Maternal epilepsy and behavioral development of the child: Family factors do matter

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ABSTRACT

Purpose: The purpose of the study was to examine whether mothers with epilepsy experience family problems and to investigate the possible mediating role of distinct family factors in the relationship between maternal epilepsy and child behavioral problems, in which it is also investigated whether more proximal family factors mediate the more distal family factors.
Methods: In an observational study, with children identified from the European Registry of Antiepileptic Drugs and Pregnancy database in the Netherlands (EURAP-NL), parents completed questionnaires on maternal epilepsy, family factors (proximal, distal, contextual, global), and child behavior. Hierarchical multilevel regression analyses were performed to examine the relative contribution of epilepsy-related and family factors on child internalizing and externalizing problems.
Results: Between January 2015 and March 2018, the questionnaires were completed for 175 children. Mothers with epilepsy showed significantly more parenting stress and problems with parenting than mothers from the general population. Family factors were significantly associated with child behavioral problems. For internalizing problems, maternal epilepsy, global, contextual, and distal family factors were each found to have significant added value. Distal family factors contributed most to internalizing problems and showed a mediating role for epilepsy-related factors and previous added family factors in the model. Global, contextual, distal, and proximal factors were all found to be significant contributors to externalizing problems, with the factor most proximal to the child (quality of parent–child interaction) showing the largest effect.
Discussion: Including family factors in research regarding children of mothers with epilepsy is important as they can have a contribution additional to the teratogenic risks of prenatal exposure to antiepileptic drugs (AEDs). Family factors, in particular distal and proximal family factors, can weaken or strengthen child development and may provide starting points for interventions.

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1. Introduction

Children of mothers with epilepsy are at higher risk of behavioral problems [1,2]. Multiple risk factors may contribute to child behavioral problems, including possible teratogenic effects of prenatal exposure to antiepileptic drugs (AEDs) and family factors [3]. We previously showed that there were no significant differences on child internalizing and externalizing problems between different AED exposure types [2]. Based on parent reports, a quarter of all children (n = 181) had behavioral problems within the borderline range or above the clinical cutoff (Box 1). In this study, we therefore make no distinction between AED exposures, we examine the children as one group, as they all have a mother with epilepsy.

Family factors such as family functioning and parent–child interaction play an important role in the development of children [4,5]. Having a mother with a chronic medical condition may also contribute to child development: epilepsy-related factors and possible psychiatric comorbidities or AED side effects may be involved [6–9]. Research into children of mothers with epilepsy has paid little attention to the influence of distinct family factors on child behavioral development [3]. The few studies that have been published show that mothers with epilepsy have problems with caring for themselves and for the child and experience more parenting stress [10–12]. Other family factors have not been studied.

Following the social–ecological model of Bronfenbrenner [13] and the transactional model of Belsky [14], four types of family factors can be distinguished, based on their proximity to the child [15,16] (Fig. 1). Factors closest to the child are *proximal family factors*. These are factors that involve the daily interaction between parent and child, such as parenting behavior and quality of parent–child

Box 1

Child behavioral problems.

Based on parent report, children of mothers with epilepsy prenatally exposed to valproate, carbamazepine, lamotrigine, or levetiracetam showed high percentages of clinical behavioral problems [2].

Means, standard deviations, and percentage of children scoring within the borderline range and above the clinical cutoff on internalizing and externalizing problems.

CBCL	Mother report			Father report		
N = 181	M (SD)	Borderline	Clinical	M (SD)	Borderline	Clinical
Internalizing problems	55.4 (9.8)	13.5%	23.6%	52.9 (10.0)	7.6%	18.1%
Externalizing problems	54.0 (10.2)	10.7%	16.9%	52.8 (9.9)	9.0%	14.6%

Note. CBCL = child behavior checklist; mean T-score 50, SD 10. Cutoff scores: T-score 60–63 = borderline; ≥64 = clinical. Multiple regression analyses with controlling for potential confounding factors (e.g., maternal behavioral problems) revealed no significant differences between the AED exposure groups on internalizing and externalizing problems.

relationship. *Distal family factors* concern characteristics of the parent, such as parenting stress and parental psychopathology, which can influence the interaction with the child. Family functioning is a *contextual family factor* that relates to other relationships within the family, including the marital relationship and the social network. *Global family factors* are structural characteristics of the family, such as socioeconomic status (SES), family type and size, and family life events. Family life events affect the whole family (e.g., birth of a child; moving house).

Family factors can function as risk or protective factors [17]. From a social–interactional perspective, it is assumed that proximal factors directly affect behavioral problems while distal, contextual, and global family factors can exert their influence via the proximal factors [15]. This is referred to as the mediational effect [4]. Thus, if family factors are simultaneously examined, the less proximally related family factors (i.e., distal, contextual, and global family factors) exert their influence indirectly rather than directly, via the proximal family factors. The same can be assumed for epilepsy-related factors. A direct contribution of maternal epilepsy-related factors on child behavioral problems may also be assumed, but when effects of epilepsy-related factors are controlled for, it may be that proximal family factors mediate the effects of epilepsy-related factors to child behavioral problems. Thus, maternal epilepsy would then impact on child psychopathology but via parenting.

The purpose of this study was firstly, to investigate whether families with a mother with epilepsy experience family problems, answering the following questions: Do mothers with epilepsy experience more family problems compared with mothers from the general population? Secondly, to investigate the possible mediating role of distinct family factors in the relationship between maternal epilepsy and child behavioral problems. The following four research questions were examined: (1) To what extent do epilepsy-related factors contribute to child internalizing and externalizing problems? (2) To what extent do distinct family factors contribute to child internalizing and externalizing problems? (3) Do family factors mediate the relationship between maternal epilepsy and child internalizing and externalizing problems? (4) Do the more proximal family factors mediate the effects of the more distal family factors on child internalizing and externalizing problems?

Following social–ecological principles, we hypothesize that (1) family factors will contribute more than epilepsy-related factors, (2) of the family factors, parenting – as the proximal family factor – will contribute most to child behavioral problems, (3) family factors will mediate the effects of epilepsy-related factors to child behavioral problems, and (4) proximal family factors will mediate the effects of the other family factors to child behavioral problems [4]. Given the already established effect of prenatal AED exposure, targeting the family factors may be used to modify the child's behavioral problems.
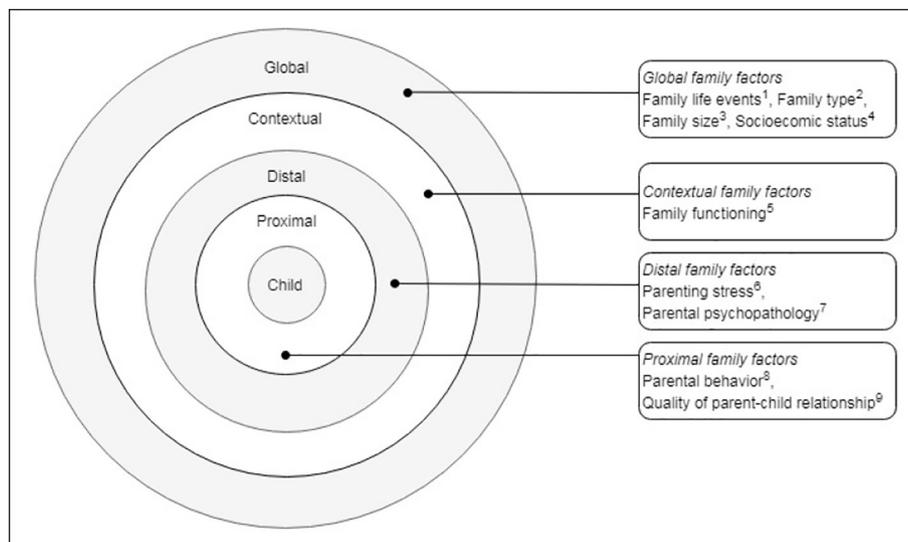

