The "maternal effect" on epilepsy risk: analysis of familial epilepsies and reassessment of prior evidence

Running head: Epilepsy maternal effect

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ABSTRACT

Objective: Previous studies have observed that epilepsy risk is higher among offspring of affected women than offspring of affected men. We tested whether this "maternal effect" was present in familial epilepsies, which are

enriched for genetic factors that contribute to epilepsy risk.

Methods: We assessed evidence of a maternal effect in a cohort of families containing ≥3 persons with epilepsy using three methods: (1) "downward-looking" analysis, comparing the rate of epilepsy in offspring of affected women versus men; (2) "upward-looking" analysis, comparing the rate of the epilepsy among mothers versus fathers of affected individuals; (3) lineage analysis, comparing the the proportion of affected individuals with family history of epilepsy on the maternal versus paternal side.

Results: Downward-looking analysis revealed no difference in epilepsy rates among offspring of affected mothers versus fathers (prevalence ratio 1.0, 95% CI 0.8, 1.2). Upward-looking analysis revealed more affected mothers than affected fathers; this effect was similar for affected and unaffected sibships (odds ratio 0.8, 95% CI 0.5, 1.2) and was explained by a combination of differential fertility and participation rates. Lineage analysis revealed no significant difference in the likelihood of maternal versus paternal family history of epilepsy.

Interpretation: We found no evidence of a maternal effect on epilepsy risk in this familial epilepsy cohort. Confounding sex imbalances can create the appearance of a maternal effect in upward-looking analyses and may have impacted prior studies. We discuss possible explanations for the lack of evidence, in familial epilepsies, of the maternal effect observed in population-based studies.

INTRODUCTION

Epilepsy is a disorder with multiple and varied genetic contributions.[1] Many previous studies have observed that epilepsy risk is higher among offspring of affected women than offspring of affected men.[2–5] Many explanations for this "maternal effect" have been considered, including genetic mechanisms (X-linked inheritance, mitochondrial inheritance, epigenetic parent-of-origin effects), environmental exposures (maternal seizures or anti-epileptic drugs during pregnancy), and methodologic biases. However, none of these possible explanations fully accounts for the observed maternal effect in common epilepsies,[2,3] and the cause of this observation remains unknown.

Evidence of a maternal effect has come from several different types of analysis (**Figure 1**): (1) comparison of the prevalence of epilepsy in the *offspring* of women versus offspring of men with epilepsy (i.e., "downward-looking" analysis); (2) comparison of the prevalence of epilepsy in the mothers versus fathers of people with epilepsy ("upward-looking"); and (3) analysis of the the proportion of affected individuals with a family history of epilepsy on the maternal vs. the paternal side of the pedigree ("lineage analysis").

In this study, we analyzed a cohort of familial epilepsies for evidence of a maternal effect, using each of the approaches described above. A familial cohort is particularly useful for this analysis because it provides large sample sizes of affected relatives, in contrast to population-based epidemiology studies. We also reassessed prior studies that utilized upward-looking analyses, accounting for confounding sex biases that may have influenced their conclusions.

METHODS

1. Data collection

Ascertainment and data collection of the Epi4K familial epilepsy cohort have been described in detail elsewhere.[6,7] Briefly, families contained three or more relatives with recurrent unprovoked seizures. Known acquired causes of epilepsy were excluded. Ascertainment occurred at seven centers in North America, Europe, Australia and New Zealand. Comprehensive phenotypic data were collected about every affected individual through diagnostic interviews and review of medical records, EEG and imaging reports. Data were reviewed to ensure consistency of methods across sites and were synthesized by an expert clinician into electro-clinical phenotypes. The multi-generational pedigrees obtained during this data collection process were the primary basis of the current analyses.

