Columbia University Mailman School of Public Health Epidemiology Master's Thesis

Title: Perceived Future Epilepsy Risk Among Unaffected Members of Multiplex Epilepsy Families: Modeling the Impacts of Number of Affected Relatives and Perceived Chance of Having Epilepsy-Related Mutation

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ABSTRACT

Background: Genetic influences on the epilepsies are increasingly being emphasized in clinical practice, and genetic testing is becoming a more routine part of clinical care. Hence, understanding of beliefs about epilepsy genetics among unaffected relatives of people with epilepsy is important.

Aims: To investigate, among individuals without epilepsy in multiplex epilepsy families, the impacts on perceived future epilepsy risk of (1) number of relatives with epilepsy and (2) perceived chance of having an epilepsy-related mutation.

Methods: A self-administered questionnaire was completed by 189 individuals without epilepsy from families containing multiple individuals with epilepsy (average 4 affected per family). Questions asked about the number of people with epilepsy in the family, perceived chance of having an epilepsy-related mutation, and perceived future epilepsy risk "compared with the average person." Complete data on all three questions were available for 103 participants. Associations among total relatives with epilepsy, perceived chance of having epilepsy-related mutation, and perceived future epilepsy risk were assessed by Poisson regression models using generalized estimating equations to adjust for non-independence among members of each family. Mediation analysis was used to test the degree to which the effect of total relatives with epilepsy on perceived future epilepsy risk was mediated by perceived chance of having a mutation. Stratified analyses and Poisson regression were used to explore interaction between number of relatives with epilepsy and perceived chance of having epilepsy-related mutation.

Results: Number of affected relatives (≥4 vs. <4) was significantly associated with perceived future epilepsy risk ("more" vs. "the same or less" than the average person) (Prevalence ratio

[PR]=1.9, 95% Confidence interval [CI]=1.08-3.22, p=0.02), and with perceived chance of having an epilepsy-related mutation (PR=1.5, 95% CI=1.04-2.04, p=0.03). Perceived chance of having a mutation was also associated with perceived future epilepsy risk (PR=3.4, 95% CI=1.55-7.46, p=0.002). Mediation analysis indicated that number of affected relatives had a significant total effect (PR=1.9, 95% CI=1.06-3.57) on perceived future epilepsy risk and a significant indirect effect, acting through perceived chance of having a mutation (PR=1.3, 95% CI=1.02-1.65). The direct effect of number of affected relatives was not significant (PR=1.6, 95% CI=0.84-2.95). The proportion of the total effect mediated by perceived chance of having a mutation was 41.0% on risk difference scale. Sub-additive interaction between number of relatives with epilepsy and perceived chance of having an epilepsy-related mutation was detected (Relative Excess Risk due to Interaction [RERI] =-1.5, 95% CI=-8.76-5.67).

Conclusions: Our study began with a conceptual mediation model that then brought us to explore interaction between exposure and mediator in their effects on the outcome. The analysis indicated that the relationship between total relatives with epilepsy and perceived future epilepsy risk was mediated by perceived chance of having an epilepsy-related mutation. A nonsignificant sub-additive interaction was detected between total relatives with epilepsy and perceived chance of having an epilepsy-related mutation, suggesting the potential competitive interaction type in our study.

INTRODUCTION

The number of genes found to be related to epilepsy susceptibility has dramatically increased, leading to an increase in genetic testing in clinical practice (1-3). Understanding of the reactions of patients and their families to this emphasis on genetic causes is essential because disease-related beliefs can have a profound effect on clinical decision making, medication adherence, and prognosis adjustment (4). Both beneficial and harmful psychological impacts of genetic causal attribution have been detected in previous studies, varying by disease (5, 6). However, little is known about beliefs about epilepsy genetics among people with epilepsy and their unaffected relatives. A previous study using qualitative research methods found that the number of affected family numbers can shape beliefs about genetics (7). Also, in a quantitative study of families containing multiple affected individuals, increased levels of genetic attribution in people with ≥4 relatives with epilepsy and higher perceived future epilepsy risks in people with higher levels of genetic attribution were recently observed (8). These findings suggest that number of affected relatives may have a causal effect on both genetic attribution and perceived future epilepsy risk, and similarly, genetic attribution may have a causal effect on perceived future epilepsy risk.

Mediation analysis is becoming increasingly prominent in epidemiology and has a long history, starting with two traditional approaches: the difference method and the product method (9-11). The latter approach is used most commonly, popularized by Baron and Kenny (12). However, this approach is limited because it relies on two untested assumptions: uncorrelated errors and linear relationships of predictors to outcome variables (13).