Fig. 1. Schematic representation of distinct family factors. Note. [1]Life Events Questionnaire (VMG) [19]; [2]One or two parent families; [3]Number of siblings; [4]Maternal educational level as measure of SES; [5]Family Functioning Questionnaire (VGFO) [23]; [6]Parenting Stress Questionnaire (OBVL) [16]; [7]Maternal behavioral problems assessed with the Adult Self Report (ASR) [22]; [8]Parenting Behavior Questionnaire (VSOG) [19]; [9]The Parent–Child Interaction Questionnaire-Revised (PACHIQ-R) [20].

2. Methods

2.1. Study design and participants

The current study is part of a larger prospective, observational longitudinal study in which long-term effects of prenatal exposure to AEDs on child neurocognitive and behavioral development are investigated from a family perspective [18]. Participants were mother–child pairs identified from the European Registry of Antiepileptic Drugs and Pregnancy database in the Netherlands (EURAP-NL). Mother–child pairs with health- and pregnancy-related factors assessed prenatally, after delivery, or up until three years of age were eligible. Inclusion criteria were maternal carbamazepine (CBZ), lamotrigine (LTG), levetiracetam (LEV), or valproate (VPA) monotherapy starting before conception and continuing during the entire pregnancy, and the child aged between 6.0 and 7.11 years during the study period. Both parents were invited to participate. Detailed information on procedures are provided in the Dutch EURAP & Development protocol [18].

2.2. Measures

2.2.1. Family factors

Parents completed several questionnaires online on parenting, parental behavior, family functioning, and family life events [19] (Fig. 1).

2.2.1.1. Proximal family factors.
The Parenting Behavior Questionnaire (VSOG) consists of 25 statements about parenting behavior in interactions with children (e.g., 'I make agreements with my child about how he/she should behave') [19]. The parent is asked to answer on a 5-point scale, choosing from the following: 'never or hardly ever', 'not often', 'sometimes', 'often', or 'always or almost always'. The VSOG contains five scales: positive parental behavior (Cronbach's alpha in our sample was 0.76 (mothers) and 0.85 (fathers)), rules, punishing (e.g., 'If my child does something that is not allowed, I discipline him/her'), rewarding, and hard punishment (physical, e.g., 'I give my child a spanking if he/she disobeys'). Raw scores are summed and converted to T-scores (with mean: 50, standard deviation (SD): 10). Lower scores indicate more problems, except for hard punishing, where a higher score indicates harsher punishment. Scores can fall in the normal range, the borderline range, or the clinical range (see Table 3 for cutoff scores).

The quality of the parent–child relationship was measured with the Parent–Child Interaction Questionnaire-Revised (PACHIQ-R) [20,21]. The PACHIQ-R contains 21 items, which are divided into two parts. In the first part, the parent is asked about the frequency at which certain behaviors are displayed (e.g., '… breaks our house rules every day'). The five response categories vary from 'does not apply at all' to 'applies exactly'. The second part concerns the prevalence of certain behaviors and feelings (e.g., 'I like to listen to stories of …'). The parent is asked to choose one of five response categories: 'never', 'hardly ever', 'sometimes', 'almost always', or 'always'. Items are summed and converted into two subscales: conflict resolution and acceptance, and a total score of quality of parent–child relationship [21]. Quintile scores (1–5) are used for interpretation of scores with a higher score indicating a more positive relationship quality. The PACHIQ-R makes a comparison with families from the general population (norm) and with a clinical population with families who have been revered to mental health services in the Netherlands. Cronbach's alpha was 0.79 (mothers) and 0.79 (fathers).

2.2.1.2. Distal family factors.
To measure parenting stress, we used the Parenting Stress Questionnaire (OBVL) [16]. The OBVL is similar to the parent domain of the Parenting Stress Index (PSI). The parent is asked to answer 34 items on a 4-point scale, from 1 'not true' to 4 'very true', about how they experience their child, how they interact with their child, and how they feel about their own health (e.g., 'I feel happy with my child'). The OBVL has a total parenting stress score and five subscale scores on the following: parent–child relationship problems,

parenting problems, depressive mood, parental role restriction, and physical health problems. Higher scores indicate more problems. Cronbach's alpha was 0.93 and 0.91 for mothers and fathers, respectively.

Parental psychopathology was conceptualized as maternal behavioral problems. Mothers were asked to complete the Adult Self Report (ASR) on emotional, behavioral, and social problems [22]. The ASR contains 123 items (e.g., 'I am unhappy, sad or depressed'), which are summed and converted into a total behavioral problems score (T-score, with mean: 50, SD: 10). Cronbach's alpha was 0.94.

2.2.1.3. Contextual family factors.
The Family Functioning Questionnaire (VGFO) contains 28 statements about the parent, the family, and the situation in which the family finds itself (e.g., 'Your family usually eats at regular times' [23]. The parent is asked to answer the questions on a 4-point scale from 1 'not true' to 4 'very true'. The VGFO gives a total family functioning score (Cronbach's alpha: 0.88 for mothers and 0.90 for fathers) and five subscale scores: basic care, parenting, social network, youth experience, and marital relationship. Raw scores are summed and converted to T-scores (mean: 50, SD: 10). Lower scores indicate more problems.

2.2.1.4. Global family factors.
The Life Events Questionnaire (VMG) was used to measure family life events [19]. It consists of 15 common life events (e.g., birth, death, disease, unemployment, and divorce). Mothers were asked whether these life events had occurred and if this was a positive or negative experience for the child. The total negative experience event score was used within the analyses. We used maternal educational level as a proxy for SES. Family type – one or two parent families – was used as a proxy for marital status, with married, living together, or registered partnership as two-parent families, and divorced, widow, or single parent as one-parent families. Family size was the number of siblings within the family.