Families were classified as "generalized" if every affected individual had generalized (or unclassified) epilepsy; as "focal" if every affected individual had focal (or unclassified) epilepsy; as "mixed" if both generalized and focal phenotypes were present in separate individuals or in one person; and as "genetic epilepsy with febrile seizures plus (GEFS+)" if at least one individual was classified as having the FS+ phenotype and at least one other individual had either FS or FS+.[6] Because individuals with structural brain lesions or moderate-or-greater intellectual disability were excluded from the study, the generalized families consisted largely of genetic generalized epilepsies and the focal families largely of non-lesional focal epilepsies. A few families in this cohort have been included in previously published familial epilepsy cohorts.[4,8]

The Epi4K study was approved by the research ethics committee at each participating site and all subjects provided informed consent to participate. The current analysis used only deidentified data from that study; therefore separate ethics approval was not required.

2. Downward-looking analysis

This analysis tested the hypothesis that the prevalence of a history of epilepsy was higher in offspring of affected women than in offspring of affected men. For each affected individual in our cohort, we determined the total number of affected offspring and number of affected offspring. Monozygotic twins were counted as one offspring (n = 6 pairs). There were no discordant monozygotic twin pairs in this cohort. Nuclear families in which both parents had epilepsy (n = 8 parent pairs) were excluded from this analysis

Statistical analysis: The prevalence ratio (PR) was calculated for offspring of affected women relative to offspring of affected men. Confidence intervals were calculated using bootstrap resampling procedures to account for possible within-family correlation of observations. The null hypothesis was equal epilepsy prevalence in these two groups of offspring (PR = 1). Subgroup analyses were performed for each familial epilepsy type.

3. Upward-looking analysis

This analysis tested the following hypothesis: among the parents of affected individuals, the prevalence of a history of epilepsy in mothers compared to fathers is higher than expected by chance. The unit of analysis was *sibships*, defined as a group of siblings with the same mother and father. This avoids counting the same parent multiple times if there were multiple affected siblings. Each sibship was classified as affected if one or more of/span>its members had epilepsy, and as unaffected in none of its members had epilepsy. For half-sibships, the shared parent was counted once while the unshared parents were each counted separately. The 8 sibships in which both parents were affected were excluded from this analysis.

Statistical analysis: We determined the ratio of affected mothers to affected fathers in affected sibships, and compared this to the same ratio in unaffected sibships. Unaffected sibships are an appropriate control group because they reveal the likelihood of observing epilepsy in mothers versus fathers in this cohort due to chance, independent of whether epilepsy is transmitted to offspring. Odds ratios (OR) and 95% confidence intervals were calculated for the comparison of affected versus unaffected sibships. Odds ratios were used here because the outcome of interest was the odds that an affected parent was female vs. male, whereas in the downward-looking analysis prevalence ratios were used because the outcome of interest was the prevalence of epilepsy among sets of offspring. The null hypothesis was that the ratio of affected mothers to affected fathers was the same in affected and unaffected sibships (OR = 1). Subgroup analyses were performed for each familial epilepsy type.

4. Lineage analysis

For affected sibships with neither parent affected, we examined the epilepsy histories of second-degree relatives (grandparents and aunts/uncles). If any of these relatives was affected, the sibship was coded as having a family history of epilepsy on the maternal side or the paternal side, depending on the unaffected parent through whom the sibship was related to the affected second-degree relative. Five sibships with affected relatives on both parents' sides were excluded from this analysis. We tested the hypothesis of more sibships with maternal family history than paternal family history.

Statistical analysis: A binomial probability test was used to compare the observed proportion of sibships with maternal vs. paternal family histories to the null hypothesis of equal proportions (0.5). Subgroup analyses were not performed due to small sample sizes.

5. Statistical analysis

Statistical analyses were performed in the R programming language, using packages *Kinship2*, *FamAgg, Publish* and *boot.* Specific analyses are described in each subsection above.