Recently, advances in mediation analysis have used causal inference approaches (14-16) first conceptualized by Robins and Greenland (17). VanderWeele and Vansteelandt extended Baron and Kenny's approach to allow for decomposition of total effects into natural direct effects and natural indirect effects, including exposure-mediation interaction and other nonlinearities (18).

The current study hypothesized that perceived chance of having an epilepsy-related mutation mediated the relationship between total relatives with epilepsy and perceived future epilepsy risk among biological relatives without epilepsy in multiplex epilepsy families. We explored the associations in analyses of data provided by participants without epilepsy who were enrolled in the follow-up study of the Epilepsy Family Study of Columbia University (EFSCU). All of these participants were members of families containing multiple individuals with epilepsy (average four affected per family), but were themselves unaffected.

METHODS

Participants

Participants were from the "Psychosocial Impact of Genetics in Epilepsy" study, which was a follow-up investigation of participants in the Epilepsy Family Study of Columbia University (EFSCU), a long-term research project that began in the 1980s as a familial aggregation study and evolved into a genetic linkage study (19-23). Families were eligible for the linkage study if they contained either a sibling pair or three or more individuals with epilepsy of unknown cause. Participants in the linkage study were eligible for the follow-up study if they previously participated in the genetic research, were able to complete a self-administered survey in English, and were willing to be contacted for future research. Among 1274 participants in 117

families, 345 were excluded because they did not meet these criteria, leaving 929 eligible individuals in 113 families. These 929 individuals included 330 who had a history of epilepsy, 441 biological relatives without epilepsy, and 158 who were married-in to the families (8).

Eligible individuals were asked to complete a self-administered questionnaire either online through an instrument implemented in Survey Monkey (Survey Monkey, Inc., Palo Alto, California, U.S.A., www.surveymonkey.com) or on paper. The Columbia University Medical Center Institutional Review Board approved the research protocols for the study.

Epilepsy history

Individuals were defined as having a history of epilepsy if they responded "yes" to either of two survey questions. The first asked, "Which of your biological relatives have had epilepsy or a seizure disorder?" followed by a list of relative types with "Yourself" at the top. The second asked, "Have you ever been told that you had epilepsy or a seizure disorder?" Self-reported data were used rather than the previous diagnoses because self-perception of epilepsy history may be more relevant to individuals' genetic attribution of epilepsy, and a long period had elapsed since the previous diagnoses, so that some people may have developed epilepsy in the interim.

Total relatives with epilepsy

Number of relatives with epilepsy was based on answers to the question: "Not including yourself, how many of your biological (or blood) relatives have had epilepsy or a seizure disorder?" Number of affected relatives was dichotomized as less than four vs. four or more.

Perceived chance of having an epilepsy-related mutation

All individuals were asked, "In your opinion, what do you think the chances are that you

have a change or mutation in a gene that affects risk for epilepsy?" Perceived chance of having an epilepsy-related mutation was originally an ordinal variable on a 4-point scale. It was dichotomized as none/small vs. moderate/high.

Perceived future epilepsy risk

Individuals without epilepsy were asked, "In your opinion, would you say your chances of getting epilepsy in the future are. . ." with five possible responses ranging from "much less than the average person" to "much more than the average person." This variable was dichotomized as "same, less, or much less" vs. "more or much more."

Covariates

Sociodemographic variables age, sex, education, and employment were potential confounders in this study. We assessed the association of each potential confounder with total relatives with epilepsy (exposure), perceived future epilepsy risk (outcome), and perceived chance of having epilepsy-related mutation (mediator). We adjusted for variables that were not theorized to be in the causal pathway and were associated with at least two of the three variables of interest (outcome, exposure, and potential mediator), using a threshold of p=0.20.

Statistical analysis

IBM SPSS Statistics for Windows, Version 24.0 (IBM Corporation, Armonk, NY, U.S.A.) and SAS software 9.4 (SAS Institute, Cary, NC, U.S.A.) were used to perform all statistical analyses.

For analysis of potential confounders and exploratory analysis of associations among exposure, mediator, and outcome, we used Poisson regression models to compute prevalence ratios (PRs) with robust standard errors (24). Generalized estimating equations (GEE) were used

to account for non-independence resulting from inclusion of multiple individuals from the same family (25).