2.2.2. Maternal epilepsy

We measured epilepsy severity as a composite variable with total scores between 1 and 9, based on seizure type (1–3), seizure frequency (0–3), and number of AED used (0–3) [5,24]. Mothers were asked, at the time of the study period, to answer questions about the activity of their epilepsy over the past twelve months. For seizure type, generalized tonic–clonic seizures were scored 3, focal seizures 2, and absences 1. Seizure frequency was scored 3 if the mother had weekly or daily seizures, 2 if the mother had monthly seizures, 1 if the mother had seizures once or twice per year, and 0 if no seizures had occurred during the previous year. The number of AEDs was scored 0 when no medication was used, 1 for monotherapy, 2 for polytherapy with two AEDs, and 3 for polytherapy with three or more AEDs. The number and type of AEDs used by the mother at the time of the current study could be different from when she was pregnant from the child under current investigation. Scores were then summed, with a scoring between 1 and 5 indicating low epilepsy severity and scores ≥6 indicating high epilepsy severity.

An adapted version of 'Impact of Pediatric Epilepsy on the Family' (IPES) [25] was used to measure impact of epilepsy on the mother and the family. The conventional IPES contains questions about the impact of child epilepsy, but we adapted this to impact of maternal epilepsy on the family. We therefore adjusted some items, for example, instead of impact of epilepsy on school, we asked about impact of epilepsy on work and education. Mothers were asked to answer 11 questions (e.g., impact on general health, relationship with child(ren) or work and education) on a 4-point severity scale with 0 'not at all' to 3 'a lot'. For each item, the question was 'To what extent did your epilepsy affect your normal daily (family) life in the past three months?'. The higher the score, the higher is the impact of maternal epilepsy with a maximum score of 33 (range: 0–33). For mothers who thought that one or more of the items was not applicable (i.e., had no spouse or had only one child), the total score was based on only the items answered. Cronbach's alpha in our sample was 0.95.

2.2.3. Child behavior

Parents completed the Child Behavior Checklist (CBCL) to measure child behavioral problems [26]. The CBCL/6-18 is a well-known validated and reliable standardized indicator, containing 118 items of problem behavior. The parent is asked to answer each question with 0 'not true', 1 'somewhat or sometimes true', or 2 'very true or often true'. Raw scores are summed and converted to T-scores (standardized for age and gender, with T-scores having a mean of 50 and SD of 10). For this study, we used the two broad band scales of the CBCL: internalizing problems and externalizing problems. Internalizing problems consist of anxious and depressed behavior and somatic complaints. Externalizing problems include delinquent and aggressive behavior. Cronbach's alpha for internalizing problems was 0.82 (mothers) and 0.91 (fathers) and for externalizing problems, 0.85 (mothers) and 0.89 (fathers).

2.3. Statistical analyses

Data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) 24. Descriptive analyses were performed to describe our sample and to examine the nature and severity of family factors. The percentages of borderline and clinical scores within our sample were examined. Subsequently, we compared the scores of mothers with epilepsy on the VSOG, OBVL, and VGFO, with two sets of Dutch population norms based on information from the validated questionnaires [16,19,23] (Binomial Proportion Test). The norm population consisted of mothers from the general population in the Netherlands, and the clinical population consisted of mothers of children with psychiatric problems revered to mental health services in the Netherlands [19]. Pearson correlations were used to examine relationships between child behavioral problems, maternal epilepsy, and proximal, distal, contextual, and global family factors. With hierarchical multilevel regression analysis, the contribution of the different epilepsy-related and distinct family factors was subsequently investigated (test of hypotheses 1 and 2). As we included both mother and father reports of child behavior, we conducted multilevel regression analyses to account for within family dependencies. Including both parents provides a more complete perspective on child behavior and a larger sample size results in more statistical power in hypothesis testing. By estimating both between-family variance and within-family variance, we accounted for dependencies between father and mother reports. The analyses were performed in a hierarchical way, in six consecutive steps (0–5), with child behavior as the outcome variable (Fig. 2). In the first step (Step 0), we included an indicator variable 'mother versus father' to represent possible differences between parents on child behavior. Subsequently, maternal epilepsy (Step 1), global (Step 2), contextual (Step 3), distal (Step 4), and proximal family factors (Step 5) were added sequentially. The last step (Step 5) controls for all factors included in the model. For each step, chi-square difference tests indicate whether the addition of a set of factors improved the fit significantly.

To test for mediation, the following conditions had to be met: there is a statistically significant association between (I) maternal epilepsy and child behavioral problems (internalizing or externalizing problems), (II) maternal epilepsy and the distinct family factors, and (III) the distinct family factors and internalizing and externalizing problems. (IV) If family factors are controlled for (Steps 2, 3, 4, 5) and the former contribution of maternal epilepsy decreases or becomes nonsignificant, this indicates that the effects of maternal epilepsy are (partially) mediated by the distinct family factors.

A summary of the steps is described and shown in Tables 5 and 6, with the chi-square test of the significance of each addition. If the contribution of a factor was significant, but this effect became nonsignificant after controlling for the effect of the factor that was added last to the model, this may be an indication of a mediation effect. To investigate which family factor specifically mediates the effect of maternal epilepsy on child behavioral problems, the intermediate steps were examined
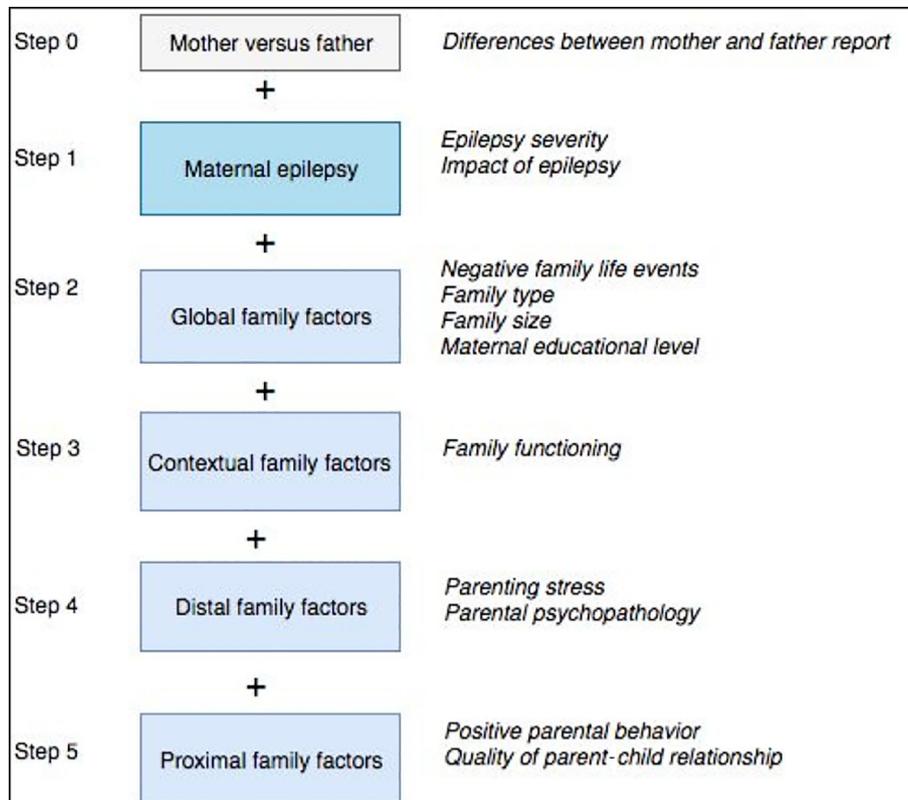

Fig. 2. Steps in hierarchical multilevel regression analyses predicting child internalizing and externalizing problems.

