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Review

Who is driving and who is prone to have traffic accidents? A systematic review and meta-analysis among people with seizures

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ABSTRACT

Introduction: Epilepsy influences the ability to drive. We aimed to systematically summarize factors associated with driving, holding a driver's license, and traffic accidents among people with seizures.
Material and methods: Eight databases were searched (from their inception to 27 June 2018). We included all published observational studies, except for case reports and studies with fewer than 50 participants. Pooled mean differences and pooled risk ratios (pRRs) with corresponding confidence intervals (CIs) were calculated using random effects.
Results: Data were available from 18 studies, reporting a wide range of factors. There were frequent biases associated with cross-sectional study designs, selection bias, poor statistical quality, small samples, and lack of validation of models. The following six variables were consistently associated with driving: male gender (pRR: 1.42; 95% CI: 1.23 to 1.64), being in paid work (pRR: 1.72; 95% CI: 1.46 to 2.03), married (pRR: 1.26; 95% CI: 1.01 to 1.57), older age at seizure onset or diagnosis (pooled mean difference: 4.83; 95% CI: 0.48 to 9.18 years), less frequent seizures (fewer than monthly, pRR: 1.32; 95% CI: 1.12 to 1.56), and taking one or no antiepileptic drug (pRR: 1.34; 95% CI: 1.09 to 1.63). Lower seizure frequency was also protective for avoiding traffic accidents (pRR: 0.26; 95% CI: 0.10 to 0.66).
Discussion: Stable multivariate models to predict driving or traffic accidents among people with seizures have not yet been developed. Current evidence shows that the likelihood of driving is associated with demographic and epilepsy-related factors, while the risk of traffic accidents is associated with seizure frequency.
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1. Introduction

In high income countries, as many as 90% of people with epilepsy drive before disease onset [1], 98% hold a driver's license 10 years after diagnosis [2], and up to 39% drive in violation of restrictions [3], while only 19% [4] to 32% [5] of people with epilepsy drive in middle income countries. It is likely that discrepancies in car ownership, availability of public transportation, and driving legislation in different countries affect decisions to drive. Disagreements remain regarding other factors, such as age [5,6], gender [4,5,7], level of education [4,7], employment [7,8], and frequency of attacks [6,7], that might facilitate a return to driving among people with seizures.

People with epilepsy who drive motor vehicles are at an increased risk of traffic accidents compared with the unaffected population [9]. In an attempt to eliminate that risk, driver-licensing authorities in some jurisdictions ban all people who have experienced a seizure from driving [4]. However, being unable to drive may have major negative influences on quality of life [10] and employment [11]. An absolute ban encourages the nonreporting of seizures to treating clinicians [12], and noncompliance with driving restrictions [13]. This results in a paradoxical increase in risk of traffic accidents because of suboptimal treatment and continued driving by drivers at risk.

The approach in most jurisdictions is to minimize rather than eliminate risk by allowing people with an acceptably low risk of a seizure-related traffic accident to continue or resume driving, while suspending

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the license of those with a higher risk. Identifying the risk of a traffic accident in people who have had one or more seizures is therefore fundamental to identifying those who are permitted to drive. In most countries, the major or sole predictive factor employed by driver-licensing authorities is the time since the last seizure. However, as well as length of seizure freedom, other factors may predict seizure recurrence, and therefore the risk of seizure-related traffic accidents, including age, type of seizure, diurnal pattern [14], duration of seizures, and abnormal electroencephalogram (EEG) [15,16].

To date, there have been two systematic reviews of driving and/or traffic accidents among people with epilepsy [17,18], both of which judged the quality of evidence using American Academy of Neurology criteria [19]. Such criteria are applicable to interventional studies in making treatment decisions [19], but may not be valid for observational ones. Because of the paucity of current evidence [17], we aimed to systematically review the published evidence regarding factors predictive of driving, holding a driver's license, and traffic accidents, assess their quality using accepted criteria relevant to observational studies [20,21], and conduct quantitative syntheses. This knowledge can help physicians and policy makers identify those most likely to drive and those at most risk of traffic accidents, fairly amend legislation, effectively inform regulations, target alternative transportation options (e.g., taxi subsidy schemes), and encourage optimal management of the disease.