For mediation analysis, we used VanderWeele and Vansteelandt's formulation (18). Let A denote total relatives with epilepsy (exposure), Y denote perceived future epilepsy risk (outcome), M denote perceived chance of having an epilepsy-related mutation (potential mediator) and C denote observed confounders (Figure 1). The total effect (TE) of the exposure on the outcome can be decomposed into natural direct effects (NDE) and natural indirect effects (NIE). To interpret the estimates of indirect effect and direct effect causally, we assumed no unobserved confounding in the relationship between a) exposure-outcome, b) mediator-outcome, c) exposure-mediator (18); we also assumed no association of the exposure with any mediator-outcome confounder (18) (Figure 2). Two regression models were fit: a log-linear regression for outcome (Eq. 1), and a logistic regression for mediator (Eq. 2):

$$\log\{\mathrm{E}(\mathrm{Y}|\mathrm{A}=\mathrm{a},\mathrm{M}=\mathrm{m},\mathrm{C}=\mathrm{c})\}=\theta_0+\theta_1\mathrm{a}+\theta_2\mathrm{m}+\theta_3\mathrm{am}+\theta_4'\mathrm{c} \quad \text{Eq. 1}$$

$$\mathrm{logit}\{\mathrm{P}(\mathrm{M}=1|\mathrm{A}=\mathrm{a},\mathrm{C}=\mathrm{c})\}=\beta_0+\beta_1\mathrm{a}+\beta_2'\mathrm{c} \quad \text{Eq. 2}$$

We used a log linear model instead of a logistic model for the outcome (perceived future epilepsy risk) because the outcome was common (>10% is often used as a cutoff) in our study sample, and odds ratios no longer approximate the risk ratios in this case (26). We estimated standard errors through bootstrap resampling with 1000 replications. All regression models in mediation analysis were adjusted for covariates and observed confounders. We first tested for interaction between the exposure (total relatives with epilepsy) and mediator (perceived chance of having epilepsy-related mutation) in their effects on the outcome. The interaction term "am" would not be included in equation 1 if it was not significant ($\theta_3=0$)(18).

We estimated PRs and confidence intervals (CIs) for a) the NDE, i.e., how much the outcome would change on average if the exposure changed from <4 to ≥4 affected relatives, but the mediator for each individual was fixed at the level it would have taken when the exposure was at the level <4 affected relatives b) the NIE, i.e., how much the outcome would change on average if the exposure were fixed at ≥4 affected relatives but the mediator (perceived chance of mutation) were changed from "none/small" to "moderate/high," and c) TE, i.e. how much the outcome would change overall if the exposure changed from <4 to ≥4 affected relatives. In this study, NDE, NIE and TE were computed on the ratio scale: $\mathrm{PR}^{\mathrm{NDE}}$, $\mathrm{PR}^{\mathrm{NIE}}$ and $\mathrm{PR}^{\mathrm{TE}}$ using VanderWeele and Vansteelandt's SAS macro (18).

Previously, Robins and Greenland (1992) and Pearl (2001) (17, 27) had derived formulae corresponding to counterfactual definitions of direct and indirect effects, based on an additive scale. In their formulation, Y_{ij} refers to the risk in individuals with exposure i and mediator j, where i, j are both binary {1,0}. The pure direct effect is represented by $\mathrm{Y}_{10} - \mathrm{Y}_{00}$, and the total direct effect by $\mathrm{Y}_{11} - \mathrm{Y}_{01}$ (28). The pure indirect effect is represented by $\mathrm{Y}_{01} - \mathrm{Y}_{00}$, and the total indirect effect by $\mathrm{Y}_{11} - \mathrm{Y}_{10}$. The terminologies "pure" and "total" used by Robins and Greenland were derived from different ways of accounting for interaction (17). When an interaction between exposure and mediator is present, the total effect includes the direct effect, indirect effect and interactive effect. The total effect $\mathrm{Y}_{11} - \mathrm{Y}_{00}$ can be decomposed in two ways: (1) total indirect effect and pure direct effect, $(\mathrm{Y}_{11} - \mathrm{Y}_{10})$+$(\mathrm{Y}_{10} - \mathrm{Y}_{00})$, or (2) total direct effect and pure indirect effect, $(\mathrm{Y}_{11} - \mathrm{Y}_{01})$+$(\mathrm{Y}_{01} - \mathrm{Y}_{00})$. When we use decomposition (1), the interaction effect is included in the total indirect effect, whereas when we use decomposition (2), the interaction effect is included in the total direct effect. The terminology

"pure" effectively indicates that either the pure direct or the pure indirect effect does not include an interactive effect. When there is no interaction between exposure and mediator, the pure direct effect is equivalent to the total direct effect, and the pure indirect effect is equivalent to the total indirect effect. In the terminology used by VanderWeele and Vansteelandt, the pure direct effect was referred to as the natural direct effect and the total indirect effect was referred to as the natural indirect effect (18).