(test of hypothesis 3). The intermediate steps also provide information on whether the more proximal family factors mediate the effects of the more distal family factors (test of hypothesis 4).

Analyses were conducted with all available scores on the outcome variables, without imputation for missing data on behavioral outcome variables. One mother, with two children, did not complete the IPES and the ASR. In addition, a number of mothers (20) had chosen 'not applicable' for all items of the IPES, which generated missing data. Some mothers did not indicate on the VMG whether a life event was positive or negative, or indicated it was neutral. In order to retain these mothers in the multilevel analyses, we conducted missing value analyses for IPES total score, ASR total behavioral problems, and negative life event score. We used expectation–maximization (EM) for the explanatory variables, to ensure that all mothers and fathers who provided child reports were retained in the analysis [27].

3. Results

3.1. Study population

Between January 2015 and March 2018, the questionnaires were completed for 175 children from 151 families (one set of twins and 23 sibling pairs) (Fig. 3). For most children (134), both parents completed the questionnaires. Children were prenatally exposed to monotherapy valproate (VPA; n = 24), carbamazepine (CBZ; n = 35), lamotrigine (LTG; n = 86), or levetiracetam (LEV; n = 30).

The majority of children (91%) lived in two-parent families (Table 1). About 58% of the mothers had a higher educational level.

The mean epilepsy severity score was 3.9 (SD: 1.3); 89% of mothers had low epilepsy severity. The impact of maternal epilepsy was generally low, with a mean score of 2.2 (SD: 4.3, range: 0–24).

3.2. Nature and severity of family factors

To examine whether families with a mother with epilepsy experience more family problems, the nature and severity of family factors was investigated. Overall, parents reported few problems on the distinct family factors (Table 2). Descriptive analyses showed average scores for mothers and fathers on quality of parent–child relationship; positive parental behavior, rewarding, rules, and (hard) punishing; the subscales of parenting stress and family functioning. Most parents seemed to experience parenting positively.

Some parents, however, experienced problems with parenting and family functioning and had scores within the borderline range or above the clinical cutoff (Table 3). In comparison with Dutch population norms, mothers with epilepsy showed significantly more parenting stress (OBVL, total parenting stress: z-score: −4.4, p = <.001). They had higher proportions of clinical scores on the subscales of depressive mood, parental role restriction, and physical health problems when compared with mothers from the general population (Table 3). No differences were found for parenting problems or parent–child relationship problems (OBVL). Regarding family functioning, mothers showed significantly more problems with parenting compared with population norms (VGFO, parenting: z-score: −2.7 p = .007). On other subscales of family functioning, there were no significant differences. Concerning parental behavior (VSOG), mothers had significantly less problems
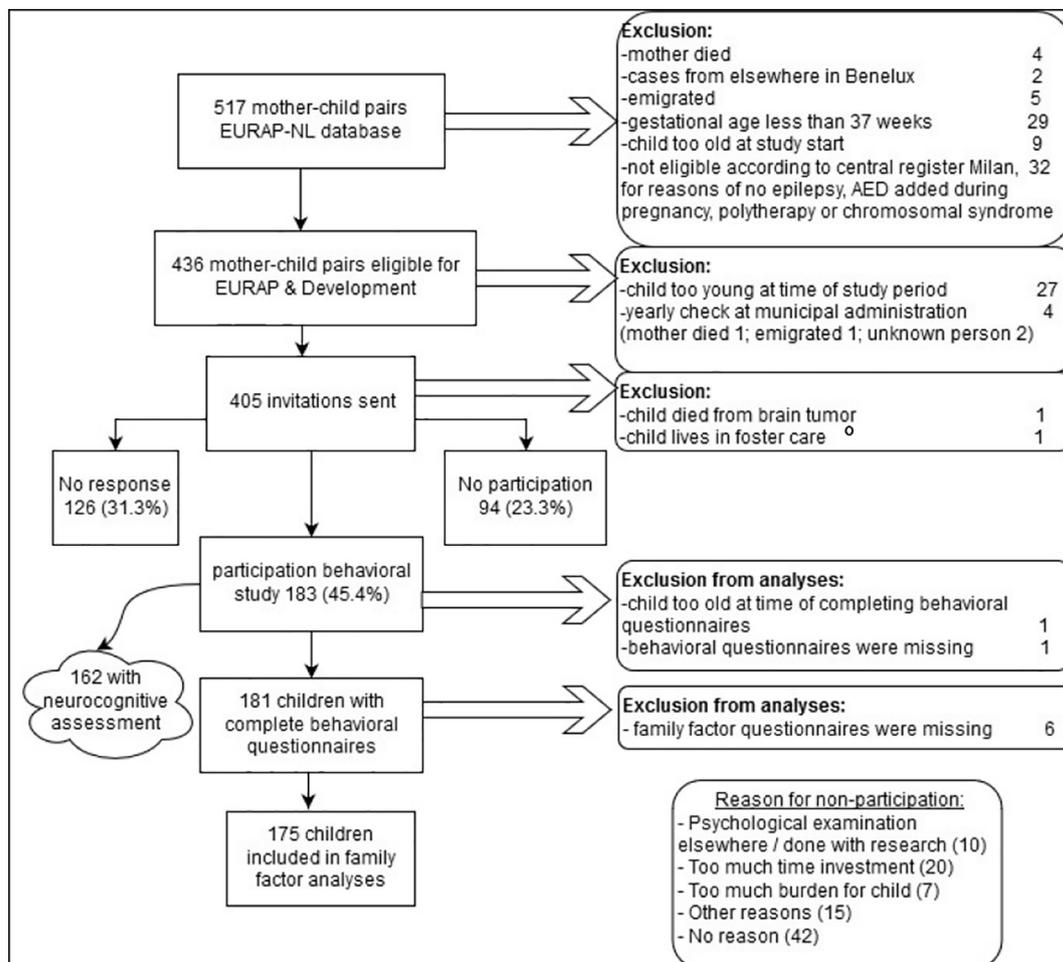

Fig. 3. Flowchart Dutch EURAP & Development study — family factor domain.

Table 1
Group demographic information and epilepsy-related factors.

	All children
Sample size	175
Child sex, n (%) male	92 (53%)
Child age, months, mean (SD)	81 (7)
Maternal age, years, mean (SD)	38 (4)
Paternal age, mean (SD)	41 (5)
Maternal education, n (%) higher education[a]	87 (58%)
Paternal education, n (%), higher education[a]	83 (55%)
Family type, n (%) two parent families	159 (91%)
Family size (number of siblings), mean (SD)	1.2 (0.8)
Maternal behavioral problems, mean (SD)[a,b]	50.0 (9.2)
Paternal behavioral problems, mean (SD)[a,c]	45.6 (9.7)
Maternal seizure type, n (%)	
Generalized tonic–clonic seizures	102 (58%)
Focal seizures	38 (22%)
Absences	35 (20%)
Maternal seizure frequency past 12 months, n (%)	
None	127 (73%)
Once or twice per year	20 (11%)
Monthly	13 (7%)
Weekly or daily	15 (9%)
Number of maternal AED use	
None	15 (9%)
Monotherapy	138 (79%)
Polytherapy with two AEDs	22 (13%)
Polytherapy with three or more AEDs	0 (0%)
Epilepsy severity, total score, mean (SD)	3.9 (1.3)
Impact of epilepsy, mean (SD)[d]	2.2 (4.3)

Note.

