ORIGINAL ARTICLE

Language impairment in children aged 5 and 8 years after antiepileptic drug exposure *in utero* – the Norwegian Mother and Child Cohort Study

E. S. N. Husebye[a,b], N. E. Gilhus[a,b], O. Spigset[c,d], A. K. Daltveit[e,f] and M. H. Bjørk[a,b]

[a]*Department of Clinical Medicine, University of Bergen, Bergen;* [b]*Department of Neurology, Haukeland University Hospital, Bergen;* [c]*Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway;* [d]*Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim;* [e]*Department of Global Public Health and Primary Care, University of Bergen, Bergen; and* [f]*Department of Health Registries, Norwegian Institute of Public Health, Bergen, Norway*

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Background and purpose: The purpose was to examine the consequences of antiepileptic drug (AED) exposure during pregnancy on language abilities in children aged 5 and 8 years of mothers with epilepsy.

Methods: The study population included children of mothers with and without epilepsy enrolled in the Norwegian Mother and Child Cohort Study 1999–2008. Mothers prospectively provided information on epilepsy diagnosis, AED use during pregnancy and the child's language abilities at age 5 and 8 years, in questionnaires with validated language screening tools. AED concentrations in gestation week 17–19 and in the umbilical cord were measured.

Results: The study population included 346 AED-exposed and 388 AED-unexposed children of mothers with epilepsy, and 113 674 children of mothers without epilepsy. Mothers of 117 and 121 AED-exposed children responded to the questionnaires at age 5 and 8 years, respectively. For AED-exposed children, the adjusted odds ratio for language impairment was 1.6 [confidence interval (CI) 1.1–2.5, $P = 0.03$] at age 5 years and 2.0 (CI 1.4–3.0, $P < 0.001$) at age 8 years, compared to children of mothers without epilepsy. Children exposed to carbamazepine monotherapy had a significantly increased risk of language impairment compared to control children at age 8 years (adjusted odds ratio 3.8, CI 1.6–9.0, $P = 0.002$). Higher maternal valproate concentrations correlated with language impairment at age 5 years. Periconceptional folic acid supplement use protected against AED-associated language impairment.

Conclusion: Foetal AED exposure *in utero* is associated with an increased risk of language impairment in children aged 5 and 8 years of mothers with epilepsy. Periconceptional folic acid use had a protective effect on AED-associated language impairment.

Introduction

Foetal antiepileptic drug (AED) exposure *in utero* is associated with adverse neurodevelopmental effects in infancy and early childhood in children of mothers with epilepsy, particularly after valproate exposure [1–3]. Such effects include low intelligence quotient (IQ), poor language abilities and an increased risk of behavioural disorders such as autism spectrum disorder and attention deficit and hyperactivity disorder [1,2]. Evidence on the long-term effects of foetal AED exposure on language abilities is emerging, but data are limited, particularly for newer AEDs such as lamotrigine, levetiracetam and topiramate [1,3]. After AED exposure *in utero*, verbal abilities and verbal IQ can be reduced in children aged 5–9 years, particularly

Correspondence: E. S. N. Husebye, Department of Clinical Medicine, University of Bergen, Jonas Lies veg 87, 5021 Bergen, Norway (tel.: 0047-467-88-489; fax 0047-55-97-27-61; e-mail: elisabeth.husebye@uib.no).

for valproate [4–8] and this reduction might be permanent [9]. Data regarding carbamazepine exposure and language performance are conflicting [1,2]. Few studies have examined the influence of AED concentrations during pregnancy on language abilities in older children. It has been shown previously that language impairment and risk of autistic traits at age 1.5 and 3 years depend on maternal plasma AED concentrations and folate status [10–12].

This study presents data from the epilepsy population in the Norwegian Mother and Child Cohort Study (MoBa) after 8 years of follow-up. The aim of the study was to examine the effect of foetal AED exposure and plasma AED concentrations during pregnancy on language abilities in children at age 5 and 8 years of mothers with epilepsy.

Material and methods

Study population

The study population consisted of children of mothers with and without epilepsy included in the MoBa. This is an ongoing, prospective, population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health and linked to the compulsory Medical Birth Registry of Norway (MBRN) [13]. The overall participation rate was 41%. The mothers answered questionnaires during week 17–19 (Q1) and week 30 (Q2) in the pregnancy, and after the child was born at age 6 months (Q3), 1.5 years (Q4), 3 years (Q5), 5 years (Q5Y) and 8 years (Q8Y) (Fig. 1). The questionnaires obtained information regarding maternal medical and social background, medication and vitamin use and maternal health during the pregnancy, and detailed information regarding child development, including language abilities. Blood samples were collected from the mothers in gestation week 17–19 and from the umbilical cord immediately after birth [13,14].

Our data were based on version X of the MoBa databank and included 734 children of 620 mothers with epilepsy and 113 674 children of 94 338 mothers without epilepsy. The epilepsy diagnosis [15] was based on self-reported information from the MoBa questionnaires as well as information from the MBRN registered by the family doctor or midwife. The epilepsy cohort in MoBa has been validated previously (Appendix S1: Methods S1), and the validity is very good [16].