The proportion of the total association that is mediated by perceived chance of having an epilepsy-related mutation can be presented on the risk difference scale:

$$\text{Proportion mediated} = \frac{P(Y_{11}=1|c)-P(Y_{10}=1|c)}{P(Y_{10}=1|c)-P(Y_{00}=1|c)+P(Y_{11}=1|c)-P(Y_{10}=1|c)} \quad \text{Eq. 3}$$

PR^{NIE} and PR^{NDE} can be presented using formulas:

$$PR^{NIE} = P(Y_{11}=1|c)/P(Y_{10}=1|c) \quad \text{Eq. 4}$$

$$PR^{NDE} = P(Y_{10}=1|c)/P(Y_{00}=1|c) \quad \text{Eq. 5}$$

Based on the formulae above, the proportion mediated can be computed on the risk difference scale using risk ratios: $PR^{NDE}(PR^{NIE}-1)/(PR^{NDE}PR^{NIE}-1)$(15).

RESULTS

Participant characteristics

Among 929 eligible individuals, 431 completed the survey, of whom 189 (43.9%) were biological relatives without epilepsy. After excluding individuals with missing data (including a "don't know" response) on total relatives with epilepsy (N=10, 5.3%), perceived chance of having an epilepsy-related mutation (N=65, 34.4%) or perceived future epilepsy risk (N=47, 24.9%), 103 individuals remained in the analytic sample. These 103 participants were in 48 families, with an average of 2 (range: 1-8) participants in each family (Table 1). The mean age

of participants was 48.2 (standard deviation [SD]=14.33) years. Most of the participants identified as white (N=96, 93.2%) and non-Hispanic (N=98, 99.0%). Forty-seven (45.6%) reported having ≥4 relatives with epilepsy; 59 (57.3%) responded their chance of having epilepsy-related mutation was moderate or high; 35 (34.0%) responded their risk of developing epilepsy was more or much more than the average person.

Covariates

Analysis of associations of potential confounders with exposure, potential mediator, and outcome indicated that current age was associated with both perceived chance of having a mutation and perceived future epilepsy risk (Table 2). Older participants were less likely than younger participants to respond they had a moderate/high chance of having an epilepsy-related mutation or more/much more risk of developing epilepsy, compared to the average person.

Associations among variables of primary interest

Consistent with our previous findings (8), we found strong relationships among total number of relatives with epilepsy, perceived chance of having epilepsy-related mutation and perceived future epilepsy risk among unaffected relatives (Table 3). Participants with ≥4 affected relatives were about twice as likely as those with fewer affected relatives to respond their chance of developing epilepsy was more or much more than the average person (PR=1.9, p=0.02). Those who perceived they had a moderate or high chance of having an epilepsy-related mutation were more than three times as likely as others to respond their chance of developing epilepsy was more or much more than average (PR=3.4, p=0.002). Participants with ≥4 affected relatives were also significantly more likely than others to respond they had a

moderate or high chance of having an epilepsy-related mutation (1.5, p=0.03). All regression models were adjusted for age of participants based on the results of tests of potential confounding.

Mediation analysis results

We assessed interaction between exposure and mediator by including an interaction term in the Poisson regression model including total relatives with epilepsy and perceived chance of having an epilepsy-related mutation, adjusting for age. The Wald test for significance of interaction was not significant (p=0.18); hence we did not include exposure-mediator interaction in the mediation analysis.

The total effect of number of relatives with epilepsy on perceived future epilepsy risk was significant (Table 4: PR=1.9 95% CI=1.06-3.57). The NDE of total affected relatives on perceived future epilepsy risk was slightly lower, and not significant (PR=1.6, 95% CI=0.84-2.95). We observed significant mediation of the effect of total relatives with epilepsy on perceived future epilepsy risk by perceived chance of having an epilepsy-related mutation (PR=1.3, 95% CI=1.02-1.65). The proportion of the total effect mediated by the perceived chance of having a mutation was 41.0% on the risk difference scale.

Further assessment of interaction

Although we omitted the interaction between exposure and mediator from mediation analysis because the Wald test for interaction was not significant (p=0.18), the relatively small sample size hampered our ability to detect interaction. A better approach, recommended by VanderWeele, is to include an interaction term by default and exclude it from the model if it does not lead to a substantial change in the estimates of the direct and indirect effects (29).

However, due to convergence failure when we added an interaction term to the mediation analysis, we decided to explore possible interaction effects using stratified analysis.