2. Material and methods

The protocol for this review was registered in Prospero [CRD42017075358], and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [22] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [23]. We restricted the review to published observational studies that reported either 1) variables associated with driving or holding a driver's license among people with seizures who reached a legal age to drive, or 2) variables associated with traffic accidents among people with seizures who drive. All observational study designs were accepted with the exception of case reports and those studies with fewer than 50 participants. All journal research articles were accepted without language limitations. Published conference abstracts were excluded unless we identified the corresponding published journal articles through database searching or contacting authors.

2.1. Search strategy and screening

The following eight databases (from inception to 27 June 2018) were searched: MEDLINE, EMBASE, PsycINFO and COCHRANE CENTRAL via OvidSP, CINAHL via Ebsco, and TRID, Physiotherapy Evidence Database (PEDro), and Campbell Collaboration's social, psychological, educational and criminological trials register (C2-SPECTR) via websites [24–26]. We used the following search terms as free text or controlled vocabulary for the corresponding database: epilepsy, seizures, convulsions and automobile driving, car driving, car, motor vehicle, automobiles, motorcycles, traffic accidents, transportation accidents, driving license, and driving ability (Table e-1). Two authors (YX, JS) screened titles and abstracts of all references and full-text of relevant articles to identify eligible studies. Further literature was sought through the reference lists of included studies.

2.2. Data extraction

Data extraction was completed independently by two authors (YX, ZZ) and checked by a third author (JS). Data extraction included year of publication, country, the last name of the first author, case selection (e.g., population-based, hospital-based), study design (e.g., case-control, cross-sectional, cohort), data collection method (e.g., interview, mailed/emailed/online survey), and variables independently associated with the dependent variable (i.e., driving status, driver's license status, or traffic accidents). We requested additional unpublished data from the authors of the included studies, if the study was published on or after 2001.

2.3. Statistical quality assessment

We assessed the quality of each multivariate model based on external validity (i.e., no exclusion criteria applied, age and sex distributions of study populations described, and prospective and consecutive recruitment), internal validity (i.e., data collection methods, response rates, and time frame for dependent variables), statistical validity (i.e., the maximum p value in univariate analyses for variables to be included in the multivariate analysis; not over-fitting of models: the minimum number of outcome events per independent variable entered into the logistic regression model is 10; stepwise analysis adopted; collinearity correctly assessed), and practicality (i.e., appropriateness and accuracy of the model to be used in clinical practice to predict outcomes).

2.4. Statistical analysis

We calculated mean differences and risk ratios, with corresponding 95% confidence intervals [CIs] for individual studies, and for all the variables that were assessed in at least half of the studies predicting each outcome. Data were extracted at the univariate level (e.g., average age of participants and standard deviation/percentage of males, in driving versus nondriving group). Pooled results were presented in forest plots using Stata 13 with random effects. Subgroup analysis was conducted based on countries' income level (defined by the World Bank) and recruitment approach (i.e., prospective and consecutive versus retrospective and/or random, convenience, or selective sampling). Statistical heterogeneity and consistency were assessed using the Cochran's Q statistic and I^2.

3. Results

The search results and selection process are summarized in a PRISMA flowchart (Fig. e-1). A total of 3371 references were identified, of which 142 full-text articles were retrieved to assess for inclusion/exclusion criteria. Eighteen studies were considered eligible for inclusion.

3.1. Study and participant characteristics

Fourteen studies were conducted in high income countries (Table e-2): eight in the United States of America [8,13,27–32], two in Greece [33,34], and one in each of United Kingdom [35], Finland [36], Republic of Korea [6], and Australia [7]. Four studies were from lower middle income countries: two from Brazil [5,37] and one of each from China [4] and Thailand [38]. In one study, participants were derived from a population-based cohort with childhood onset epilepsy, who were still available at 30 years follow-up [36]. Thirteen studies were hospital-based, single center including 2043 participants [4,8,28–30,33,37,38] or multicenter including 980 participants [5,6,13,31,34]. Four studies were community-based and included 17,015 participants [7,27,32,35]. Few studies had prospective and consecutive recruitment [4,6–8,13,27,29,34,36]. Studies were cross-sectional [4–6,8,13,27–29,34,37,38], case-control [31,33,35], or cohort [7,30,32,36]. There were 12 studies investigating factors associated with driving or holding a driver's license [6–8,13,27–29,32–34,36,37], three studies investigating factors associated with traffic accidents [31,35,38], and three studies examining both [4,5,30].