Variables

Antiepileptic drug use and plasma AED concentrations
Information on type of AED use during the pregnancy was obtained from Q1 and Q2, and from MBRN data [13]. Plasma concentrations of valproate, lamotrigine, carbamazepine, oxcarbazepine monohydroxyderivative metabolite, levetiracetam and topiramate were analysed in 226 maternal blood samples (gestational week 17–19) and 198 umbilical cord samples for altogether 254 AED-exposed children (73%) [14,16]. The reported AED was detected in samples from 237 of the 254 children (93%) (Appendix S1: Methods S1).

Maternal folate status
Mothers in the MoBa reported on the use and frequency of intake of folic acid supplement during pregnancy in Q1 and Q2 (Appendix S1: Methods S1). Periconceptional folic acid supplement use was defined as use 4 weeks before pregnancy and/or during the first trimester. There are no compulsory folic acid food fortifications in Norway. Plasma folate concentrations were analysed in maternal blood samples from gestation week 17–19 (Appendix S1: Methods S1) [14].

Language impairment
The definition of language impairment was based on the following parent-reported screening instruments in the MoBa: the communication scale from the Ages and Stages Questionnaires (ASQ) [17,18] the Speech and Language Assessment Scale (SLAS) [19] and the Norwegian instrument Twenty Statements about Language-related Difficulties (Language 20) (Appendix S1: Methods S1 and Table S1) [20]. All three instruments were available in Q5Y, only the latter being available in Q8Y. Children at age 5 years with results outside the cut-off for at least one of the three parent-reported instruments in Q5Y were defined to have language impairment. Similarly, children at age 8 years with a result above cut-off for the Language 20 semantic subscale in Q8Y were classified with language impairment. Criteria for language impairment at age 1.5 and 3 years have been described elsewhere [12]. Children who fill criteria for language impairment by any of the screening instruments are recommended for referral for clinical assessment and diagnosis [18–20]

Covariates

Covariates from the MoBa questionnaires and MBRN based on clinical relevance were included [12,21] (Table 1, Appendix S1: Methods S1 and Fig. S1).

Statistical analysis

Missing data analyses were performed by comparing the clinical characteristics of children who responded and did not respond to Q5Y and Q8Y (Appendix S1: Methods S1, Tables S2 and S3). AED-exposed and

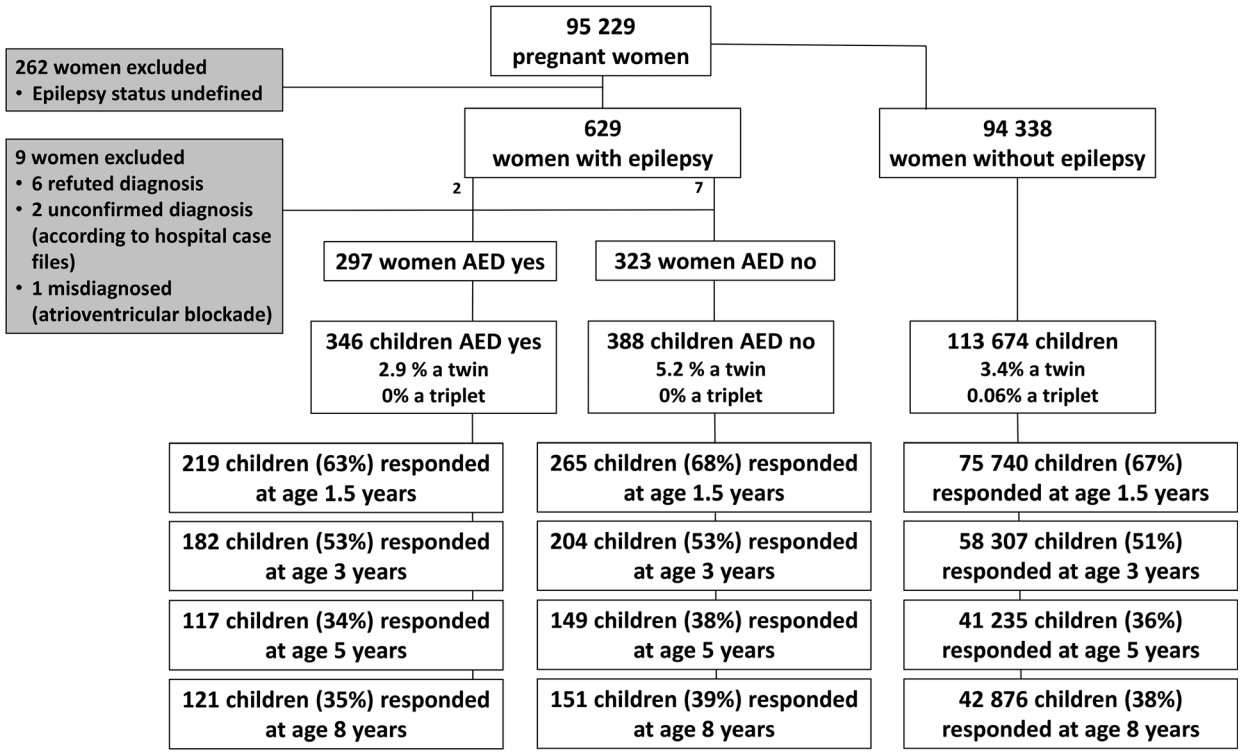

Figure 1 Flow chart of included and excluded cases. AED yes, AED-exposed children, AED no, AED-unexposed children.