Figure 3 presents the prevalence of the outcome (perceived future epilepsy risk more/much more than the average person) in the four subgroups defined by exposure and mediator. Using the formulation of Robins and Greenland, we obtain P($Y_{11} = 1$) =0.53, P($Y_{01} = 1$) =0.44, P($Y_{10} = 1$) =0.27, P($Y_{00} = 1$) =0.07. On the risk difference scale, the pure direct effect is P($Y_{10} = 1$) - P($Y_{00} = 1$) =0.20 and the total direct effect is P($Y_{11} = 1$) - P($Y_{01} = 1$) =0.09. The pure indirect effect is P($Y_{01} = 1$) - P($Y_{00} = 1$) =0.37 and the total indirect effect is P($Y_{11} = 1$) - P($Y_{10} = 1$) =0.26. To assess interaction on an additive scale, we computed the difference between the total and pure effects using the following equation proposed by Rothman and Greenland, which is also termed the "interaction contrast" (IC) (30): P($Y_{11} = 1$)-P($Y_{10} = 1$)-P($Y_{01} = 1$) +P($Y_{00} = 1$) =-0.11. We obtained a similar pattern through Poisson regression with an interaction term and adjusting for age and family clustering via a GEE model. On the risk ratio scale, pure and total direct effects were $\frac{P(Y_{10}=1)}{P(Y_{00}=1)} = 4.04$ and $\frac{P(Y_{11}=1)}{P(Y_{01}=1)} = 1.25$ respectively; pure and total indirect effects were $\frac{P(Y_{01}=1)}{P(Y_{00}=1)} = 5.96$ and $\frac{P(Y_{11}=1)}{P(Y_{10}=1)} = 1.85$ respectively. Since the results from Poisson regression were on a ratio scale, we assessed interaction on an additive scale by the Relative Excess Risk due to Interaction (RERI) (30): $\frac{P(Y_{11}=1)}{P(Y_{00}=1)} - \frac{P(Y_{10}=1)}{P(Y_{00}=1)} - \frac{P(Y_{01}=1)}{P(Y_{00}=1)} + \frac{P(Y_{00}=1)}{P(Y_{00}=1)} = -1.54$. The 95% CI of RERI, computed based on the formula used by VanderWeele, was -8.76-5.67 (31). Overall, pure effects were larger than total effects, and a nonsignificant sub-additive interaction was detected.

DISCUSSION AND CONCLUSIONS

We used a causal inference approach for mediation analysis to investigate perceived chance of having an epilepsy-related mutation as a potential mediator of the relationship of total relatives with epilepsy to perceived future epilepsy risk. We measured the proportion mediated on the risk difference scale to avoid the issue that natural direct and indirect effect on risk ratio scales use different reference levels of risk. The results demonstrated a significant total effect of total number of relatives with epilepsy on perceived future epilepsy risk and a significant natural indirect effect of total number of relatives with epilepsy on perceived future epilepsy risk through perceived chance of having an epilepsy-related mutation.

Important considerations must be acknowledged when interpreting the findings of mediation analysis in this study. First, although interaction between exposure and mediator was not significant in regression analysis, we cannot exclude the possibility of interaction because our statistical power was hampered by the relatively small sample size. Second, again because of relatively small sample size, regressions in mediation analysis allowing for interaction between exposure and mediator failed to converge and to produce robust estimates of pure and total effects.

Accounting for interaction between exposure and mediator is important to capture the dynamics of mediation even if the interaction coefficient is not significant. Thus, we went back to stratified analyses and the Poisson regression model to explore potential interaction effects. Comparing the pure and total effects, we found that participants' perception that they had a moderate/high chance of having an epilepsy-related mutation had relatively less impact on their perceived future epilepsy risk among those with ≥4 relatives with epilepsy than among

those with <4 relatives with epilepsy (total indirect effect < pure indirect effect). Similarly, having ≥4 relatives with epilepsy had relatively less impact on perceived future epilepsy risk among individuals who responded that they had a moderate/high chance of having an epilepsy-related mutation than among those who responded that they had a none/small chance of having an epilepsy-related mutation (total direct effect < pure direct effect). Based on negative values of IC and RERI, a nonsignificant sub-additive interaction was present under the monotonicity assumption, which indicates the potential presence of competitive interaction in our sample (32) (also called redundant causation) (33). Competitive interaction refers to a situation in which either having ≥4 relatives with epilepsy or a moderate/high perceived chance of having an epilepsy-related mutation can cause a perceived future epilepsy risk higher than average person when the other factor is absent. In theory, whichever risk factor is obtained first is the true cause of the high perceived future epilepsy risk.

Our study has several limitations. First, we did not allow for interaction term between exposure and mediator and did not adjust for non-independence of individuals within each family in mediation analysis because of the relatively small sample size. Second, cross-sectional data made it impossible to infer temporality of associations and to draw strong conclusions about the causal effects of variables of primary interest. However, the number of relatives with epilepsy cannot reasonably be caused by either perceived chance of having epilepsy-related mutation or perceived future epilepsy risk among unaffected relatives. In addition, a causal effect of a moderate/high perceived chance of having an epilepsy related mutation on perceived future epilepsy risk appears more plausible than the reverse, although causal mechanisms of psychological beliefs are complex. Restricted assumptions of mediation analysis

used in this study is the third limitation. Sensitivity analyses should be used to assess how robust the evidence for mediation and the estimates of the direct and indirect effects are if assumptions are violated (16, 34-37). Finally, our study cannot be generalized to all individuals with epilepsy because it is focused on a special subgroup: individuals from families containing multiple affected individuals.