[a] 151 mothers/fathers.

[b] Maternal behavioral problems measured with the Adult Self report (ASR, T-score with mean of 50), missing for one mother.

[c] Paternal behavioral problems was missing for 32 fathers.

[d] Impact of maternal epilepsy (IPES) was missing for one mother with two children. In addition, for 20 children, the IPES score was missing, because mothers had chosen 'not applicable' on all items.

Table 2
Means and standard deviations of distinct family factors.

	All children (175)	
	M (SD)	
	Mothers	Fathers
Sample size	173	138
PACHIQ-R[a]		
Total score	3.2 (1.5)	3.5 (1.4)
Conflict resolution	3.2 (1.5)	3.3 (1.4)
Acceptance	3.6 (1.2)	3.8 (1.3)
VSOG[b]		
Positive parental behavior	48.8 (9.3)	43.9 (12.0)
Rules	51.3 (11.4)	48.4 (11.3)
Punishing	52.2 (10.9)	51.3 (9.6)
Rewarding	51.6 (9.6)	54.4 (9.0)
Hard punishing	52.1 (4.9)	52.3 (5.3)
OBVL		
Total parenting stress	53.8 (11.0)	51.3 (10.4)
Parent–child relationship	53.5 (8.4)	52.7 (8.1)
Parenting problems	52.5 (10.2)	51.5 (9.6)
Depressive mood	55.6 (8.8)	54.0 (8.0)
Parental role restriction	55.3 (10.3)	54.4 (9.0)
Physical health problems	58.0 (8.1)	54.3 (7.4)
VGFO		
Total family functioning	49.4 (9.3)	48.6 (9.8)
Basic care	50.7 (8.9)	49.6 (9.6)
Parenting	50.0 (11.8)	47.7 (11.8)
Social network	52.8 (12.2)	50.1 (12.3)
Youth experience	53.7 (11.0)	54.7 (11.3)
Marital relationship[c]	51.3 (10.4)	52.1 (10.4)

Note. PACHIQ-R = Parent Child Interaction Questionnaire – Revised. Quintile scores, with higher scores indicating a more positive relationship quality [21]. VSOG = Parenting Behavior Questionnaire — T-scores, with lower scores indicating more problems, except for hard punishing [19]. OBVL = Parenting Stress Questionnaire — T-scores, higher scores indicating more problems [16]. VGFO = Family Functioning Questionnaire — T-score, lower scores indicating more problems [23].

[a] One mother and one father missing.

[b] One father missing.

[c] Only completed by married or cohabiting parents, therefore, missing for 14 mothers.

with punishing (disciplining) but significantly higher scores on hard punishment (physical punishment) compared with the population norm (Table 3).

When compared with the clinical population, however, fewer mothers with epilepsy had parenting stress and problems with family functioning and parental behavior. The nature and degree of problematic family factors of mothers with epilepsy seems to fall in between the general (norm) and the clinical population.

3.3. Relationships between child behavior, maternal epilepsy, and family factors

Epilepsy severity was significantly associated with impact of epilepsy and parental psychopathology but was not related to other distinct family factors or child behavioral problems (Table 4). Impact of epilepsy was significantly associated with most family factors (quality of parent–child relationship, parenting stress, parental psychopathology, and family functioning) and with child internalizing problems but not with externalizing problems. Significant associations were found between almost all family factors and internalizing and externalizing problems. Positive parental behavior was associated with externalizing problems only: more positive parental behavior was related to lower levels of externalizing problems. A lower quality of parent–child relationship was associated with more internalizing and externalizing problems. More parenting stress was significantly related with both higher levels of internalizing and externalizing problems. Parental psychopathology was also significantly associated with internalizing and externalizing problems. Family functioning was negatively associated with child behavioral problems. Finally, having experienced negative family life events was associated with higher levels of internalizing and externalizing problems.

The conditions for mediation were partly met. For maternal epilepsy, only impact of epilepsy was significantly associated with child internalizing problems (I) and distinct family factors (II). Family factors were significantly associated with internalizing problems (III). Thus, for internalizing problems, mediation could be examined. For externalizing problems, mediation of epilepsy-related factors could not be tested, because there was no significant association found between maternal epilepsy and externalizing problems (I). However, by examining the intermediate steps, it could still be investigated whether the more proximal family factors mediate the more distal family factors.

As expected, family factors were all interrelated. Strong associations were found between two proximal family factors: positive parental behavior and quality of parent–child relationship. Parenting stress was strongly negatively related to quality of parent–child relationship and family functioning. Other associations among family factors varied between 0.17 and 0.52, suggesting that, although related, each of these factors measured different aspects of the family.

3.4. Hierarchical multilevel regression analyses

The contributions of maternal epilepsy and distinct family factors to child internalizing and externalizing problems were investigated with hierarchical multilevel regression analyses (Tables 5 and 6). For internalizing problems, Table 5 shows that consecutively, maternal epilepsy, global, contextual, and distal family factors each had a significant additional effect (Table 5, chi-square test). Adding proximal family factors to the final model, however, did not significantly add to the previous factors. In accordance with correlation analyses, maternal epilepsy did not significantly contribute to externalizing problems while all other

Table 3
Percentages of parents within the borderline range and above the clinical cutoff on distinct family factors — including a comparison of mothers with epilepsy with mothers from a general (norm) and clinical population.

	All children (175)											
	Mother/Father							Mother/Father				
	Comparison norm population							Comparison clinical population				
	Borderline				Clinical			Borderline				Clinical
PACHIQ-R[a]												
Total score	17.1/12.2				16.0/9.4			6.1/7.2				0.6/2.2
Conflict resolution	9.9/17.1				22.7/8.8			7.2/6.6				1.7/2.2
Acceptance	13.3/9.9				5.5/6.6			3.9/4.4				1.7/2.2