AED-unexposed children of mothers with epilepsy were compared with the control group of all children of mothers without epilepsy (Appendix S1: Methods S1).

Ethics

This study was approved by the Regional Committee for Medical Research Ethics (reference number 2011/1616) (Appendix S1: Methods S1).

Results

Sample characteristics

The study population consisted of 346 AED-exposed and 388 AED-unexposed children of mothers with epilepsy, and a control group of 113 674 children of mothers without epilepsy (Table 1 and Fig. 1). Of the AED-exposed children, 280 children were exposed to AED monotherapy and 64 to AED polytherapy (Appendix S1: Table S4). For two children, the AED regime was unspecified. The most frequent AED exposures in monotherapy were lamotrigine (n = 112), carbamazepine (n = 72) and valproate (n = 40). Of the early pregnancy folic acid users, 97% of the total study population used it four times per week or more (Q1), and the same was true for 91% of the late users (Q2). Mothers of 117 and 121 of the AED-exposed children responded to Q5Y and Q8Y (Fig. 1). For AED-exposed children, no periconceptional folic acid supplementation, smoking during pregnancy, male offspring and previous language impairment at an earlier age were predictors of language impairment at age 5 or 8 years (Table 2). Of the AED-exposed children with language impairment at age 1.5 or 3 years, 41% (n = 22) continued to have such at age 5 or 8 years (Appendix S1: Fig. S2).

Antiepileptic drug use and language impairment

At age 5 years, 30% (n = 35) of AED-exposed children had language impairment compared to 22% (n = 9011) amongst children of mothers without epilepsy (P = 0.04). The adjusted odds ratio (aOR) for language impairment was 1.6 [confidence interval (CI) 1.1–2.5, P = 0.03) (Table 3). At age 8 years, 32% (n = 38) of AED-exposed children had language impairment compared to 19% (n = 8250) in the control group (P < 0.001); the aOR was 2.0 (CI 1.4–3.0, P < 0.001) (Table 3). There were no significant differences in language impairment between AED-unexposed children of mothers with epilepsy and the control group.

Children exposed to carbamazepine monotherapy had significantly higher risk of language impairment compared to control children at age 8 years (aOR 3.8,

Table 1 Characteristics of children of mothers with and without epilepsy

Characteristics	AED-exposed children of mothers with epilepsy n = 346	AED-unexposed children of mothers with epilepsy n = 388	Children of mothers without epilepsy n = 113 674
Male offspring; n (%)	168 (49)	195 (51)	57 958 (51)
Gestational age at birth[a] (weeks); median (range)	40.0 (27.0)	39.0 (18.0)	40.0 (32.0)
Apgar score 5 min after birth; median (range)	10 (10.0)	10 (10.0)	10 (10.0)
Twin or triplet child; n (%)	10 (3)	20 (5)	3918 (4)
Parity[b]; median (range)	1.0 (4.0)	1.0 (4.0)	1.0 (4.0)
Maternal age (years); median (range)	29.0 (24.0)	29.0 (25.0)	30.0 (39.0)
Maternal prepregnancy BMI (kg/m^2); median (range)	23.6 (26.4)	23.6 (25.9)	23.1 (47.0)
Periconceptional folic acid use[c]	259 (79)	289 (75)	77 895 (76)
Single mother; n (%)	15 (5)	17 (4)	2418 (2)
Paternal low education[d]; n (%)	20 (6)	23 (6)	4692 (4)
Maternal low education[d]; n (%)	12 (4)	21 (5)	2825 (3)
Low total household income[e]; n (%)	35 (11)	35 (10)	6464 (7)
Unplanned pregnancy; n (%)	76 (24)	90 (24)	19 725 (19)
Alcohol during pregnancy[f]; n (%)	12 (4)	9 (2)	2670 (3)
Smoking during pregnancy; n (%)	40 (12)	32 (8)	9525 (9)
Maternal anxiety/depression during pregnancy[g]; n (%)	62 (20)	56 (15)	10 821 (11)
≥1 epileptic seizure during pregnancy; n (%)	42 (26)	13 (7)	NA
TC seizure(s) during pregnancy; n (%)	20 (12)	5 (3)	NA
Maternal report of familial language impairment[h] at age 5 years	47 (41)	63 (42)	14 163 (35)
Maternal report of seldom/never helping their child read letters and sounds during a typical week at age 5 years	17 (15)	22 (15)	6675 (16)
Maternal report of never reading to their child at age 8 years	6 (5)	9 (6)	2959 (7)
Language impairment age 1.5 years[i]	43 (20)	24 (9)	7896 (11)
Language impairment age 3 years[j]	22 (12)	14 (7)	4182 (7)