The time between epilepsy diagnosis and assessment of driving status/accidents was not stated in most studies, but ranged from less than one year to 64 years for participants in one study [28], one year in one [7], at least one year in two [4,6], and at least two years in another [33]. Three studies included people with epilepsy as well as those with a

single seizure [30,32,35]. Participants had drug-resistant epilepsy in two studies [13,28] and nondrug-resistant in one [33]. Participants were patients assessed for epilepsy surgery in two studies [13,28], and those who had undergone epilepsy surgery in one [29]. There was one study [36] of childhood onset unprovoked epilepsy. Two studies included only those who had a private driver's license [28,33].

3.2. External and internal validity

Some studies excluded people with illiteracy [5], those with cognitive deficits or psychiatric problems that would compromise their understanding of the questions [5,6,34,37], those with suspected psychogenic seizures [5], and those forbidden from driving a motor vehicle because of a condition other than epilepsy (e.g., heart disease, Meniere's disease, drug abuse) (Table e-3) [4,6,37,38].

All studies used a structured or semistructured questionnaire or register data. The response rate or percentage of participants included in the analysis varied greatly (Table e-3). The response rate to a mailed or emailed/online survey was low, 28% [27], 34% [8], and 56% [29], or adequate, 71% [35]. It was 98% in another survey study [34], where the questionnaire was administered in a hospital. Driving status was categorized as current [28], after surgery [29], or in the preceding eight [7] or 12 months [4,6,13]. Licensing status was categorized as in the preceding two years [30], or during a two-year period 2004 to 2005 [32]. Traffic accidents occurred in the past three years [35] or over a four-year period (1985 to 1988) [30].

3.3. Statistical validity

Statistical quality was poor in many studies (Table e-3). Multivariate analysis was not conducted in three studies investigating variables associated with holding a driver's license [30,32,37] and in one study examining variables associated with traffic accidents [4]. Four studies may have excluded potentially important variables by adopting rigorous p values of 0.05 [6,28,33] or 0.1 [34]. Stepwise removal of nonsignificant variables in multivariate analysis was clearly reported in only two studies [7,36]. The final model was over fitted and unstable in one study, where 16 variables were included but only 147 people held a driver's license [27], while one multivariate study adjusted only for age [30]. Collinearity was correctly assessed in only two studies [4,7].

3.4. Evaluation and practicality of model

In no study was the final model validated with the data used to generate the model (internal validation, Table e-3) or on another dataset (external validation). Data collection of the demographic and clinical information was conducted at the same time as information on driving status, holding a driver's license, and traffic accidents were collected in all expect for two cohort studies [7,36], resulting in variables associated with but not predictive of the outcome. Three studies reported variances in associations with driving, the C statistics, which were 33% [34], 63% [28], and 79% [7].

3.5. Variables associated with driving, holding a driver's license, or traffic accidents

As shown in Table e-4, a total of 43 variables were assessed across 10 studies to determine associations with driving, although only eight variables were assessed in five or more studies. Of those, six variables showed a consistently positive association (i.e., a significant association in over half of the studies that tested this variable, Table e-4). These were male gender (pooled risk ratio [pRR]: 1.42; 95% CI: 1.23 to 1.64), being in paid employment (pRR: 1.72; 95% CI: 1.46 to 2.03), being married (pRR: 1.26; 95% CI: 1.01 to 1.57), being older at seizure onset or at diagnosis (pooled mean difference: 4.83 years older; 95% CI: 0.48 to 9.18), having a seizure frequency of less than once a month (pRR: 1.32; 95% CI: 1.12 to 1.56), and receiving monotherapy or receiving no antiepileptic drugs (AEDs) (pRR: 1.34; 95% CI: 1.09 to 1.63). Pooled mean differences or pRRs of the eight variables that were assessed in five or more studies are shown in Fig. 1. There was a high degree of statistical heterogeneity (all $p < 0.05$ and all $I^2 > 50\%$) between estimations. Subgroup analysis showed that studies from high income countries with prospective and consecutive recruitment were homogeneous in estimating associations between age, age at seizure/epilepsy onset, and treatment with one or no AED, with driving (all $p > 0.05$ and all $I^2 < 50\%$).

Twenty-nine variables were assessed across five studies to determine associations with holding a driver's license, although only two variables were assessed in three or more studies, with one variable, male gender (pRR: 1.64; 95% CI: 1.21 to 2.21; $I^2 = 52\%$), showing a consistent positive association (Table e-4 and Fig. 1).