			Proportion mothers in problem range[d]		Norm population				Clinical population			
	Borderline	Clinical	N	Proportion	N	Proportion	z-score	p value	N	Proportion	z-score	p value
VSOG[b]												
Positive parental behavior	1.7/6.1	3.3/12.2	173	0.05	944	0.065	−0.7483	.453	3291	0.20	−4.8775	<.001***
Rules	8.8/8.8	1.7/2.2	173	0.105	944	0.07	1.6026	.110	3291	0.09	0.6695	.503
Punishing	1.7/1.1	2.8/2.2	173	0.045	944	0.09	−2.9172	.004**	3291	0.17	−5.7184	<.001***
Rewarding	5.5/1.1	1.1/0.6	173	0.066	944	0.12	−1.0335	.303	3291	0.23	−3.5938	.0003***
Hard punishing	3.3/1.7	2.2/2.2	173	0.055	944	0.02	2.6887	.007**	3291	0.07	−0.7575	.447
OBVL												
Total parenting stress	11.6/8.3	20.4/10.5	173	0.320	1428	0.180	−4.3883	<.001***	2635	0.570	6.409	<.001***
Parent–child relationship	8.8/5.5	3.3/2.2	173	0.121	1428	0.120	−0.0382	.968	2635	0.370	6.6315	<.001***
Parenting problems	6.6/5.5	5.0/1.7	173	0.116	1428	0.090	−1.1131	.267	2635	0.430	8.1324	<.001***
Depressive mood	13.3/6.1	5.5/3.3	173	0.188	1428	0.090	−4.0473	<.001***	2635	0.370	4.8347	<.001***
Parental role restriction	9.9/7.7	9.4/4.4	173	0.193	1428	0.100	−3.6915	.0002***	2635	0.310	3.2445	.001***
Physical health problems	7.7/5.5	12.7/4.4	173	0.204	1428	0.080	−5.2934	<.001***	2635	0.340	3.6806	.0002***
VGFO												
Total family functioning	8.3/8.8	8.8/8.8	173	0.171	1426	0.160	−0.3716	.711	1801	0.480	7.7988	<.001***
Basic care	2.2/4.4	2.2/1.1	173	0.044	1426	0.05	0.3441	.727	1801	0.130	3.2959	.001***
Parenting	3.9/5.5	6.1/5.5	173	0.10	1426	0.05	−2.7147	.007**	1801	0.310	5.8049	<.001***
Social network	3.9/5.0	3.3/3.3	173	0.072	1426	0.06	−0.6214	.535	1801	0.270	5.7247	<.001***
Youth experience	3.9/3.3	0/0.6	173	0.039	1426	0.07	1.5439	.124	1801	0.190	4.973	<.001***
Marital relationship[c]	1.7/1.1	3.3/1.7	159	0.05	1280	0.05	0.0	1.0	1176	0.250	5.9812	<.001***

PACHIQ-R = Parent Child Interaction Questionnaire — Revised [21], consisting of a comparison of a norm population with families from the general population and a clinical population with families who have been revered to mental health services in the Netherlands, with Quintile score: 2 = borderline; 1 = clinical. VSOG = Parenting Behavior Questionnaire [19], with cutoff scores for T-score: 31–35 = borderline; ≤30 = clinical, except for hard punishing with T-score: 63–66 = borderline; ≥67 = clinical. OBVL = Parenting Stress Questionnaire [16], with T-score: 60–31 = borderline; ≥64 = clinical, for the total score of parenting stress, and T-score: 65–69 = borderline; ≥70 = clinical for subscale scores. VGFO = Family functioning questionnaire [23], with T-score: 37–40 = borderline; ≤36 = clinical, for total score of family functioning, and T-score: 31–35 = borderline; ≤ 30 = clinical for subscale scores.

[a] Missing for one mother and one father.
[b] One father missing.
[c] Only completed by married or cohabiting parents, therefore missing for 14 mothers.
[d] Problem range is borderline and clinical range combined [16]. Norm population: consisting of mothers from the general population of the Netherlands. Clinical population: consist of mothers of children with psychiatric problems revered to mental health services in the Netherlands.
** $p < .01$.
*** $p < .001$.

successive family factors contributed significantly in the subsequent models (Table 6, chi-square test).

Table 5 gives a summary of the regression coefficients for all explanatory variables in the hierarchical multilevel regression model for internalizing problems. From the comparison between the step by step results in Table 5, we learn that the effect of maternal epilepsy on internalizing problems (significant in Step 1) is fully mediated by the family factors that are added later, as in the final model (Step 5), the effect of maternal epilepsy is no longer significant. The added value of maternal epilepsy is at first significant (Table 5, chi-square: 7.962, $p = .02$), with a significant contribution of impact of epilepsy, but after controlling for distinct family factors, this influence becomes nonsignificant (Table 5, epilepsy severity, $p = .105$; impact of epilepsy, $p = .221$). The intermediate steps show that with the addition of distal family factors (Step 4), the previous significant contribution of impact of epilepsy (Step 1) and other family factors (Step 2, 3) became nonsignificant, except for family size (larger family associated with more internalizing problems). The distal family factors with parenting stress and parental psychopathology both significantly contributed to internalizing problems and showed a mediating role for factors that were earlier added in the model: impact of epilepsy, negative family life events, and family functioning.

For externalizing problems (Table 6), the intermediate steps showed a significant contribution of global family factors: negative life events and maternal educational level (Step 2) significantly contributed to externalizing problems. Adding contextual family factors in Step 3, the contribution of family functioning was significant while negative family life events were no longer significant. In adding distal family factors (Step 4), the contribution of family functioning became nonsignificant. Parenting stress and parental psychopathology were both significant and showed a mediating effect for previous family factors. The added value of the final step with proximal family factors (step 5) was also significant. Maternal education, parenting stress, parental psychopathology, positive parental behavior, and quality of parent–child interaction were all found to be significant contributors to externalizing problems, with the factor most proximal to the child (quality of parent–child interaction) showing the largest effect (largest regression coefficient). Distal and proximal family factors showed a mediating role for the global and contextual family factors.

In this last model (Step 5), epilepsy severity also became, against expectations, significant and seems to act as a suppressor (Table 6). Thus, epilepsy severity was not significant in the previous steps but after adding family factors, it contributed with a significant effect to the model. This suppression effect can be explained from a nonsignificant

Table 4

Means, standard deviations, and correlations between child behavioral problems, maternal epilepsy, proximal, distal, contextual, and global family factors.

Variable	M	SD	1	2	3	4	5	6	7	8	9	10
1. Internalizing problems[a]	54.1	9.9	–									
2. Externalizing problems[a]	53.4	10.2	0.59**	–								
Maternal epilepsy												
3. Epilepsy severity[b]	3.9	1.3	0.01	−0.04	–							
4. Impact of epilepsy[c]	2.3	4.1	0.19*	0.10	0.28**	–						
Proximal family factors												
5. Positive parental behavior[d]	46.6	10.8	−0.06	−0.18**	−0.06	−0.11	–					
6. Quality of parent–child relationship[e]	90.1	6.5	−0.26**	−0.52**	−0.09	−0.15**	0.60**	–				
Distal family factors												
7. Parenting stress[f]	52.7	10.8	0.35**	0.56**	0.04	0.20**	−0.39**	−0.61**	–			
8. Parental psychopathology[g]	49.9	9.4	0.38**	0.40**	0.23**	0.30**	−0.22**	−0.27**	0.39**	–		
Contextual family factors												
9. Family functioning[h]	49.0	9.5	−0.29**	−0.43**	−0.08	−0.16**	0.44**	0.52**	−0.70**	−0.40**	–	
Global family factors												
10. Negative family life events[i]	0.8	0.9	0.14*	0.18*	0.10	0.04	−0.17**	−0.20**	0.20**	0.26**	−0.21**	–