AED, antiepileptic drug; BMI, body mass index; TC seizure(s), tonic–clonic seizure(s). N may vary within the groups due to missing data. The chi-squared test for independence or Fisher's exact test was used for categorical variables, the Mann–Whitney U test for continuous variables due to violation of the assumption of normal distribution. AED-exposed and AED-unexposed children are compared to children of mothers without epilepsy. [a]Calculated from the ultrasonographic measurements performed at 18–19 weeks of gestation. When ultrasound data were unavailable, gestational age was estimated on the basis of the first day of the last menstrual period. [b]Number of all pregnancies >21 gestation weeks including the current pregnancy. Maximum value is 5, representing a parity of 5 or more. [c]Maternal folic acid supplement use 4 weeks before pregnancy and/or during the first trimester. [d]9 or fewer years of schooling. [e] < 400 000 NOK (equals approximately 41 000 EUR) annually. [f]Alcohol consumption ≥1 time per month. [g]Mean score >1.75 on the Hopkins symptom check list in gestational week 17–19. [h]Maternal report of a biological relative (sibling, parent, grandparent, aunt, uncle or cousin) who was a late talker or had difficulties with either reading or writing or pronunciation. [i]Defined as children who score 1.5 standard deviations or more below the mean score of the three-item version of the communication scale from the Ages and Stages Questionnaires at age 1.5 years. [j]Defined as children who score 1.5 standard deviations or more below the mean score of the six-item version of the communication scale from the Ages and Stages Questionnaires at age 3 years and/or are talking in two- to three-word phrases or fewer (expressive language impairment) at age 3 years.

CI 1.6–9.0, P = 0.002, n = 23) but not at age 5 years (aOR 1.9, CI 0.6–5.6, P = 0.26, n = 17) (Table 3). Children exposed to valproate monotherapy *in utero* had the poorest mean language scores at both ages (Table 4).

Antiepileptic drug concentrations and language impairment

Higher maternal plasma valproate concentration during pregnancy correlated with a lower ASQ score (Spearman's rho −0.77, P = 0.02, n = 9) and a higher Language 20 score (Spearman's rho 0.82, P = 0.01, n = 9), both indicating language impairment at age 5 years (Fig. 2 and Appendix S1: Table S5). A significant correlation between higher maternal carbamazepine concentration and lower Language 20 score (Spearman's rho −0.47, P = 0.04, n = 19), indicating less language impairment, appeared at age 5 years, but the scatter plot contained outliers influencing the association (Appendix S1: Table S5).

Maternal folate status and language impairment

In the mothers not taking folic acid supplementation, 63% (n = 5) of AED-exposed children had language

Table 2 Clinical characteristics of AED-exposed and AED-unexposed children of mothers with epilepsy and children of mothers without epilepsy with language impairment at age 5 or 8 years

	AED-exposed children of mothers with epilepsy*n* total = 164		AED-unexposed children of mothers with epilepsy*n* total = 202		Children of mothers without epilepsy*n* total = 55 192	
Language impairment[a]	Yes*n* = 57 (35%)	OR (95% CI)	Yes*n* = 66 (33%)	OR (95% CI)	Yes*n* = 14 392 (26%)	OR (95% CI)
Male offspring; *n* (%[b])	39 (47)	**3.1 (1.6–6.1)***	34 (33)	1.0 (0.6–1.9)	8503 (30)	**1.6 (1.5–1.6)***
Gestational age at birth[c] (weeks); median (range)	40.0 (17.0)	1.0 (0.9–1.2)	39.0 (14.0)	0.9 (0.8–1.0)	40.0 (22.0)	**1.0 (1.0–1.0)***
Apgar score 5 min after birth; median (range)	9.0 (5.0)	1.0 (0.7–1.4)	9.0 (10.0)	0.9 (0.7–1.1)	10.0 (10.0)	**0.9 (0.9–1.0)***
Twin or triplet child; *n* (%)	2 (33)	0.9 (0.2–5.3)	3 (38)	1.2 (0.3–5.3)	485 (31)	**1.3 (1.1–1.4)***
Parity[d]; median (range)	2.0 (4.0)	1.3 (0.9–1.8)	1.0 (3.0)	1.0 (0.7–1.5)	2.0 (4.0)	**1.0 (0.9–1.0)***
Maternal age (years); median (range)	31.0 (21.0)	1.0 (0.9–1.1)	29.0 (20.0)	1.0 (0.9–1.0)	30.0 (32.0)	**1.0 (1.0–1.0)***
Maternal prepregnancy BMI (kg/m^2); median (range)	23.2 (23.7)	1.0 (0.9–1.1)	22.8 (24.0)	1.0 (0.9–1.1)	23.2 (38.2)	**1.0 (1.0–1.0)***
Periconceptional folic acid use[e]	42 (31)	**0.4 (0.2–0.9)***	54 (34)	1.2 (0.6–2.6)	11,538 (26)	1.0 (0.9–1.0)
Single mother; *n* (%)	2 (50)	1.9 (0.3–14.2)	1 (33)	1.0 (0.1–11.3)	298 (31)	**1.3 (1.1–1.5)***
Maternal low education[f]; *n* (%)	0 (0)	NA	4 (80)	8.7 (1.0–79.5)	323 (41)	**2.0 (1.7–2.3)***
Low total household income[g]; *n* (%)	5 (50)	2.2 (0.6–8.0)	5 (46)	1.8 (0.5–6.0)	851 (32)	**1.4 (1.3–1.5)***
Unplanned pregnancy; *n* (%)	12 (36)	1.1 (0.5–2.5)	11 (37)	1.2 (0.5–2.8)	2599 (28)	**1.1 (1.1–1.2)***
Alcohol during pregnancy[h]; *n* (%)	1 (50)	1.9 (0.1–31.4)	2 (67)	4.2 (0.4–47.4)	358 (27)	1.0 (0.9–1.2)
Smoking during pregnancy; *n* (%)	8 (62)	**3.3 (1.0–10.7)***	4 (40)	1.4 (0.4–5.1)	856 (31)	**1.3 (1.2–1.4)***
Maternal anxiety/depression during pregnancy[i]; *n* (%)	8 (36)	1.1 (0.4–2.7)	10 (40)	1.5 (0.6–3.5)	1737 (35)	**1.6 (1.5–1.7)***
≥1 epileptic seizure during pregnancy; *n* (%)	13 (41)	1.4 (0.6–3.2)	7 (70)	**5.8 (1.4–23.9)***	NA	NA
TC seizure(s) during pregnancy; *n* (%)	6 (35)	1.0 (0.3–3.0)	4 (100)	NA	NA	NA
AED polytherapy during pregnancy; *n* (%)	11 (33)	0.9 (0.4–2.1)	NA	NA	NA	NA
AED monotherapy during pregnancy; *n* (%)	45 (35)	1.0 (0.5–2.3)	NA	NA	NA	NA
Plasma AED (μmol/l)[j]; median (range)	53.2 (170)	1.0 (1.0–1.0)	NA	NA	NA	NA
Maternal report of familial language impairment[k] at age 5 years	17 (36)	1.4 (0.6–3.0)	24 (38)	1.4 (0.7–2.8)	4844 (34)	1.6 (1.6–1.7)
Maternal report of seldom/never reading to their child[l]	9 (39)	1.2 (0.5–3.1)	12 (43)	1.7 (0.7–3.7)	3354 (37)	**1.8 (1.8–1.9)***
Language impairment age 1.5 years[m]	17 (59)	**3.9 (1.7–9.2)***	12 (67)	**4.8 (1.7–13.6)***	2608 (51)	**3.4 (3.2–3.6)***
Language impairment age 3 years[n]	14 (82)	**12.0 (3.2–44.4)***	3 (33)	1.0 (0.2–4.0)	2080 (71)	**7.9 (7.3–8.6)***