In conclusion, our study began with a conceptual mediation model that then brought us to explore interaction effect between exposure, mediator, and outcome. Despite limitations discussed above, our results revealed several important insights regarding the impacts on perceived future epilepsy risk of number of relatives with epilepsy and perceived chance of having an epilepsy-related mutation among individuals without epilepsy in multiplex families. The proportion of the total effect of number of relatives with epilepsy on perceived future epilepsy risk mediated by the perceived chance of having a mutation was found to be 41.0% on the risk difference scale. We assessed interaction between number of relatives with epilepsy and perceived chance of having an epilepsy-related mutation on both multiplicative and additive scales. Sub-additive interaction between number of relatives with epilepsy and perceived chance of having an epilepsy-related mutation indicates the potential presence of individuals of competitive interaction in our study. Future study that allows for interaction between number of relatives with epilepsy and perceived chance of having an epilepsy-related mutation in mediation analysis would be extremely important to understand the effect of number of relatives with epilepsy and perceived chance of having an epilepsy-related mutation on perceived future epilepsy risk, as well as the role that perceived chance of having an epilepsy-related mutation plays on the association between number of relatives with epilepsy

and perceived future epilepsy risk.

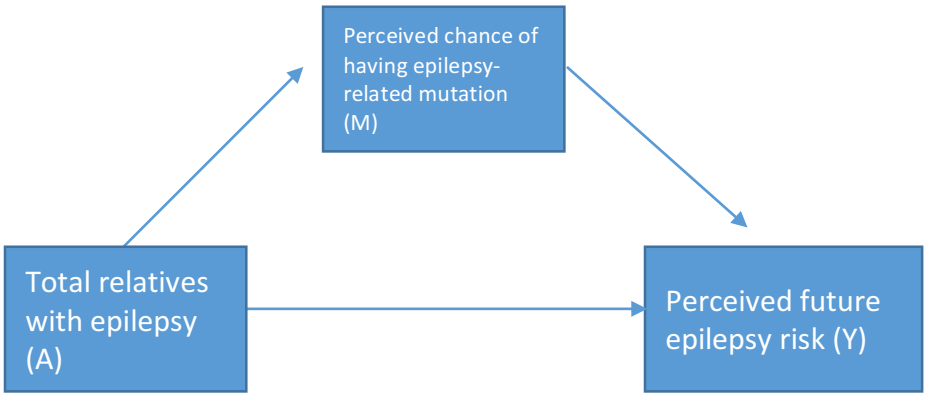

Figure 1. Simple mediation diagram.