RESULTS

1. Cohort characteristics

A complete description of this cohort of familial epilepsies has been previously reported.[6]

The cohort contained 1,120 individuals with epilepsy from 303 families: 117 families with only generalized epilepsy (417 affected individuals), 62 families with only focal epilepsy (220 individuals), 102 mixed families manifesting both generalized and focal epilepsies (387 individuals), and 22 GEFS+ families (96 individuals). Of the pedigrees used in this analysis, 280/303 (92%) spanned three or more generations. Among people with epilepsy in the cohort, 57% were female.

2. Downward-looking analysis

Among offspring of affected individuals, prevalence of a history of epilepsy did not differ in offspring of affected women compared to offspring of affected men (**Figure 2**). This was true in the cohort overall and in each familial epilepsy type. There were also no differences among the specific epilepsy syndromes within the

generalized or focal families (data not shown). We emphasize that the offspring epilepsy rates observed in this highly selected cohort of familial epilepsies do not reflect offspring risk in the general population.

3. Upward-looking analysis

Among affected sibships we observed more affected mothers than affected fathers (**Figure 3**). This was true in the cohort overall and in each familial epilepsy type except for GEFS+. Rather than compare these values to a null hypothesis of 50% affected mothers, we used unaffected sibships as a control group. Among unaffected sibships, we also observed more affected mothers than affected fathers. Comparison of affected versus unaffected sibships revealed no statistically significant differences in the odds that an affected parent was the mother vs. the father. Results were similar when stratified by specific epilepsy syndromes within generalized and focal families (data not shown).

We next explored possible reasons for the enrichment of affected mothers compared to affected fathers, observed in *both* affected and unaffected sibships. In our cohort, there were 1.8-times as many affected women who were mothers as affected men who were fathers (255 vs 141). Put another way, ifsibship with an affected parent is chosen at random from this cohort, the odds are 1.8 (or a 64% chance) that the affected parent is the mother, regardless of whether the sibship is affected or unaffected.

This enrichment of affected mothers resulted from a combination of two independent sex imbalances. First, there were more affected female than male subjects with epilepsy overall (57% female; F:M ratio = 1.3). Second, the likelihood that an affected subject was a parent (i.e., had ≥1 offspring) was higher for affected female than for affected male subjects (40% vs 29%, F:M ratio = 1.4). Multiplying these two ratios (1.3 x 1.4) yields the observed 1.8-fold enrichment in affected mothers. These observations fully account for the findings of our upward-looking analysis.

4. Lineage analysis

Among 474 affected sibships with neither parent affected, 83 had a family history of epilepsy in at least one second-degree relative (grandparent or aunt/uncle). This family history was on the maternal side in 46 and on the paternal side in 37, which was not significantly different from chance ($p = 0.38$).

DISCUSSION

We did not find evidence of a maternal effect in this familial epilepsy cohort. Downward-looking analysis revealed similar prevalence of a history of epilepsy among offspring of affected mothers compared to offspring of affected fathers. Upward-looking analysis revealed more affected mothers than affected fathers; this effect was similar for affected and unaffected sibships, and was explained by other confounding sex imbalances. Lineage analysis revealed no significant difference in the likelikhood of family history on the maternal versus the paternal side of the pedigrees.

Downward-looking analysis

Most previous studies that utilized downward-looking analyses have found higher rates of epilepsy in offspring of affected women than affected men (**Supplementary Table 2**). In contrast to the upward-looking approach, the discrepancy between our study and prior downward-looking studies is not readily explained by our analysis. We do not refute the observations of those studies, and a true maternal effect may exist in cohorts other than the one studied here, as discussed below.

The strongest evidence for a maternal effect comes from the Rochester Epidemiology Project, a population-based sample of residents of Olmsted County, Minnesota.[3,9–11] Annegers et al. (1976) observed epilepsy in 10/351 (2.8%) offspring of affected women and in 0/229 (0%) offspring of affected men.[9] In a later study of this cohort, Peljto et al. (2014) observed epilepsy in 14/355 (3.9%) offspring of affected women and 4/279 (1.4%) offspring of affected men.[10] This maternal effect was present only for offspring of parents with focal epilepsy (7/210 vs. 1/152) and not for those with generalized epilepsy (5/82 vs. 3/60). Othr studies have observed a maternal effect in generalized epilepsies.[12] Studies of the Rochester data observed a low epilepsy risk in offspring of affected men, similar to the baseline population risk. However, the numbers of affected offspring in the Rochester studies were small, and the findings warrant confirmation in an independent population-based study. Preliminary analyses of offspring risks from the large Danish population registry are also consistent with a maternal effect (Jakob Christensen, personal communication).

