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Risk factors for injury in a community-treated cohort of patients with epilepsy in Australia

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Objective

There remains a paucity of knowledge regarding specific epilepsy-related risk factors for accidents and injuries in people with epilepsy. Injury studies in people with epilepsy are over-represented with tertiary based populations that are prone to bias from severe disease. This study aims to assess the contribution of epilepsy-related risk factors on injuries in a community-based cohort.

Method

We performed a retrospective nested case-control study on patients recruited into the Tasmanian Epilepsy Register (TER) from July 1, 2001 to June 30,2002. The TER is a community-based cohort of patients with epilepsy in Tasmania, Australia, recruited from the national prescription database and interviewed for epilepsy diagnosis, injuries and risk factors using validated questionnaires with diagnosis made by an epilepsy specialist. The primary outcome measures were lifetime and recent 12-month injury. Multivariable logistic regression with multiple imputation modelling responder non-disclosure was performed, adjusting for age, gender, region, socioeconomic status, seizure frequency and epilepsy duration.

Results

819 patients with epilepsy were included in this study. Ten percent of patients experienced an injury in the preceding year. Before adjusting for seizure frequency, any seizure over the last 12-months was associated with recent injury (adjusted odds ratio 7.90 (95%CI 4.17-14.96). Impaired awareness, cluster seizures, sleep-only seizures and convulsive seizure were characteristics found to significantly influence injuries irrespective of seizure frequency. Although a warning appeared initially protective for recent injuries (OR 0.39 (95%CI 0.22-0.69) this was entirely explained by seizure frequency, with the effect becoming non-

significant.

Significance

Likely due to their unpredictable nature, seizures expose patients with epilepsy to a high risk of life-threatening injury. These findings emphasise the importance of seizure freedom for maximising the safety of patients with epilepsy.

Introduction

Compared to the general population, people with epilepsy (PWE) have a high occurrence of injury[1-4]. These studies have investigated the risk of injury in people with epilepsy[1-4], with few examining potentially modifiable epilepsy-related risk factors that contribute to injury[5-7]. Of these epilepsy-related risk factor studies, only one was sourced from a community based population[6], justifying the need for more community-based studies that may give greater insight on disease outside of a hospital context. Although a few community-based studies exist, these examined the occurrence of disease and relied on self-reporting an epilepsy diagnosis[4] or the variable accuracy of administrative datasets to estimate both disease and injury outcome[3].

This study aims to estimate the lifetime and 12-month occurrence of seizure-related injuries along with identifying specific epilepsy-related risk factors from a large cohort of PWE. Its strengths lie in its well documented community-based ascertainment[8], and comprehensive validated epilepsy diagnoses using written rater guidelines[8,9].

Methods

The Tasmanian Epilepsy Register (TER) is a community-based cohort of 820 primary care treated PWE enrolled from the Australian national prescription database from July 1, 2001 to June 30, 2002 (see Figure 1). These patients reside in the geographically well-defined island state of Australia.

The Tasmanian Epilepsy Register (TER)

Details of the methodology of TER have been previously described[8,10]. In brief, participants were invited from a national prescription database, initially self-reported their

epilepsy diagnosis and underwent a modified validated questionnaire[11,12] by computer-assisted-telephone-interviewing[10]. When possible, both the participant and a witness were questioned by the interviewer for verification of responses. Patients were only included into this registry if their diagnosis of epilepsy was confirmed by an epilepsy specialist (WD)[9]. Seizures and syndromes were classified according to ILAE year 2017 definitions[13]. The lifetime and 12-month frequency of seizure-related immersion events, head injury, dental injury, burns, fracture and seizures whilst driving were recorded[5]. The TER has ethical approval from the Southern Tasmania Health and Medical Human Research Ethics Committee.

Study design

We performed a nested case-control study within this community-based prevalence cohort. We extracted important risk factors and potential confounders a priori from the questionnaire based on a review of the literature of seizure-related injuries, drownings/submersions and seizures whilst driving[14].

Case Ascertainment

Cases were defined as subjects who reported either a lifetime injury or recent injury. Lifetime injuries were defined as having ever experienced immersions, head injury, grazes, fractures, burns or seizures whilst driving. Recent injuries were defined as experiencing the outcomes within the last 12 months from the time of interview.

Controls

Controls were sampled from the remainder of subjects who did not report sustaining the injury of interest, independent of exposure.

Exposure Variables

Exposure (explanatory) variables included seizure frequency and duration, epilepsy-related risk factors, seizure types, seizure timing, and markers for disease severity.