AED, antiepileptic drug; BMI, body mass index; CI, confidence interval; OR, odds ratio; TC seizure(s), tonic–clonic seizure(s). *N* may vary slightly within the groups due to missing data. Significant results are marked with bold values. [a]Language impairment at age 5 years according to the Ages and Stages Questionnaires, the Speech and Language Assessment Scale or the Twenty Statements about Language-related Difficulties or at age 8 years according to the Twenty Statements about Language-related Difficulties semantic subscale. [b]Percentage was calculated from the number of children with that characteristic and language impairment out of all children with that characteristic in each of the three groups. [c]Calculated from the ultrasonographic measurements performed at 18–19 weeks of gestation. When ultrasound data were unavailable, gestational age was estimated on the basis of the first day of the last menstrual period. [d]Number of all pregnancies >21 gestation weeks including the current pregnancy. Maximum value is 5, representing a parity of 5 or more. [e]Folic acid supplement use 4 weeks before pregnancy and/or during the first trimester. [f]9 or fewer years of schooling. [g]<400 000 NOK (equals approximately 41 000 EUR) annually. [h]Alcohol consumption ≥1 time per month. [i]Mean score >1.75 on the Hopkins symptom check list in gestational week 17–19. [j]Median of standardized concentration (see text) in maternal plasma at gestational week 17–19 and umbilical cord blood. [k]Maternal report of a biological relative (sibling, parent, grandparent, aunt, uncle or cousin) who was a late talker or had difficulties with either reading or writing or pronunciation. [l]Maternal report of seldom/never helping their child read letters and sounds during a typical week at age 5 years or maternal report of never reading to their child age 8 years. [m]Defined as children who score 1.5 standard deviations or more below the mean score of the three-item version of the communication scale from the Ages and Stages Questionnaires at age 1.5 years. [n]Defined as children who score 1.5 standard deviations or more below the mean score of the six-item version of the communication scale from the Ages and Stages Questionnaires at age 3 years and/or are talking in two- to three-word phrases or fewer (expressive language impairment) at age 3 years. **P* value <0.05.

impairment at age 5 years compared to 23% (n = 1422) of children of mothers without epilepsy (P = 0.02) (Appendix S1: Table S6). Similarly, at age 8 years, 52% (n = 11) of AED-exposed children had language impairment compared to 22% (n = 1712) in the non-supplemented control group (P = 0.002) (Appendix S1: Table S6). The aORs for language impairment in AED-exposed children compared to control children with no folic acid use were 10.5 (CI 1.9–56.3, P = 0.006) at age 5 years and 3.8 (CI 1.6–9.1, P = 0.003) at age 8 years, respectively. When the mothers were using periconceptional folic acid