Upward-looking analysis

Most prior studies that utilized upward-looking analyses have observed more affected mothers than affected fathers. Several studies have reported a statistically significant difference when compared to a null hypothesis of equal proportions affected mothers and fathers.[4,5,12] However, our results demonstrate that these analyses are

affected by two important confounders, namely (1) differences in the proportions of women and men in the cohort (here, more women than men) and (2) higher likelihood of parenthood for women than for men with epilepsy. Each of these sex imbalances, if present in a cohort, will affect the ratio of affected mothers to fathers with epilepsy.

We used unaffected sibships as a control group. Other studies have also observed more mothers than fathers with epilepsy among the parents of unaffected control groups,[13–15] although the cause of this imbalance has not been demonstrated until now. We suspect that previous studies reporting a maternal effect on the basis of upward-looking analyses were affected by the same biases present in our data. Indeed, in our own data the ratio of affected mothers to fathers would have appeared statistically significant in all families and in the subset of generalized families had we tested (incorrectly) against a null hypothesis of equal numbers of mothers and fathers.

Women with epilepsy are more likely to marry and to become parents compared to men with epilepsy (**Supplementary Table 3**). In our cohort, women with epilepsy were 1.4-times more likely than men to have any offspring, consistent with prior evidence. The imbalance in parenthood rates between women and men with epilepsy must be accounted for in any upward-looking analysis of maternal transmission of epilepsy risk.

On the basis of the two confounding sex imbalances (sex ratio and parenthood ratio) identified in our data, we reassessed previous studies that utilized upward-looking analyses (**Supplementary Table 4**). Most studies reported the numbers of female and male subjects, but none reported parenthood rates. Assuming a parenthood ratio of 1.4 based on the evidence presented above, we calculated for each study the *expected ratio* of affected mothers to affected fathers, similar to the approach of Ottman et al (1985).[2] Under the assumptions of this reassessment, none of the previous studies demonstrated a statistically significant increase in affected mothers above the expected value.

Lineage analysis.

Five previous studies have conducted similar analyses.[5,12,16–18] All have reported that family history of epilepsy more commonly occurred on the maternal side than the paternal side, and this difference was statistically significant in two studies.[12,16] In our data there was no difference in the likelihood of maternal versus paternal family history of epilepsy. This analysis is not subject to the same biases as the upward-looking analysis because the sex of the affected second-degree relatives is not considered. However, reporting bias is a concern,

as mothers may be more likely to provide family histories and to know their own family history better than their partner's. Several studies have observed more maternal than paternal family histories of epilepsy in unaffected control subjects, consistent with reporting bias.[14,15] Our dataset did not allow us to perform lineage analysis on unaffected sibships.

Is a maternal effect confined to certain cohorts?

The possible biological and methodological causes of the maternal effect have been extensively discussed, with no single explanation fully explaining the observed data.[2] Of special interest here is why this effect is not present in our study nor in one previous study of familial epilepsies.[8] Are there explanations for a maternal effect present in unselected epilepsy cases but not in families ascertained through multiple affected individuals?

One possibility is that the distribution of causal genetic and nongenetic factors is different in the families analyzed here than in the general population. Our data collection strategy was specifically designed to enrich the sample for genetic causes of epilepsy, whether involving rare variants of large effect or combinations of common variants of smaller effect. If the maternal effect is due to another type of mechanism underlying risk in the general population, this enrichment for genetic causes might have made it more difficult to detect in the families we studied.