Statistical Methods

Statistical analysis was performed in StataSE 15 (Statacorp). A dichotomous 'injury' response variable for lifetime and recent injuries was created to pool all reported injuries into one response variable. The distribution of continuous variables was examined and found to be non-Gaussian. We reported the medians with interquartile ranges, and performed non-parametric tests such as the Mann-Whitney to determine whether the difference between 2 medians was significant (defined as $p<0.05$). Continuous variables were grouped into categorical ranges for use in logistic regression. A univariate analysis was performed to estimate the crude odds ratios (OR) and 95% confidence intervals (95%CI) through use of logistic regression with likelihood ratio tests. Explanatory variables significant at the 10% level underwent adjustment with multivariable logistic regression for age, gender, region, socioeconomic index for area (SEIFA), and epilepsy duration to control for confounding[15]. Likelihood ratio tests were performed to examine for effect modification. The SEIFA is a socioeconomic index constructed by the Australian Bureau of Statistics, utilising the subcategory for relative advantage/disadvantage[16]. A significant result is defined as an OR with the 95%CI not overlapping the null

value. Any significant OR and 95%CI overlapping the null value were subsequently excluded. Although the survey was performed by computer-assisted telephone interview that required a mandatory response, we elected to take a stringent approach to all responses other than yes or no e.g. don't know, unsure, classifying them as 'missing' and considering this as potential non-disclosure rather than presume this was a no response. To ensure these non-definitive responses did not potentially represent responder bias, we performed multiple imputation with chained equations, initially on a randomly selected small dataset of 60 observations to test and verify statistical and data manipulation methods before application onto the full dataset. A review of the pattern of non-definitive responses identified a monotone pattern, with stable means and standard deviations. A monotone pattern occurs when 'missing' information is always followed by 'missing' subsequent measurements. An example was seen with specific seizure types, where 'missing' subsequent measurements existed for the corresponding seizure frequency. Based on the fraction of 'blank' information a series of imputations was performed to achieve a relative (variance) efficiency of an imputation in excess of 99%[17]. To assess the robustness of the multiple imputation models, we performed 30 independent multiple imputations on random samples of the dataset. Further details of the multiple imputation process and 'missing' variables are provided in Appendix 1 and eTable 2. We report the imputed OR for the effect of exposure adjusted for the stratifying variable, however, where effect modification is present, we report the stratum-specific exposure effects[15].

Results

1077 PWE initially agreed to participate in The Tasmanian Epilepsy Registry of whom 820 were available for this study (see Figure 1). Subsequently one participant was excluded from the analysis due to missing age, leaving 819 participants for the final analysis. Across the variables that we utilised in our analysis, the non-definitive response proportions ranged between 60-93% for recent injuries and 8-10% for lifetime injuries. The notable exception was lifetime seizures whilst driving, where the non-definitive response rate was 31%. Table 1 describes the patient characteristics. 127 (15.5%) subjects were aged 65 or over with 381 (46.5%) subjects having epilepsy for over 20 years. 353 (43.1%) reported experiencing a lifetime injury, and 81 (9.9%) experiencing a recent injury prior to interview. Epilepsy duration was only associated with increased risk for lifetime injuries, and reduced risk for recent injuries (see Table 2). There was no significant association with age, gender, region, or socioeconomic status.

The severity of injuries are included in the appendix table (eTable 1). Lifetime immersion events, although not significant, tended to mostly occur at home followed by a public space and an open area (Fisher’s exact=0.152) with the majority occurring whilst showering or bathing followed by swimming (Fisher’s exact=0.016). Although dental injuries represented the lowest number of reported injuries, over 40% were significant injuries including lost teeth, fractured jaw and major dental surgery.

eFigure 1 represents the imputed corrected odds ratios for lifetime and recent injuries, adjusted for age, gender, region, socioeconomic status and epilepsy duration. Imputation for missing values led to only minor changes in the

odds ratios. This was further verified with 30 independent multiple imputations on random samples where the odds ratios remained stable. No risk factors for seizures whilst driving were observed on univariate analysis.

Any seizure over the last 12-months was associated with recent injury (adjusted odds ratio 7.90 (95%CI 4.17-14.96). A gradient effect was observed with the degree of risk increasing with seizure frequency (eFigure 1). The risk for recent and lifetime injury was influenced by seizure frequency even if occurring only yearly particularly for convulsive and cluster events (see Figure 2). Warning, status epilepticus, awake and sleep seizures, and awake seizures were non-significant for recent injuries following additional adjustment for seizure frequency. Similarly, epilepsy duration remained significant for increased risk in lifetime injuries, and became non-significant for recent 12-month injuries following adjustment for seizure frequency.