[a] Child Behavior Checklist (CBCL 6-18) [26].
[b] Composite variable based on seizure type, frequency, and number of antiepileptic drug used [5,24].
[c] Adapted version of the Impact of Pediatric Epilepsy on the Family [18,25].
[d] Subscale from the Parenting Behavior Questionnaire (VSOG) [19].
[e] Total score of Parent–Child Interaction Questionnaire-Revised (PACHIQ-R) [20,21].
[f] Total score of the Parenting Stress Questionnaire (OBVL) [16].
[g] Maternal behavioral problems assessed with the Adult Self Report (ASR) [22].
[h] Total score of the Family Functioning Questionnaire (VGFO) [23].
[i] Total negative experience event score of the Life Events Questionnaire (VMG) [19].
* $p < .05$.
** $p < .01$.

zero-order correlation between epilepsy severity and externalizing problems, while epilepsy severity was significantly associated with parental psychopathology (measured as maternal behavioral problems). Parental psychopathology was also significantly related to child externalizing problems (Table 4). Therefore, in the last model, when all factors are considered, these factors may reinforce each other, resulting in a significant effect for epilepsy severity (Table 6, Step 5). This indicates that mothers with severe epilepsy are more likely to experience behavioral problems that affect child externalizing problems.

4. Discussion

This study examined whether mothers with epilepsy experience more family problems and investigated the possible mediating role of distinct family factors in the relationship between maternal epilepsy and child behavioral problems. Prenatal exposure to AEDs may sometimes directly impact child psychopathology. As children of mothers with epilepsy bear multiple risks, child psychopathology may as well be impacted by other factors, such as having a mother with a chronic condition. With this study, we examined the contribution of epilepsy-related factors and distinct family factors to child behavioral problems. We also examined whether proximal family factors would mediate the effects of epilepsy-related factors and the more distal family factors to child behavioral problems.

We found that mothers with epilepsy were more likely to show parenting stress and problems with parenting than mothers from the general population. Compared with a clinical population – mothers of children with psychiatric problems – they were less likely to have problems. This suggests that mothers with epilepsy have moderate problems with distinct family factors, with some mothers experiencing more problems than others.

The impact of maternal epilepsy was associated with most family factors while the more objective measure of maternal epilepsy, epilepsy severity, was not significantly related to as many factors. Epilepsy severity and impact of epilepsy were, however, significantly related to each other. They were also both significantly correlated with parental psychopathology, measured as maternal behavioral problems. Impact of maternal epilepsy was associated with child internalizing problems only. In a pediatric study, epilepsy-related factors were not associated with child behavior while family factors were strong predictors of child psychopathology [5]. We found that a higher score on impact of maternal epilepsy was related to more parenting stress, lower family functioning, and negative quality of parent–child relationship, suggesting that the burden of epilepsy also affects family factors and vice versa.

Family factors were significantly associated with child behavioral problems. In a previous study, we showed that a high proportion of children of mothers with epilepsy, prenatally exposed to AED, had behavioral problems [2]. Results of the current study showed that distinct family factors have an additional contribution on child internalizing and externalizing problems and have a mediating role in the relationship between maternal epilepsy and child internalizing problems. Distal family factors, consisting of parenting stress and parental behavioral problems, were each found to contribute the most and were shown to mediate the effects of impact of epilepsy, global (negative family life events), and contextual family factors (family functioning) on child internalizing problems.

Parenting stress was conceptualized as depressive mood and physical health problems. Depression, health- and behavioral problems are common in women with epilepsy [28]. These (psychiatric) comorbidities may be the result of an interaction between genetic and epilepsy-related factors, or of possible drug side effects [7,8,28]. Child behavior may, in itself, also contribute to parental behavioral problems. This study shows that parenting stress and maternal mental health problems are important in the behavioral development of children of mothers with epilepsy. It seems that mothers with epilepsy with comorbid behavioral problems are more vulnerable, and for their children, this is associated with more problem behavior. The effect of the impact of epilepsy on internalizing problems proceeds through parenting stress and maternal behavioral problems. Therefore, maternal mental health problems, including impact of epilepsy and parenting stress, need to be treated in relation to the child and the family, as having a chronic medical condition can affect family life and the behavioral development of children [6].

Table 5
Summary of hierarchical multilevel regression analysis — internalizing problems.

Internalizing problems	Step 0			Step 1			Step 2			Step 3			Step 4			Step 5		
	B	CI	p	B	CI	p	B	CI	p	B	CI	p	B	CI	p	B	CI	p
Intercept	55.3	53.7 to 56.8	<.001	54.7	50.2 to 59.3	<.001	59.4	51.1 to 67.6	<.001	72.6	62.7 to 82.5	<.001	45.5	29.6 to 61.4	<.001	53.4	29.3 to 77.4	<.001
Mother vs father	−2.5	−3.9 to −1.1	.001	−2.5	−3.9 to −1.1	.001	−2.5	−3.9 to −1.0	.001	−2.8	−4.2 to −1.4	<.001	−2.3	−3.7 to −0.8	.002	−1.9	−3.4 to −0.4	.013
Maternal epilepsy																		
Epilepsy severity				−0.2	−1.3 to 1.0	.785	−0.4	−1.6 to 0.7	.445	−0.5	−1.6 to 0.6	.362	−0.8	−1.9 to 0.2	.132	−0.9	−1.9 to 0.2	.105
Impact of epilepsy				0.5	0.1 to 0.8	.006	0.4	0.1 to 0.8	.009	0.4	0.04 to 0.7	.027	0.2	−0.1 to 0.5	.219	0.2	−0.1 to 0.5	.221
Global family factors																		
Negative family life events							1.7	0.2 to 3.3	.028	1.3	−0.2 to 2.8	.101	0.7	−0.8 to 2.1	.354	0.7	−0.7 to 2.2	.310
Family type							−1.3	−6.4 to 3.7	.603	−2.0	−6.8 to 2.9	.426	−1.9	−6.5 to 2.8	.428	−2.1	−6.7 to 2.5	.364
Family size							−1.9	−3.7 to −0.2	.032	−1.7	−3.4 to −0.1	.043	−1.8	−3.4 to −0.2	.025	−1.8	−3.3 to −0.2	.028
Maternal education							−1.9	−4.7 to 0.9	.180	−1.7	−4.4 to 1.0	.221	−0.9	−3.5 to 1.6	.474	−0.8	−3.3 to 1.7	.521
Contextual family factors																		
Family functioning										−0.2	−0.4 to −0.1	<.001	−0.1	−0.2 to 0.1	.267	−0.1	−0.2 to 0.05	.186
Distal family factors																		
Parenting stress													0.2	0.03 to 0.3	.014	0.1	0.01 to 0.3	.036
Parental psychopathology													0.2	0.1 to 0.4	.001	0.3	0.1 to 0.4	.001
Proximal family factors																		
Positive parental behavior																0.1	−0.01 to 0.2	.064
Quality of parent–child relationship																−0.1	−0.3 to 0.1	.222
Chi-square difference tests				χ2(df 2) = 7.962, p = .02*			χ2(df 4) = 9.943, p = .04*			χ2 (df 1) = 18.46, p = <.001*****			χ2 (df 2) = 17.524, p = <.001*****			χ2 (df 2) = 3.587, p = .166		

B = unstandardized coefficients, CI = Confidence, χ² = chi-square value, df = number of parameters.
* $p < .05$.
** $p < .01$.
*** $p \leq .001$.