"Selective fertility" is another possible explanation for the maternal effect.[2,10] If people with genetic forms of epilepsy have reduced fertility compared to people with *non*-genetic forms of epilepsy, then given that fertility reductions are greater in men than in women with epilepsy, offspring of affected men will come disproportionately from men with *non*-genetic epilepsies (compared with offspring of affected women), and relatively fewer of their offspring will inherit the disorder. Epilepsies in our familial epilepsy cohort can be presumed to be strongly influenced by genetic factors, and so this selective fertility might be present in the population but not in our cohort. One previous study explicitly tested this hypothesis and found that men with epilepsy who had a family history of epilepsy did not have reduced fertility compared to men without a family history;[19] however, additional studies are needed.

Environmental exposures during fetal development, such as maternal seizures or anti-epileptic drugs, could lead to increased epilepsy risk in the offspring of affected mothers. These factors might play a larger role in sporadic cases and a smaller role in familial cases where the influence of genetics is stronger. However, these hypotheses have been tested and did not explain the maternal effect in population studies.[3,9,11] Anti-epileptic

drugs did not increase risk in offspring; maternal seizures during pregnancy were associated with increased risk in offspring, but the maternal effect persisted after adjusting for this variable.[3]

Finally, ascertainment biases are likely to differ across methodologies, and are particularly relevant to studies of multiplex families, which over-sample individuals with affected offspring or parents relative to their occurrence in the general population. If for some reason this oversampling were more pronounced for men than for women, this could lead a maternal effect that is present in the population to be missed in studies of familial epilepsies.

Limitations

We studied a selected cohort of families containing multiple individuals with epilepsy. Such a cohort is useful for analysis of the genetic architecture of familial epilepsies, but this is not an epidemiologic study. In particular, theates of epilepsy in offspring in these families are greatly inflated -- 10-times higher than the risk to offspring of unselected persons with epilepsy.[10] Second, our data were based on interviews, supplemented with medical records and additional family informants when possible, but are still subject to the inaccuracies and potential biases of subjects' reports. Third, data on unaffected individuals were limited, particularly for branches of the pedigrees without any affected individuals, which precluded some analyses.

Conclusions

We did not find evidence of a maternal effect on epilepsy risk in a cohort of familial epilepsies, using three different methods of analysis. Imbalances in sex ratio and parenthood ratio can confound upward-looking analyses and may explain the findings of previous studies that utilized this approach. Our data do not refute previous downward-looking analyses in population-based studies. It remains to be determined why the maternal effect seen in those studies is not evident in familial epilepsies. To clarify the reasons for these findings, the most informative analyses would compare, within a single dataset, offspring risks and fertility rates for probands with epilepsy with and without a family history of epilepsy in parents and siblings. Such an analysis would require a population-based dataset that is large enough to yield sufficient power and systematically ascertained, so that selection bias can be avoided.

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Author Contributions:

C.A.E. and R.O. contributed to study concept and design. C.A.E., S.F.B., M.P.E., R.O., and the Epi4K Consortium contributed to data acquisition and analysis. C.A.E., S.F.B., M.P.E., and R.O. contributed to drafting of the manuscript and figures.

Potential Conflicts of Interest:

Nothing to report.

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FIGURE LEGENDS

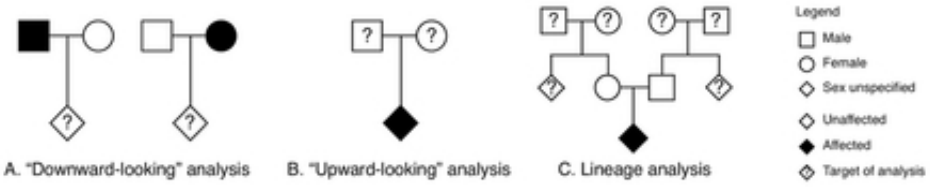
Figure 1. Methods of observing maternal transmission of epilepsy risk. (A) Downward-looking analysis, comparing the prevalence of a history of epilepsy in offspring of affected women versus men; (B) Upward-looking analysis, comparing the prevalence of a history of the epilepsy among mothers versus fathers of affected individuals; (C) Lineage analysis, comparing family history of epilepsy on the maternal side vs. the paternal side of the pedigree.