Table 3 Language impairment for specific AED therapies in monotherapy, AED polytherapy and any AED exposure

	n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Language impairment age 5 years[a]			
Children of mothers without epilepsy	9011 of 41 194 (22)	NA	NA
Valproate	5 of 14 (36)	2.0 (0.7–5.9)	2.2 (0.7–7.0)
Carbamazepine	6 of 17 (35)	1.9 (0.7–5.3)	1.9 (0.6–5.6)
Lamotrigine	9 of 39 (23)	1.1 (0.5–2.3)	1.0 (0.5–2.3)
Levetiracetam	2 of 9 (22)	1.0 (0.2–4.9)	1.0 (0.2–5.3)
Topiramate	2 of 4 (50)	3.6 (0.5–25.4)	5.8 (0.5–64.0)
AED monotherapy	28 of 91 (31)	**1.6 (1.0–2.5)***	**1.7 (1.0–2.7)***
AED polytherapy	7 of 26 (27)	1.3 (0.6–3.1)	1.4 (0.6–3.4)
Any AED	35 of 117 (30)	**1.5 (1.0–2.3)***	**1.6 (1.1–2.5)***
Language impairment age 8 years[b]			
Children of mothers without epilepsy	8250 of 42 550 (19)	NA	NA
Valproate	5 of 16 (31)	1.9 (0.7–5.4)	2.2 (0.7–6.4)
Carbamazepine	10 of 23 (43)	**3.2 (1.4–7.3)****	**3.8 (1.6–9.0)****
Lamotrigine	9 of 41 (22)	1.2 (0.6–2.4)	1.2 (0.6–2.6)
Levetiracetam	1 of 6 (17)	0.8 (0.1–7.1)	0.7 (0.1–6.0)
Topiramate	1 of 4 (25)	1.4 (0.1–13.3)	1.1 (0.1–10.9)
AED monotherapy	30 of 97 (31)	**1.9 (1.2–2.9)****	**2.0 (1.3–3.0)****
AED polytherapy	7 of 21 (33)	2.1 (0.8–5.2)	2.4 (0.9–6.1)
Any AED	38 of 120 (32)	**1.9 (1.3–2.8)*****	**2.0 (1.4–3.0)*****

AED, antiepileptic drug; CI, confidence interval; OR, odds ratio. AED-exposed children were compared to children of mothers without epilepsy. Significant results are marked with bold values. [a]Language impairment at age 5 years according to the Ages and Stages Questionnaires, the Speech and Language Assessment Scale or the Twenty Statements about Language-related Difficulties. [b]Language impairment at age 8 years according to the semantic subscale of the Twenty Statements about Language-related Difficulties. Covariates in the model: maternal age, parental socioeconomic status (single mother, low maternal education (≤9 years), low household income [<400 000 NOK (equals approximately 41 000 EUR)/year]), parity (pregnancies >21 gestation weeks), maternal prepregnancy body mass index, maternal report of familial language delay [sibling, parent, grandparent, aunt, uncle or cousin who was a late talker or had difficulties with either reading or writing or pronunciation (only in 5 years model)], smoking during pregnancy, alcohol use during pregnancy (consumption ≥1 time per month) (only 8 years model), maternal anxiety/depression symptoms (mean score >1.75 on the Hopkins symptom check list in gestational week 17–19) during pregnancy, Apgar score 5 min after birth, gestational age (calculated from the ultrasonographic measurements performed at 18–19 weeks of gestation; when ultrasound data were unavailable, gestational age was estimated on the basis of the first day of the last menstrual period), maternal report of seldom/never helping their child read letters and sounds during a typical week at age 5 years (5 years model) or maternal report of never reading to their child at age 8 years (8 years model). *P value < 0.05. **P value < 0.01 ***P value < 0.001

supplement, the corresponding aORs for language impairment were 1.4 (CI 0.9–2.2, $P = 0.14$) at age 5 years and 1.7 (CI 1.1–2.6, $P = 0.02$) at age 8 years, respectively.

After adjustment for covariates, a significant interaction was found between periconceptional folic acid use and AED exposure for ASQ score at age 5 years ($P = 0.009$, standardized beta 0.03), but not for SLAS or Language 20 scores at age 5 or 8 years. In the linear regression model, maternal folate concentration correlated with Language 20 score at age 5 years in the unadjusted, but not in the adjusted, model.

Discussion

An increased risk of language impairment was found in AED-exposed children at age 5 and 8 years of mothers with epilepsy compared to children of mothers without epilepsy. Valproate and carbamazepine exposure affected language outcome the most. Periconceptional folic acid use had a protective effect on the risk of language impairment. There was no increased risk of language impairment in AED-unexposed children of mothers with epilepsy compared to children of mothers without epilepsy. A large number of other possible confounders was considered, and these did not have any consistent effect on language outcome. AED exposure, and especially if the mother did not take folic acid, was the single most important factor for language outcome.