Seizure frequency accounted for the risk observed in many intermediate univariate risk factors: seizures only whilst awake or if occurring both awake and asleep; warning and a history of status epilepticus for recent injuries; and status epilepsy for lifetime injuries. However impaired awareness, convulsive cluster seizures and seizures exclusively out of sleep remained significant risk factors even after seizure frequency adjustment. The protective effect of seizures exclusively out of sleep was enhanced by 16% after adjusting for seizure frequency.

Discussion

Summary of findings

This is a nested case-control study of a prevalence cohort with epilepsy recruited from a national prescription database. The cohort is relatively unique as it represents essentially 70% exclusively primary care treated disease with comprehensively validated epilepsy diagnoses. A high lifetime seizure-related injury occurrence of 43.1% was observed, with most injuries occurring in the domestic rather than public setting. This contrasts with other less chronic populations where seizure-related injuries were observed relatively infrequently[6]. Unlike previous studies where epilepsy-related factors did not predict injury[2], we observed disease characterized by impaired awareness and cluster seizures increased the risk for injuries, whilst a protective effect was observed in those with exclusive sleep seizures. The apparent protective effect of 'warning' observed with recent injuries became non-significant when seizure frequency was taken into account. Our observations highlight the risk posed by a disease, invariably affecting consciousness and occurring unpredictably in timing, manifestation and without reliable warning. These findings emphasise the importance of seizure freedom, rather than simply seizure reduction, or alternatively reducing uncertainty with seizure forecasting techniques with continuous biometric monitoring (eg. EEG or heart rate), if we are to eliminate injury risk.

It is now well established that the incidence of injury is elevated in PWE[3]. At 43.1%, our lifetime injury occurrence estimate appears high compared to 12-16% in some previous works[2,6,18]. These studies were of newly diagnosed and untreated paediatric epilepsy patients[18], with durations of epilepsy ranging between 1-11 years[2] and 3-17 years[6]. Whereas, our chronic sample with a median duration of 22 years

(IQR 10-36 years) would be expected to have a higher injury occurrence with cumulative risk of a first seizure-related injury shown to increase over time from 5.4% at 12 months to 26.1% at 20 years[6]. Other studies of chronic epilepsy that included subjects with severe disease are also consistent with our estimates, reporting the lifetime seizure-related injury rates between 30-54%[19,20] Our observations of high lifetime risk of seizures compared to others almost certainly relates to the chronic nature of our epilepsy cohort, emphasising both the importance of seizure freedom and the potential of better seizure forecasting techniques to mitigate injury risk across the whole of the epilepsy lifespan.

In contrast, the observed recent injury occurrence in our sample was 9.9%, which is lower compared with some other community-based studies[3-5] estimating 12-month injury rates of 15-24%, and hospital-based samples with more severe epilepsy having rates of up to 45%[7]. However, this may be partly explained by the differing duration of epilepsy, which was not readily identified in these studies.

The increased risk of epilepsy duration on lifetime injury is unsurprising, as the cumulative risk of injury over time has previously been demonstrated by Lawn et al to be 26.1% at 20 years[6]. This initially appeared to be in contrast to the protective effect of epilepsy duration seen only in the univariate analysis for recent 12-month injury. In fact, this apparent reduction was completely explained after adjusting for the effect of seizure frequency.

After falling, drowning is the most frequent cause of death in PWE[21] and these types of events are the most preventable injuries addressed by raising awareness among PWE and their families[22]. Of all recent injuries, immersions were most frequently reported in our population and remained unchanged

after imputation correction. This major non-fatal event was readily recalled compared to other injuries, possibly because of the potentially fatal consequences. The majority of immersion events occurred in the domestic setting, whilst showering or bathing at home, and reinforces domestic prevention as a key setting[5,23-26]. As the risk of drowning in PWE is increased by 15-19 times[27], maintaining public awareness and vigilance on the domestic risk of immersion injury and fatality is essential if we are to reduce this potentially preventable consequence.

Injury risk factors specific to PWE are poorly understood[22]. Unlike prior studies where epilepsy-related factors did not predict injury[2], we saw several epilepsy related factors contribute to increased risk for both lifetime and recent injures. Although the risk of recent injury is useful clinically, unfortunately the smaller overall numbers involved limit their usefulness in our cohort.