Thirty-six variables were assessed across five studies to determine associations with traffic accidents, although only four variables were assessed in three or more studies (Table e-4). Seizure frequency of less than once a month showed a consistent negative association with traffic accidents (pRR: 0.26; 95% CI: 0.10 to 0.66; $I^2 = 0\%$, Fig. e-2), but data were available in only two studies, and CI was wide.

4. Discussion

Firm conclusions are limited by the heterogeneity and methodological limitations of published studies. A wide range of variables has been tested across studies among people with one or more seizures. Being of male gender, in paid work, married, of older age at seizure onset or diagnosis, having less frequent seizures, and receiving fewer AEDs were all associated with driving. Male gender was associated with holding a driving license. Not surprisingly, a lower frequency of seizures was protective against traffic accidents among those who drove.

Most of the included studies were cross-sectional. Only two multivariable models accounted for >50% of the variance in predicting driving. No model was validated using the data that generated it or using another dataset. In many studies, the time frames for the dependent variables were unclear. Few studies collected information on whether participants were driving in violation of local driving restrictions. Further longitudinal research is required to confirm whether driving laws are being enforced effectively, and to build stable, clinically useful multivariate models to predict those who are likely to be noncompliant, and to predict traffic accidents.

We found a significant gender effect, with males being more likely to drive or hold a driver's license. Healthy older males drive significantly more frequently than females in Australia [39] and Malta [40], and in the 2-year predementia phase, females cease driving earlier than males [41]. These differences may be explained by different attitudes towards driving and safety between healthy males and females, with men feeling safer than women driving in higher risk situations, for example, at night, in unfamiliar areas, after drinking, or when they are tired [42].

Employment played an important role. This is consistent with research in the general community from Switzerland [43], Australia [44], and the USA [45], where employment [43,44] and getting/keeping a job [45] were associated with higher rates of adult licensing [43,44] and car ownership [43,45]. An association between employment and driving was also found when the study populations were people with epilepsy who had at least one seizure a year [8] and who were not legally allowed to drive [6,33].

A lower seizure frequency and taking fewer AEDs are surrogates for milder epilepsy and better seizure control. Both increase the chance of meeting the required duration of seizure freedom for driving. A lower seizure frequency also protected drivers with seizures from traffic accidents. This supports duration of seizure freedom as the criterion employed most widely by driver-licensing authorities in legislation.

The minimum duration of seizure freedom required to legally drive varies greatly between countries [16,46] and even within countries,