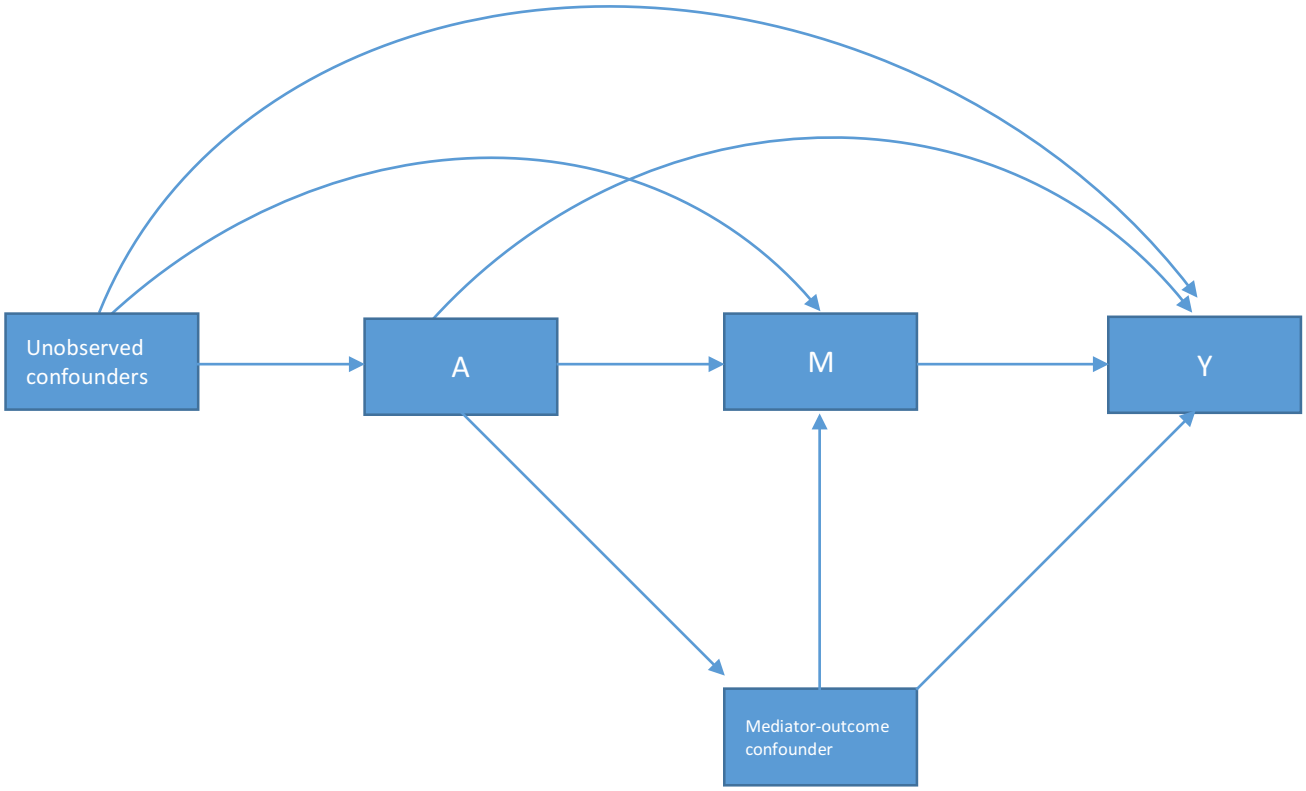

Figure 2. Assumptions for mediation analysis using causal inference approaches.

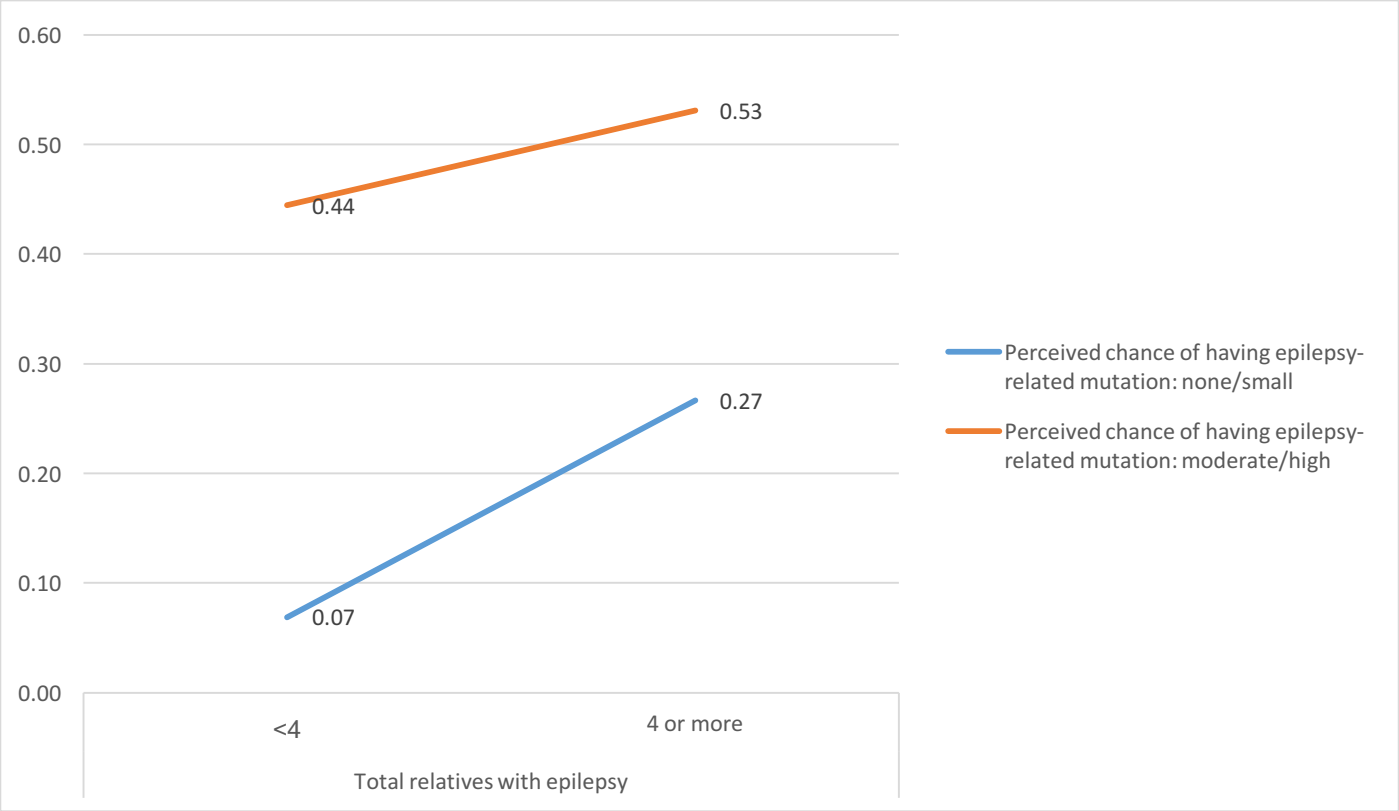

Figure 3. Prevalence of perceived future epilepsy risk more/much more than average person by different exposure/mediator levels.