The AED-associated risk of language impairment was particularly evident in the carbamazepine monotherapy group at age 8 years. The aOR for language impairment in this group was almost fourfold compared to children of mothers without epilepsy. Poor neurodevelopmental outcomes after AED exposure *in utero* have mostly been associated with valproate exposure [1,2]. For children exposed to carbamazepine and other AEDs such as lamotrigine, levetiracetam and topiramate, evidence regarding any effect on specific cognitive skills in older children is lacking [1,2]. Valproate and carbamazepine exposure in monotherapy have been associated with language impairment in several studies [4–9,11,22] but other

Table 4 Mean language scores in children of mothers with and without epilepsy

	ASQ score[a] 5 years Mean (SD, 95% CI)	Language 20 score[b] 5 years Mean (SD, 95% CI)	SLAS score[c] 5 years Mean (SD, 95% CI)	Language 20 score[b] 8 years Mean (SD, 95% CI)
Children of mothers without epilepsy	66.0 (6.7, 65.9–66.1)	25.3 (8.3, 25.3–25.4)	3.5 (0.6, 3.5–3.6)	10.6 (3.8, 10.6–10.6)
AED-unexposed children	66.2 (5.2, 65.4–67.1)	26.1 (8.3, 24.8–27.5)	3.5 (0.5, 3.4–3.6)	**11.3 (4.1, 10.6–11.9)***
AED-exposed children	65.7 (7.9, 64.3–67.2)	**27.1 (9.0, 25.4–28.7)****	**3.4 (0.6, 3.3–3.5)***	**12.1 (5.2, 11.2–13.0)****
Valproate monotherapy	64.3 (6.2, 60.7–67.8)	29.4 (12.8, 22.1–36.8)	**3.1 (0.6, 2.8–3.5)***	**13.0 (6.4, 9.6–16.4)***
Carbamazepine monotherapy	65.3 (7.9, 61.2–69.3)	**28.6 (8.1, 24.4–32.8)***	3.3 (0.5, 3.1–3.6)	**12.9 (5.3, 10.7–15.2)****
Lamotrigine monotherapy	65.3 (11.4, 61.6–69.1)	24.7 (6.1, 22.7–26.7)	3.4 (0.7, 3.2–3.7)	10.9 (3.7, 9.7–12.1)
Levetiracetam monotherapy	68.0 (2.3, 66.2–69.7)	24.1 (7.0, 18.7–29.5)	3.7 (0.8, 3.1–4.4)	10.0 (2.5, 7.4–12.7)
Topiramate monotherapy	64.6 (6.7, 53.9–75.2)	27.8 (11.2, 10.1–45.6)	3.5 (0.4, 2.9–4.1)	11.0 (3.5, 5.5–16.5)
AED monotherapy	65.6 (8.8, 63.8–67.5)	27.0 (9.4, 25.0–29.0)	3.4 (0.6, 3.3–3.6)	**11.9 (4.8, 11.0–12.9)****
AED polytherapy	66.1 (3.5, 64.7–67.5)	**27.4 (7.8, 24.2–30.6)***	3.4 (0.5, 3.2–3.6)	13.0 (6.8, 9.9–16.1)

AED, antiepileptic drug; ASQ, Ages and Stages Questionnaires; CI, confidence interval; Language 20, Twenty Statements about Language-related Difficulties; SLAS, Speech and Language Assessment Scale. AED-exposed and AED-unexposed children were compared to children of mothers without epilepsy by using the Mann–Whitney *U* test due to violation of the assumption of normal distribution. Significant results are marked with bold values. [a]Ages and Stages Questionnaires score (0–70 points). A low score indicates language impairment. [b]Twenty Statements about Language-related Difficulties score (0–100 points total score, 0–40 points semantic subscale). A high score indicates language impairment. [c]Composite scale mean score (1–5 points) from the Speech and Language Assessment Scale. A score below 3 points indicates language impairment. **P* value < 0.05. ***P* value < 0.01.