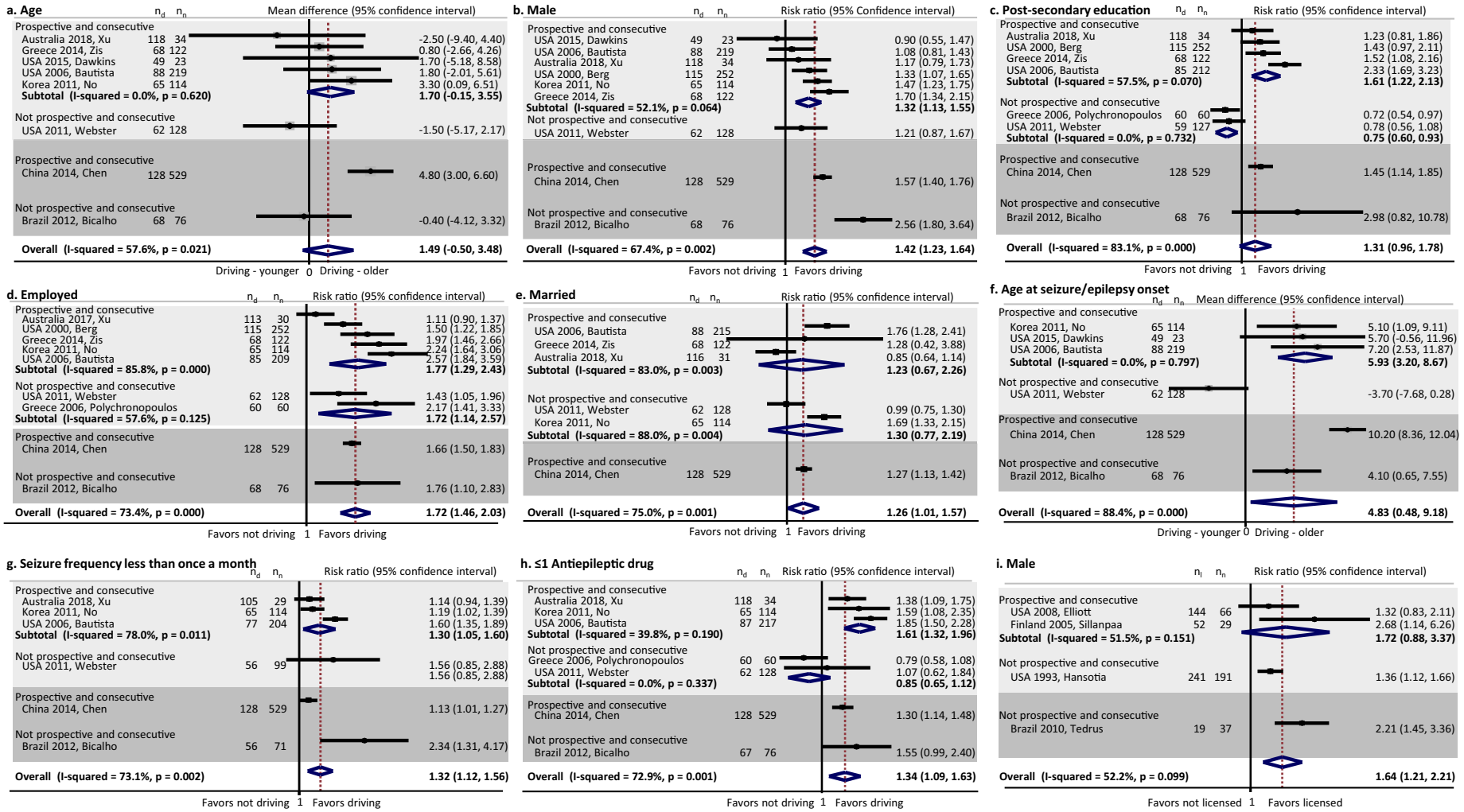

Fig. 1. Mean differences and risk ratios of variables associated with driving or holding a driver's license. (a–h) Associations between variables and driving, n_d denotes number of participants who drove, n_n number of participants who did not drive. (i) Association between male gender and holding a driver's license, n_l denotes number of participants who hold a driver's license, n_n number of participants who did not hold a driver's license. Studies in light gray background are from the World Bank defined high income countries; studies in darker gray background are from lower middle income countries.

particularly the USA [46]. This variability may be explained by the paucity of evidence to inform legislation. Only two studies that tested associations between shorter seizure-free duration and traffic accidents have shown positive relationships after adjustment for potential confounders [31,35]. Several studies have demonstrated that, in drivers with epilepsy who were compliant with local restrictions, the risk of motor vehicle accidents was not higher than in the rest of the population [47,48]. Conversely, a 1991 literature review found that most people with epilepsy causing traffic accidents did not fulfill the criterion of two to three years free of seizures [49]. In addition, the awareness of driving restrictions and laws among people with epilepsy is of concern, with only around half (44% [27] or 52% [34]) of the participants in studies in the USA [27] and Greece [34] being aware of laws.

The strengths of this review include the inclusion of additional unpublished data supplied by the authors of several of the included published studies. It is also the first systematic review with meta-analysis on this topic. One limitation of this systematic review is that, because of the observational study design, each independent variable may be confounded by other factors. The studies included were predominantly from high income countries, and the results may not be generalizable to middle and low income countries. Middle and low income countries have a higher incidence of epilepsy (median: 68.7/100,000) than high income countries (43.4/100,000) [50]. In addition, the annual road traffic fatality rate is higher in middle (20.1 per 100,000 population) and in low income countries (18.3 per 100,000), than in high income countries (8.7 per 100,000) [51]. Finally, an important but unavoidable weakness of studies of driving safety in people with epilepsy and of legislation to improve safety is reliance on self-reported seizure freedom. Seizures may be underreported because a person is unaware of their occurrence [52]. In a study of people undergoing video-EEG, only 26% were aware of all of their seizures [52]. Alternatively, some people may willfully withhold information in order to retain their driving license [12,53].

5. Conclusions

Additional prospective, longitudinal research in this area is needed to assist healthcare providers to give better advice regarding driving and to inform effective licensing policies in people with seizures that maximize individual freedom, while providing acceptable degrees of safety to the driver and other road users.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.03.032.

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