Despite seizure frequency being a key component of epilepsy severity, seizures are often under-reported and unpredictable[28]. Basing severity of epilepsy on seizure frequency alone fails to capture other relevant aspects, such as the effect of the intensity of seizures, the preservation of consciousness, and the unpredictability and location of their timing. There is some consensus in what defines severity, as a review of published seizure severity scales demonstrated they typically encapsulate seizure frequency, seizure type, seizure duration, post-ictal events, post-ictal duration, automatisms, seizure clusters, warning, tongue biting, incontinence, injury and impaired function[29]. Whilst seizure freedom, seizure-related disability, the impact of AEDs, and the presence of depression and anxiety on global

ratings of epilepsy severity are recent additions to severity assessment[30], making PWE free of seizures remains the cornerstone of epilepsy treatment. Poor control of convulsive seizures is the strongest risk factor for premature mortality, specifically SUDEP[31]. Accidents and drowning also contribute to premature mortality and in low and middle income countries is amongst the leading causes of mortality in addition to status epilepticus and SUDEP[32]. Similarly, those with clustering of convulsive seizures were more likely to have drug resistant epilepsy and higher mortality risk[33].

Seizure frequency had a powerful effect on the risk of injury, being the primary factor driving many of our other associated risks, with a large proportion of recent injury risk factors explained following its adjustment. This is unsurprising, as seizure frequency alone is a predictor of seizure related injuries[5-7]. The gradient effect we observed with the degree of risk increasing with seizure frequency reinforces its important biological plausibility for causality in both lifetime and recent injuries[6].

In line with what is captured by seizure severity scales[29], impaired awareness, cluster seizures and convulsive seizures remained risk factors for lifetime injury, even after adjusting for seizure frequency. Patients often raise their perception of a warning with their treating doctor as a protective mechanism, particularly when negotiating driving ability, however this is likely unreliable[34] and is more likely to occur in patients with more frequent seizures negating its perceived protective effect.

The practical utility of impaired awareness is difficult to

assess, as awareness may be either fully impaired or relatively spared during a seizure. Its objective assessment remains one of the most challenging to assess by patient report[35]; often pragmatically at least requires corroborative history from an observer. Understandably, we observed these conferred increased risk for lifetime injuries. Although not observed in this study, likely due to small number of patients, absence seizures contributes to injury probably through loss of awareness without warning, suggesting the risk of injury is dependent on the task at hand at the onset of the seizure[36]. Focal seizures with loss of awareness may also lead to injury by a similar mechanism, particularly in the case of burns where it has been attributed to routine daily activities such as cooking over open flames[37]. This may underpin the increased risk of head injury in these two groups, and if leading to convulsive[5,7,19] or drop events[6], result in patients unable to utilise protective reflexes to avoid injury[38].

The imprecision arising from being a chronic cohort with retrospective recall of events remains a limitation of this study. As this study is not representative of early disease, there is a greater chance of sustaining a lifetime injury in our subjects with chronic epilepsy due to the cumulative risk over time[6]. We corrected for this by adjusting for duration of epilepsy, however over time, subjects may more readily recall an event resulting in significant injury compared to events where negligible injury occurred. Some subjects may also have achieved remission or died prior to the study due to fatal disease and be subsequently missed. This is possible given all cause mortality in people with epilepsy between 18-64 years age is highest in the first 12 months following diagnosis, and decreases over time before plateauing after 10

years[39]. This early increase in mortality is largely attributable to the underlying cause of epilepsy (eg. cancer or cerebrovascular disease) rather than being accident-related[39]. Conversely, more mild disease may be missed in those who achieve remission early. The identification of similar risk factors to other prevalent epilepsy studies suggests these effects may be minimal[5,7,19].

Another important limitation to acknowledge is the presence of non-disclosure in epilepsy[40]. The computerised surveying technique employed by trained call centre interviewers required mandatory prompting and participant responses. Rather than categorising 'unknown' or 'not sure' responses to the absence of injury or risk factor, we classified these non-definitive responses conservatively as 'missing'. This may have contributed to the recent driving injury non-response that approached almost 90% as the consequence involves restrictions on driving[41]. Rather than eliminate these data records, we addressed the issue of non-definitive responses potentially leading to missing data by performing the analysis with multiple imputation, utilising chained equations to deal with the 'missing' data in the multiple regression model. This was followed by an assessment of the robustness of the model with 30 independent multiple imputations on random samples of the dataset. The imputation for 'missing' values led to only minor changes in the odds ratios, strengthening the study and implying the non-definitive responses had minimal influence on the results.

In addition to multiple imputation, controlling for confounders strengthens this rich, community-based source of specific epilepsy-related clinical data study. Variables that may influence the risk for injury include gender, age,

socio-economic status and epilepsy duration. Males with epilepsy are known to demonstrate more risk-taking behaviour when compared to their male controls without epilepsy[42] whilst females are thought to have more injuries sustained at home[37]. Two important confounders that were not measured in this study include occupation and sport/recreational activities, whereby manual occupations and environmental exposures associated with both occupation and sport may render a subject more likely to experience an injury.