Figure 2. Results of downward-looking analysis

Prevalence of a history of epilepsy among offspring of affected mothers versus offspring of affected fathers.
Abbreviations: GEFS+, genetic epilepsy with febrile seizures plus; PR, prevalence ratio (offspring of affected mothers relative to fathers).

Figure 3. Results of upward-looking analysis

Prevalence of a history of epilepsy among mothers versus fathers of subjects with epilepsy.
Abbreviations: F, female; M, male; OR, odds ratio (affected sibships relative to unaffected sibships); GEFS+, genetic epilepsy with febrile seizures plus.



Methods of observing maternal transmission of epilepsy risk. (A) Downward-looking analysis, comparing the rate of epilepsy in offspring of affected women versus men; (B) Upward-looking analysis, comparing the rate of the epilepsy among mothers versus fathers of affected individuals; (C) Lineage analysis, comparing family history of epilepsy on the maternal side vs. the paternal side of the pedigree.

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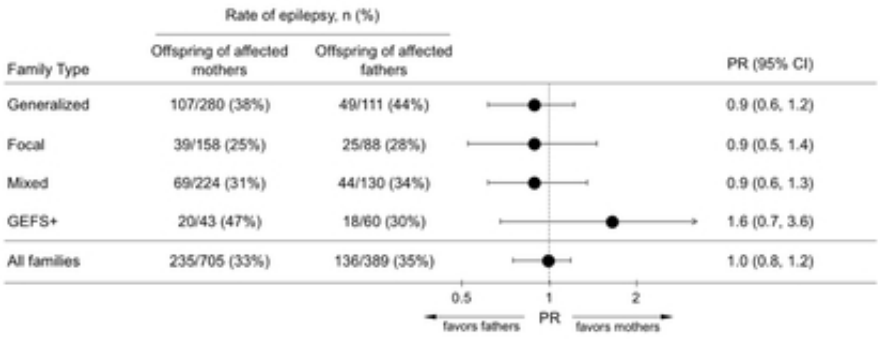

Results of downward-looking analysis. Rate of epilepsy among offspring of affected mothers versus offspring of affected fathers. Abbreviations: GEFS+, genetic epilepsy with febrile seizures plus; PR, prevalence ratio (offspring of affected mothers relative to fathers).

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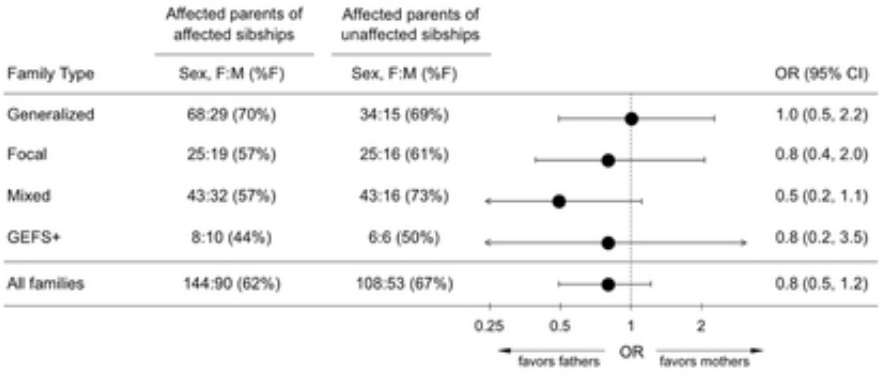

Results of upward-looking analysis. Rate of epilepsy among mothers versus fathers of subjects with epilepsy. Abbreviations: F, female; M, male; OR, odds ratio (affected sibships relative to unaffected sibships); GEFS+, genetic epilepsy with febrile seizures plus.