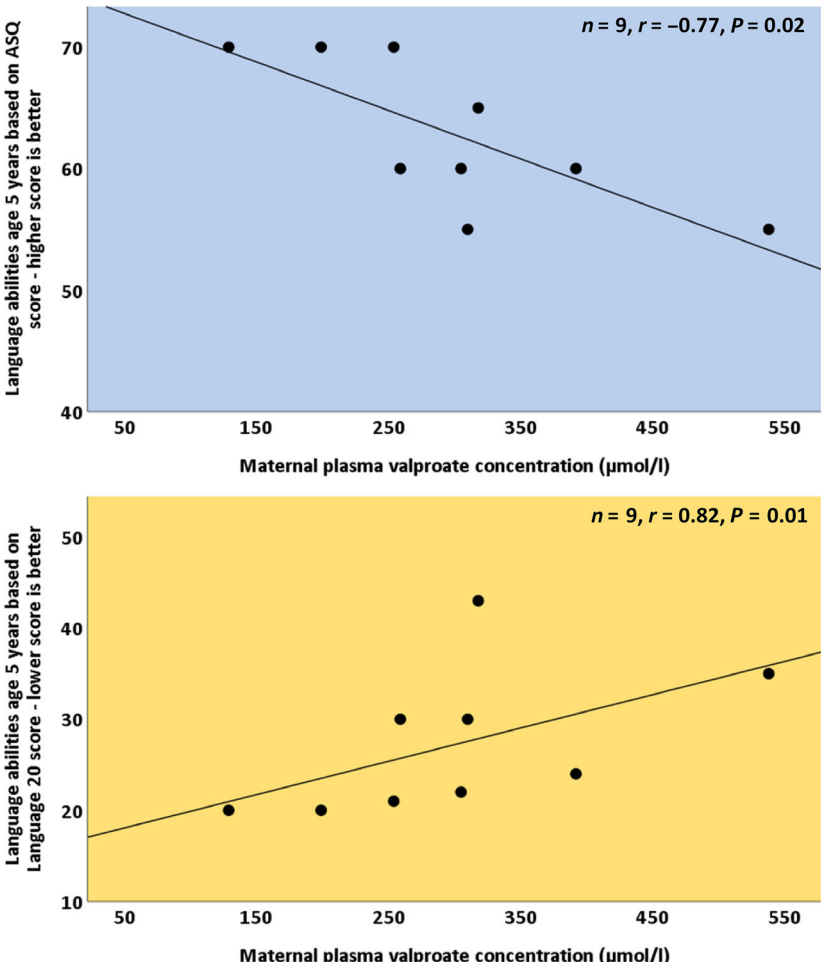

Figure 2 The correlation between language score and maternal plasma valproate concentration (µmol/l) during pregnancy at age 5 years.

studies reported no such association for carbamazepine [8,9]. Two studies based on neuropsychological assessment reported reduced verbal abilities in children aged 3 and 6 years after foetal carbamazepine exposure [6,22]. Our results are based on validated screening instruments. Different study designs and different maternal folate status [23] could explain divergent results between studies. The lack of significantly increased aORs for language impairment after valproate exposure in monotherapy at age 5 and 8 years is probably due to small numbers of children and low concentrations of valproate [16]. Nevertheless, a correlation was found between maternal valproate concentrations during pregnancy and language impairment. This is consistent with our previous study of children aged 18 months in the MoBa [12] and with previous reports on dose-dependent valproate-mediated language impairment [4,5,8].

In this study, the previously reported AED-associated poorer language abilities in preschool years [11] have been shown to persist into school age in AED-exposed children of mothers with epilepsy. Our data shows that the language impairment at age 5 and 8 years may develop early or emerge later in the preschool years in children of mothers with epilepsy, as in children from the general population [24]. Our findings suggest a possible long-term AED-associated effect on language abilities in offspring after foetal AED exposure. Reduced total brain volume and grey matter volume compared to healthy children have been reported in valproate-exposed children aged 10 years with low IQ and language dysfunction [25]. Similarly, adults aged 23 years with antenatal exposure to mainly valproate, carbamazepine, phenytoin or primidone in monotherapy or polytherapy had reduced grey matter volume compared to healthy controls, and particularly in the left hemisphere controlling language [26]. These findings support the notion of permanently affected language abilities associated with foetal AED exposure. The protective effect of periconceptional folic acid supplementation on AED-associated language impairment was highly evident in our study. This protection, previously reported for age 1.5 and 3 years [12] remained equally evident at age 5 and 8 years. This strongly suggests a role of folate in the mechanism of AED-associated language impairment. Furthermore, these findings emphasize the importance of folic acid supplement use in the periconceptional period in all women with epilepsy who use AEDs [5,10,12,22]. Language impairment in children requires intervention, as it may have severe consequences for language skills in adulthood, academic achievements, mental health, behaviour and social life [21,27].

The strengths of our study include a validated, large dataset comprising epilepsy groups with and without AED exposure and a control group without epilepsy. Plasma AED and folate concentrations were analysed in the mothers during the pregnancy, as well as umbilical cord AED concentrations. Relevant covariates were adjusted for. Selection bias in the MoBa has been reported as moderate and with no or minimal effects on exposure–outcome association measurements [28]. The response rates for the two epilepsy groups and the control group were similar, and thus the exposure–outcome association measurements are unlikely to be biased.

Our missing data analyses indicated that children with normal language may be overrepresented. Children where mothers reported language impairment at age 1.5 and 3 years, no exposure to folic acid supplementation and with a lower socioeconomic status were more often missing from the study at age 5 and 8 years. Our findings may have been even more pronounced without any such selection bias. Mothers who used AEDs during pregnancy may be aware of the potential neurodevelopmental effects of AED exposure and might therefore have reported their children's language skills more vigilantly. If true, this would make the true results less pronounced. However, the association between foetal AED exposure, poor language abilities and maternal folate status was not well known during the inclusion period of the MoBa and is therefore unlikely to have influenced our results. There was no formal neuropsychological assessment of the children, but parents are considered good evaluators of the language abilities of their children [29]. Mothers who use AEDs during pregnancy are likely to have more severe epilepsy with a higher risk of epileptic seizures than untreated mothers with epilepsy. It cannot be excluded that such non-AED factors contribute to our observed language impairment. Information on maternal IQ was not available and this variable could not be controlled for, but education was controlled for in the analyses.

In this study, an association between language impairment and foetal AED exposure in children aged 5 and 8 years of mothers with epilepsy was found. Children of mothers with untreated epilepsy had no increased risk of language impairment. Periconceptional folic acid supplement use had a protective effect on AED-associated language impairment. Clinicians should be aware of the risk of poor language abilities in children exposed to AEDs *in utero*, particularly valproate and carbamazepine, with early intervention for signs of language impairment. The importance of folic acid supplement use in all AED-using women with epilepsy with a chance of becoming pregnant is emphasized.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementaty data.

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