternal epilepsy. Absolute risk was 1.53% for ASD and 0.48% for childhood autism. VPA had an absolute risk of 4.42% for ASD and an absolute risk of 2.50% for childhood autism.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
37	Wood et al. (2015) *Australia*	Prospective follow up study	105 exposed	VPA (26); CBZ (34); other monotherapy (11) and polytherapy (34 including 15 with VPA)	6-8 years *M* age 7.4 years				CARS		Children exposed to polytherapy with VPA scored significantly higher than all other groups. Linear regression analysis showed that the mean VPA dose during pregnancy was a significant predictor of CARS scores after controlling for polytherapy, mean CBZ dose, folic acid use, seizures during pregnancy, tobacco and marijuana use, maternal IQ, and SES.
38	Dean et al. (2002) *Scotland/UK*	Retrospective	293 CME with 255 exposed and 38 nonexposed	CBZ; PB; VPA; PHT	Age 2 days – 39 years (*M* age 9 years)	Developmental delay, including speech delay			Behavioral problems		Developmental delay occurred in 24% of exposed children, compared with 11% of non-exposed sibs. The frequency of developmental delay in PB was not significantly different from non- exposed, while the frequencies for those exposed to CBZ, VPA, PHT, and polytherapy were significantly higher. Of exposed children 20% had behavior disorders (vs 5% of non-exposed). Behavior disorders were not significantly more common in exposed children, but analysis of specific drug exposure groups showed significantly more behavior problems in CBZ and VPA monotherapy, and polytherapy group.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
39	Rasalam et al. (2005) *Scotland/UK [subgroup Dean 2002]*	Retrospective	260 of which 14 exposed children are further reviewed	VPA ; CBZ	*M* age 9;10 years	Characteristics of fetal anticonvulsant syndrome; speech and language development			Social and behavior problems; ASD diagnosis (DSM-IV)		Prenatal exposure to AED is a risk factor for the development of an ASD. 26 children were reported by parents to have social or behavioral difficulties. 11 children fulfilled the criteria for autistic disorder and one fulfilled the criteria for Asperger syndrome (AS). These children comprised 4.6% of the exposed children studied, and 1.9% of all exposed children born during the study period. VPA was most associated with autistic disorder, 8.9% of children exposed to VPA had either autistic disorder or AS.
40	Erikson et al. (2005) *Finland*	Population based observational study	26 exposed 13 non-exposed	VPA (13); CBZ (13)	6.6-13.4 years (*M* age 9.7 years)		WISC-III	Touwentest; NEPSY (Attention and Executive functions, Language, Sensormotor and Visuospatial domain, and Memory and Learning functions)			Prevalence of low intelligence (FIQ < 80) was 19%, and exceptionally low intelligence (FIQ < 70) 10% in VPA exposed children. Children exposed to CBZ and children of WWE not exposed to AED during pregnancy had all at least low average intelligence. Mean IQs of children exposed to VPA were 11–17 points lower than CBZ and non-exposed group, however mean difference of children on FIQ, VIQ and PIQ were not statistically significant. On NEPSY subtests VPA exposed children performed significantly lower on Memory for Faces compared with CBZ and lower than non-exposed on List Learning.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
41	Viinikainen et al. (2006) *[Same sample as Erikson et al. 2005)*	Observational population based	26 exposed 13 non-exposed	VPA (13); CBZ (13)	6.6-13.4 years (*M* age 9.7 years)	School problems/ additional educational needs			Conners teacher rating scale (CTRS)		62% of children exposed to VPA and 15% each in the CBZ-exposed and non-exposed groups required educational support. Children exposed to VPA had higher scores in all the domains analyzed, indicating behavioral problems, but because of small number, these differences did not reach statistical significance. However, results in two domains (Social Problems, $p = 0.07$, and Cognitive Problems/ Inattention, $p = 0.09$) indicated a trend for the VPA-exposed children to have more behavioral problems. CBZ-exposed and non-exposed children had very similar scores, and no statistical differences were found between these two groups.
42	Adab, Kini et al. (2004) *UK*	Retrospective	249 CME with 169 exposed and 80 non-exposed	Monotherapie: CBZ (52); VPA (41); PHT (21); other (6) polytherapy (49)	6-16 years (*M* age 10.4 years)	-	WISC				FSIQ was at the low end of the average range for children exposed to monotherapy and was similar to the mean score in unexposed children. The mean PIQ was within or close to the average range in all AED groups, with no significant difference among the different exposures. Mean VIQ was significantly lower in VPA group compared to unexposed and other monotherapy groups. Multiple regression analysis showed that both VPA exposure and frequent tonic-clonic seizures in pregnancy were significantly associated with lower verbal IQ despite adjusting for other confounding factors.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
43	Vinten et al. (2005) *UK* [*Same sample as Adab, Kini, et al. 2004]*	Retrospective	249 CME with 169 exposed and 80 non-exposed	Monotherapie: CBZ (52); VPA (41); PHT (21); other (6) polytherapy (49)	6-16 years (*M* age 10.4 years)		WISC-III	Memory test (RMBTC)			Children exposed to VPA had a significantly lower VIQ when compared to children exposed to other AEDs or non-exposed children. VPA exposed were more likely to have IQ < 69 and more likely to have memory impairment when compared to other groups. Maternal IQ, exposure to VPA, and number of tonic-clonic seizures during pregnancy were significant predictors of VIQ.
44	Vinten et al. (2009) *UK* [*Same sample as Adab, Kini, et al. 2004]*	Retrospective	242 CME with 162 exposed 80 unexposed	Monotherapy: CBZ (49); VPA (41); PHT (20); Polytherapy with VPA (28) and without (24)	6-16 years (*M* age 10.4 years)				Adaptive behavior and maladaptive behavior (VABS)	Parental stress (PSI)	VPA exposure was associated with high levels of parental stress induced by child maladaptive behavior. VPA exposed children also had poorer daily living skills and socialization skills. VABS and PSI were strongly affected by child FSIQ; however, no significant differences were found between the groups on FSIQ.
45	Kantola-Sorsa et al. (2007) *Finland*	Prospective	154 exposed 130 non-exposed	Among others CBZ and VPA both mono- and polytharpy	5-11 years (*M* age 7 years)	Developmental interview	WPPSI-R; WISC-R	Attention, Language skills, Fine motor skills, Visuospatial skills and Memory and learning (NEPSY)			Despite similar IQ CME scored significantly lower than control children on measures of attention, memory, and fine-motor function. Deficits were more marked in but not limited to the subset of the study group exposed to maternal AEDs. Group differences on auditory attention were found only in younger children. VPA-exposed children had lower scores on sentence repetition and on the more demanding part of auditory attention, than other children in the study group, suggesting weaknesses in working memory.