Table 6
Summary of hierarchical multilevel regression analysis – Externalizing problems.

Externalizing problems	Step 0			Step 1			Step 2			Step 3			Step 4			Step 5		
	B	CI	p	B	CI	p	B	CI	p	B	CI	p	B	CI	p	B	CI	p
Intercept	54.1	52.5 to 55.7	<.001	55.4	50.4 to 60.3	<.001	52.6	43.9 to 61.3	<.001	71.9	62.1 to 81.6	<.001	27.2	12.3 to 42.1	<.001	73.9	51.9 to 95.8	<.001
Mother vs father	−0.9	−2.3 to 0.6	.235	−2.5	−2.3 to 0.6	.240	−0.7	−2.2 to 0.7	.308	−1.2	−2.7 to 0.2	.087	−0.2	−1.6 to 1.3	.817	0.1	−1.3 to 1.6	.854
Maternal epilepsy																		
Epilepsy severity				−0.5	−1.7 to 0.7	.416	−0.4	−1.5 to 0.9	.554	−0.5	−1.6 to 0.6	.381	−0.8	−1.7 to 0.2	.111	−0.9	−1.8 to −0.1	.035
Impact of epilepsy				0.3	−0.1 to 0.7	.095	0.3	−0.1 to 0.6	.099	0.2	−0.1 to 0.5	.273	−0.1	−0.3 to 0.2	.621	−0.1	−0.4 to 0.2	.434
Global family factors																		
Negative family life events							1.8	0.2 to 3.4	.026	1.2	−0.2 to 2.7	.101	0.5	−0.8 to 1.8	.462	0.5	−0.7 to 1.7	.416
Family type							2.3	−2.9 to 7.6	.382	1.3	−3.4 to 6.1	.584	1.6	−2.5 to 5.8	.444	0.7	−3.1 to 4.6	.710
Family size							0.3	−1.5 to 2.2	.710	0.5	−1.1 to 2.2	.524	0.2	−1.3 to 1.6	.834	0.1	−1.2 to 1.4	.877
Maternal education							−3.9	−6.8 to −0.9	.011	−3.6	−6.2 to −1.0	.008	−2.7	−4.9 to −0.4	.023	−2.3	−4.4 to −0.2	.035
Contextual family factors																		
Family functioning										−0.4	−0.5 to −0.2	<.001	−0.1	−0.2 to 0.1	.434	−0.05	−0.2 to 0.1	.485
Distal family factors																		
Parenting stress													0.3	0.2 to 0.5	<.001	0.2	0.1 to 0.4	<.001
Parental psychopathology													0.3	0.1 to 0.4	<.001	0.3	0.2 to 0.4	<.001
Proximal family factors																		
Positive parental behavior																0.2	0.1 to 0.3	<.001
Quality of parent–child relationship																−0.5	−0.7 to −0.4	<.001
Chi-square difference tests				χ2 (df 2) = 2.894, p = .235			χ2 (df 4) = 12.572, p = .01**			χ2 (df 1) = 35.657, p = <.001*****			χ2 (df 2) = 48.284, p = <.001*****			χ2 (df 2) = 33.796, p = <.001*****		

B = unstandardized coefficients, CI = Confidence, χ² = chi-square value, df = number of parameters.
* $p < .05$.
** $p < .01$.
*** $p \leq .001$.

Proximal family factors did not add a significant effect on internalizing problems, after other family factors were controlled for. This might be explained by the interrelations between family factors [16], or the possibility that all variance was already explained by the previous factors. For externalizing problems, a strong effect of contextual, distal, and proximal family factors was found, but not for maternal epilepsy. From the distinct family factors, proximal family factors contributed most to externalizing problems. In addition, distal and proximal family factors appeared to mediate the effects for the global (negative family life events) and contextual family factors (family functioning).

These results offer specific targets for interventions, for the mother herself [29,30], for families with a mother with epilepsy, or their children. With internalizing problems, interventions should target at decreasing parenting stress and parental behavioral problems, such as mindful parenting [31–33]. Intervening with parenting stress may buffer the child against the effects of the impact of maternal epilepsy. For externalizing problems, interventions should target on factors closest related to the child, such as amelioration of the parent–child interaction (e.g., with haptotherapy for children) [34].

As far as we know, this is the first study that has extensively studied the nature and severity of distinct family factors in a large group of mothers with epilepsy and investigated the possible mediating role of distinct family factors in the behavioral development of children of mothers with epilepsy. Other strengths of this study are the use of standardized measures, mother and father reports, and inclusion of families across the Netherlands.

There are also some limitations. Pregnancy registers reach only some of the women with epilepsy. This may limit the generalization of the results to the population of mothers with epilepsy. Generalization may also be limited because of the relatively high educational level of mothers. The majority of mothers had low epilepsy severity whereas in families with a mother with severe epilepsy, the impact of the burden of epilepsy on the family and the child is likely to be even greater.

We measured epilepsy severity as composite variable [5,24]. This may not give a reliable representation of the mother's epilepsy. For example, it can be argued whether generalized tonic–clonic seizures are more severe or have more impact than absences. It is also possible that the effects of the different components are lost because of the composition variable. In additional analyses, we therefore added the three separate components (seizure type, seizure frequency, and number of AEDs) to the analysis, with similar results. It only showed that of the three components, seizure frequency had the largest impact on child behavior. However, the hierarchical multilevel regression analyses with the chi-square difference tests revealed no change in significances (not shown).

We used parent reports of behavioral problems and distinct family factors. This reflects parental perceptions of child behavioral problems, and adult and family functioning, but may have caused common-method variance. It is subjective and possibly biased by parents' perspective on maternal epilepsy or concerns about teratogenic effects of prenatal exposure. For future research, it is recommended to use multiple informants in order to gain more insight into the influence of family factors on the development of children of mothers with epilepsy.

It should also be noted that our analyses do not provide answers on causality. Associations may be bidirectional, with more parenting stress leading to more child behavioral problems, or the other way around. The development of children of mothers with epilepsy prenatally exposed to AEDs is a complex entity, where multiple factors are involved and which may have a direct or indirect effect, independently or in interaction with the teratogenic and genetic make-up of the child. Regardless of the direction of effects, our results show the importance of including family factors in research of children of mothers with epilepsy as they can have a contribution additional to the teratogenic risks of prenatal exposure to AEDs. Family factors, in particular distal and proximal family factors, can weaken or strengthen child development and may provide starting points for interventions [5,15].

This study contributes to the knowledge about the role of family factors, in a population of mothers with epilepsy, including maternal psychopathology, to child behavioral problems. For clinical practice, it is important to pay attention to family factors in children of mothers with epilepsy, as they can contribute to child development and parent–child relationship quality. This may ultimately increase the quality of life of mothers, their children, and their families.

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