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The "maternal effect" on epilepsy risk: analysis of multiplex families and reassessment of prior evidence

SUPPLEMENTARY CONTENT

Supplementary Table 1. Epi4K Consortium collaborators

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Supplementary Table 2. Studies utilizing downward-looking analyses

Study	Cohort	Ascertainment	Rate of epilepsy		PR (95% CI)
			Offspring of affected women	Offspring of affected men	
Current study	Familial epilepsy	Multiplex families	235/705 (33%)	136/389 (35%)	1.0 (0.8, 1.1)
[8]Afawi, 2016	Familial GGE	Multiplex families	30/111 (26%)	15/48 (31%)	0.9 (0.5, 1.5)
[10]Peljto, 2014	Epilepsy	Population	14/355 (3.9%)	4/279 (1.4%)	2.8 (0.9, 8.3)
[3]Ottman, 1988	Epilepsy	Population	17/369 (3.9%)	6/318 (1.9%)	2.4 (1.0, 6.1)
[20]Janz, 1986	JME	Clinic	3/59 (5.1%)	3/31 (9.7%)	0.5 (0.1, 2.5)
[21]Tsuboi, 1986	Epilepsy	Clinic	16/443 (3.6%)	9/434 (2.1%)	1.7 (0.8, 3.9)
[22]Beck-Mannagetta, 1986	Epilepsy	Clinic	26/453 (5.7%)	13/387 (3.4%)	1.7 (0.9, 3.3)
[23]Janz, 1982	Epilepsy	Clinic	16/397 (4.0%)	10/371 (2.7%)	1.5 (0.7, 3.3)
[11]Annegers, 1978	Epilepsy	Population	11/422 (2.6%)	2/265 (0.8%)	3.0 (0.7, 14)
[24]Tsuboi, 1977	Epilepsy	Clinic	8/273 (2.9%)	4/233 (1.7%)	1.7 (0.5, 5.6)

[9]Annegers, 1976	Epilepsy	Population	10/351 (2.8%)	0/229 (0%)	N/A
[12]Tsuboi, 1973	JME	Clinic	12/142 (8.5%)	2/133 (1.5%)	5.6 (1.3, 24)
[25]Echeverria, 1880	Married epileptics	Not reported	57/298 (19%)	21/255 (8%)	2.3 (1.4, 3.7)

Abbreviations: GGE, genetic generalized epilepsy; JME, juvenile myoclonic epilepsy; PR, prevalence ratio.

Comments
Several studies utilized data from the Rochester Epidemiology Project and their cohorts overlap: Peljto et al. (2014), Ottman et al. (1988), Annegers et al. (1978), Annegers et al. (1976). There is likely overlap in the cohorts of Beck-Mannagetta et al. (1986) and Janz et al. (1982). There is likely overlap in the cohorts of Tsuboi (1986), Tsuboi & Christian (1977), and Tsuboi & Endo (1973).

Supplementary Table 3. Parenthood and marriage rates for women versus men with epilepsy.

A. Parenthood rates

			Parenthood Rate, N (%)		
Study	Cohort	Location	Women	Men	OR
Current study	Familial epilepsy	USA/Eur/AU/NZ	263/637 (41%)	149/483 (31%)	1.4
[26]Starck, 2019	Childhood onset epilepsy	Finland	59/143 (41%)	40/164 (24%)	1.7
[27]Schupf, 1994	Idiopathic epilepsy	USA	586/960 (61%)	232/586 (40%)	1.5
Median OR					**1.5**