Table 4. Continued

	Study (publication year) *Country*	Design	Sample size	AEDs (*n*)	Age of assessment	Domain of measurement					Results
						DQ / developmental outcomes	IQ	Neurocognition	Behavior	Family/ parenting	
46	Gopinath et al. (2015) *India*	Prospective	190 CME with 115 exposed 11 non-exposed and 149 controls	Monotherapy (67): VPA (36); PB (22); PHT (11); CBZ (40); LTG (1); CNZ (1) and polytherapy (48)	10-12 years (*M* age 11.4 years)		WISC-IV	Attention (TMT), Visual and verbal memory (RAVLT; WMS-VR)			IQ, attention and memory of CME were significantly lower compared to control children. Predictors of low FSIQ were AED dose, maternal IQ, and parental education. FSIQ of CME (77.9) was with 8.5 points significantly lower than controls (86.4). FSIQ of polytherapy was significantly lower than monotherapy group. In monotherapies, PB was significantly associated with low IQ, whereas VPA had FSIQ comparable to CBZ, LTG and PHT. This apparent difference is suggested to be possible due to low dose of VPA (*M* 480.06 mg/ day) .

Note. CME: children of mothers with epilepsy; WWE: women with epilepsy; AED: antiepileptic drug; VPA: valproate; CBZ: carbamazepine; LTG: lamotrigine; PHT: phenytoin; PB: Phenobarbital; LEV: levetiracetam; OXC: oxcarbazepine; TPM: topiramate; GBT: gabapentine; BSID: Bayley Scale of Infant Development; GMDS: Griffiths Mental Development Scale; WISC: Weschler Intelligence Test for Children; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; DAS: Differential Ability Scale; SB: Stanford Binet Intelligence Scales; SDQ: strength and difficulties questionnaire; ABAS: Adaptive behavior assessment system; BASC: behavior assessment system for children; CBCL: Child Behavior Checklist; NEPSY: Developmental Neuropsychological Assessment; TMT: Trail Making Test; RAVLT: Rey Auditory Verbal Learning test; WMS-VR: Wechsler Memory Scale - Visual Reproduction; TCAM: Thinking Creatively in Action and Movement; BRIEF: Behavior Rating Inventory of Executive Function; CELF: Clinical Evaluation of Language Fundamentals; DCDQ: Developmental Coordination Disorder Questionnaire; M-FUN: Miller Functions & Participation Scales; CMS: Children's Memory Scale; BEERY: Visual Motor Integration; PPVT: Peabody Picture Vocabulary Test; CARS: Childhood Autism Rating Scale; VABS: Vineland Adaptive Behavior Scales; PSI: Parenting Stress Index; DQ: Developmental Quotient; IQ: Intelligence Quotient; FSIQ: Full Scale IQ; VIQ: Verbal IQ; PIQ: Performace IQ; MeDQ: Mental Developmental Quotient; MoDQ: Motor Development Quotient; ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder.

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