Table 1. Characteristics of biological relatives without epilepsy (N=103)

Variables	N	%
Age (years)		
<40	31	30.1
40-59	49	47.6
60+	23	22.3
Sex		
male	42	40.8
female	61	59.2
Education		
Less than college graduate	41	40.2
College graduate or higher	61	59.8
Employment		
Employed/retired	86	86.0
Unemployed	14	14.0
Religion		
None/atheist/prefer not to say	15	14.9
Catholic	29	28.7
Protestant	43	42.6
Other	14	13.9
Hispanic or Latino origin		
No	98	99.0
Yes	1	1.0
Race		
White	96	93.2
Non-White	7	6.8
Total relatives with epilepsy		
<4	56	54.4
≥4	47	45.6
Perceived chance of having mutation		
None/small	44	42.7
Moderate/high	59	57.3
Perceived future epilepsy risk, compared with average person		
Same/less/much less	68	66.0
More/much more	35	34.0

Table 2. Association of potential confounders with exposure, mediator, and outcome

		Total relatives with epilepsy		Perceived chance of having mutation		Perceived future epilepsy risk	
Potential confounders	N	% ≥4	PR (95% CI)	% moderate/ high	PR (95% CI)	% more/much more than average person	PR (95% CI)
Age	103	45.6	1.0 (0.99,1.03)	57.3	1.0 (0.98,1.00)	34.0	1.0 (0.97,1.00)
p-value*			0.44		0.02		0.05
Sex							
female	61	52.5	1.5 (0.91,2.36)	59.0	1.1 (0.75,1.54)	36.1	1.2 (0.73,1.86)
male	42	35.7	1.0 (reference)	54.8	1.0 (reference)	31.0	1.0 (reference)
p-value*			0.11		0.68		0.52
Education							
College graduate or higher	61	45.9	1.0 (0.62,1.57)	57.4	1.0 (0.70,1.50)	31.1	0.9 (0.53,1.37)
Less than college graduate	41	46.3	1.0 (reference)	56.1	1.0 (reference)	36.6	1.0 (reference)
p-value*			0.97		0.91		0.51
Employment							
unemployed	14	35.7	0.7 (0.37,1.50)	50.0	0.9 (0.50,1.54)	28.6	0.8 (0.37,1.93)
employed/retired	86	47.7	1.0 (reference)	57.0	1.0 (reference)	33.7	1.0 (reference)
p-value*			0.41		0.65		0.69

*P-value from Wald test in Poisson regression models adjusted for clustering in each family (GEE).

Table 3. Associations among total relatives with epilepsy, perceived chance of having an epilepsy-related mutation and perceived future epilepsy risk

		Perceived future epilepsy risk, compared with average person		Perceived chance of having mutation	
Predictors	N	% more/ much more	PR (95% CI)	% moder-ate/high	PR (95% CI)
Total relatives with epilepsy					
≥4	47	44.7	1.9 (1.08,3.22)	68.1	1.5 (1.04,2.04)
<4	56	25.0	1.0 (reference)	48.2	1.0 (reference)
p-value*			0.02		0.03
Perceived chance of having mutation					
Moderate/high	59	49.2	3.4 (1.55,7.46)		
None/small	44	13.6	1.0 (reference)		
p-value*			0.002		

*P-value from Wald test in Poisson regression models adjusted for age and clustering in each family (GEE).

Table 4. Mediation analysis results

Effect*	PRs	SE	95% CI	Percent mediated
Natural direct effect	1.6	0.51	0.84, 2.95	41.0
Natural indirect effect	1.3	0.16	1.02, 1.65	
Total effect	1.9	0.62	1.06, 3.57	

*Causal effects on ratio scales, adjusted for age.

Table 5. Causal effects of competitive interaction and synergism

	Y			
Interaction type	X= 1 M= 1	X= 1 M= 0	X= 0 M= 1	X= 0 M= 0
Competitive	1	1	1	0
Synergistic	1	0	0	0

Note: total relatives with epilepsy (X): 1= ≥4, 0= <4; perceived future epilepsy risk (Y): 1= more than average person, 0=the same or less than average person; perceived chance of having epilepsy-related mutation (M): 1=moderate/high, 0=none/small.

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