B. Marriage rates

			Marriage Rate, N (%)		
Study	Cohort		Women	Men	OR
[21]Tsuboi, 1986	Epilepsy	Japan	305/440 (69%)	257/484 (53%)	1.3
[28]Lindsay,1979	Temporal lobe epilepsy	UK	25/37 (68%)	17/63 (27%)	2.5
[29]Dansky, 1980	Epilepsy	Canada	61/100 (61%)	38/100 (38%)	1.6
[30]Wada, 2004	Epilepsy, normal intellect	Japan	84/136 (62%)	76/142 (53%)	1.2
[31]Kim, 2010	Epilepsy, normal intellect	Korea	202/308 (66%)	131/276 (47%)	1.4
[26]Starck, 2019	Childhood onset epilepsy	Finland	50/143 (35%)	37/164 (23%)	1.5
Median OR					**1.4**

Abbreviations: OR, odds ratio

Comments
(A) Parenthood rate refers to the likelihood that an individual had ≥1 offspring. This is distinct from fertility, which is typically expressed as number of offspring per person. (B) Marriage rates were examined as a surrogate measure of reproductive potential. These studies are largely consistent, even across cultures, in demonstrating that women with epilepsy are more likely to marry than men with epilepsy.

Supplementary Table 4. Studies utilizing upward-looking analyses

		Probands		Affected Parents		
Study	Cohort	N	SR	F:M	SR (95% CI)	Expected SR
[8]Afawi, 2016	Familial GGE	179	1.7	45:15	3.0 (1.6, 5.8)	2.4

[5]Pal, 2006	JME or EEG trait	89	2.7	22:4	5.5 (2.0, 15)	3.8
[4]Marini, 2004	Familial GGE	55	1.4	17:9	1.9 (0.9, 3.9)	2.0
[32]Doose, 2001	Absence and MAE	82	1.0	9:6	1.5 (0.6, 4.0)	1.4
[17]Doose, 1987	Absence and MAE	400	0.8	29:29	1.0 (0.6, 1.6)	1.1
[16]Doose, 1969	Photosensitive epilepsy	99	1.4	4:1	4.0 (0.5, 35)	2.0
[20]Janz, 1986	JME	181	1.3	4:4	1.0 (0.3, 3.9)	1.8
[18]Gerken, 1977	Focal epilepsy	203	0.6	6:3	2.0 (0.5, 7.7)	0.9
[12]Tsuboi, 1973	JME	319	1.0	15:6	2.5 (1.0, 6.4)	1.4
[14]Metrakos, 1960	Convulsions	63	NR	9:4	2.2 (0.7, 7.0)	(1.4)
[33]Ounsted, 1952	Convulsions	327	NR	26:10	2.6 (1.3, 5.2)	(1.4)
[34]Harvald, 1951	Epilepsy	1200	NR	28:26	1.1 (0.6, 1.8)	(1.4)
[13]Stein, 1933	Epilepsy	1000	1.1	35:23	1.5 (0.9, 2.6)	1.5
[35]Clarke, 1880[a]	Epileptic prisoners	119	0.34[a]	17:8	2.1 (1.0, 4.7)	(1.4)
[25]Echeverria, 1880	Married epileptics	136	1.2	10:8	1.2 (0.5, 3.1)	1.7

Abbreviations: GGE, genetic generalized epilepsy; JME, juvenile myoclonic epilepsy; MAE, myoclonic-atonic epilepsy; SR = Sex Ratio, females to males

[a]Clarke (1880) sex ratio reflects prison population, thus not used to calculate expected SR.

Comments

Expected sex ratio (SR) was calculated by multiplying the sex ratio reported in the study by the assumed parenthood ratio of 1.4. This assumed parenthood ratio is based on evidence presented in Supplementary Table 2; see main text for discussion. As demonstrated in our primary analysis, the combination of these two factors estimates the ratio of affected mothers to fathers that is expected in the cohort due to chance alone. When a study did not report the sex ratio of its cohort, an expected SR value of 1.4 is shown in parentheses, representing the contribution of the assumed parenthood ratio. This reassessment demonstrates that the expected value accurately predicts the observed value in many studies; in no study does the observed SR significantly differ from the expected SR; and in nearly half (6/14) the observed value is less than or equal to the expected value. A few families in our cohort were included in the studies by Afawi et al. (2016) and Marini et al. (2004).