Conclusion

This study helps improve our understanding of epilepsy related risk factors and their contribution to injury in patients with chronic epilepsy. It also provides insight into potentially important risk assessment opportunities clinicians have when assessing these long-term patients, as there remains an important role for injury prevention in this group. The titration goal to seizure freedom remains a key goal of injury prevention with any seizure exposing patients to serious life threatening risks.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Key Points

Epilepsy related risk factors contribute to seizure-related injuries.

Impaired awareness, cluster seizures and prolonged convulsive seizures were risk factors for injury.

After adjusting for seizure frequency, a warning was not protective.

Aspiring toward seizure freedom or accurate forecasting with continuous biometric monitoring rather than seizure reduction may reduce injury.

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Figure Legend

Figure 1: Flow chart depicting the number of participants from recruitment to final analysis (modified from D'Souza 2007[8]).

Figure 2: Risk factors for recent and lifetime injuries in patients with community-treated epilepsy in Tasmania (n=819), adjusted for age, gender, region, SEIFA, epilepsy duration and seizure frequency. Data points indicate the fully adjusted odds ratio following multiple imputation. Error bands indicate the 95% confidence interval. Legend: # odds ratio (95% confidence interval); ^ adjusted for age, gender, region, socioeconomic index for area (SEIFA), and epilepsy duration; MI multiple imputation; + adjusted for seizure frequency. Significant sub-analysis findings are indicated for the following: immersion (i), head injury (h), burns (b), fracture (f) and dental injuries (d).

eFigure 1: Risk factors for recent and lifetime injuries in patients with community-treated epilepsy in Tasmania (n=819), adjusted for age, gender, region, SEIFA and epilepsy duration. Data points indicate the adjusted odds ratio following multiple imputation. Error bands indicate the 95% confidence interval.

Table 1 - Clinical characteristics

	All patients (n)	%
Epilepsy	819	
Median age (IQR)	47 (29-58)	
Gender		
male	416	50.8
female	403	49.2
SEIFA^		
1	178	21.7
2	172	21.0
3	152	18.6
4	159	19.4
5	158	19.3
Childhood onset epilepsy	332	45.6
Median epilepsy duration (years) (IQR)	22 (10-36)	
Onset type		
generalised	201	24.3
no syndrome	13	

childhood absence	47	
juvenile absence	44	
juvenile myoclonic	52	
unspecified	33	
SGE	12	
focal	546	66.4
uncertain	72	9.3

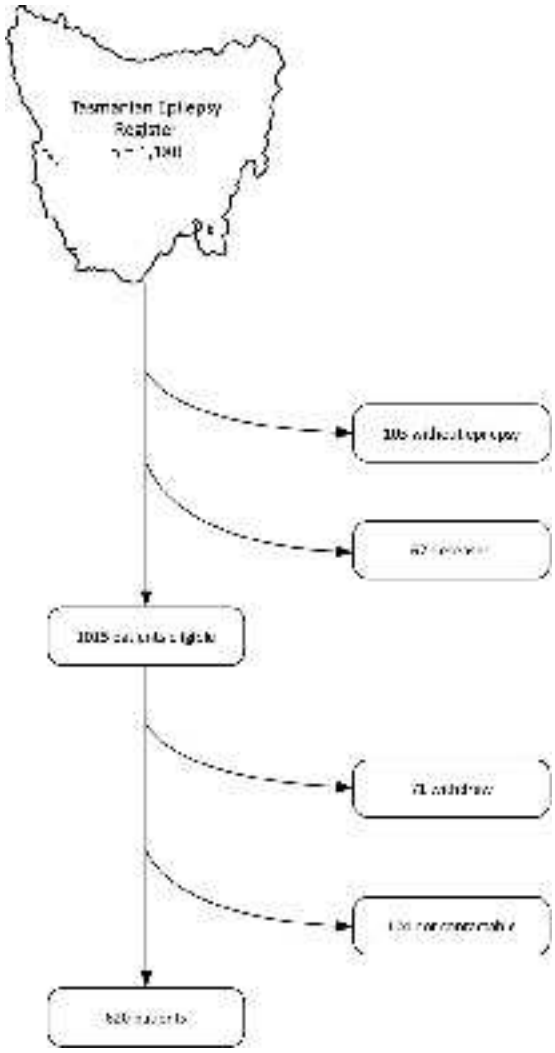
^ Socioeconomic index for area - index of relative socioeconomic advantage/disadvantage (disadvantage=1, advantage=5) - constructed by the Australian Bureau of Statistics, utilising the subcategory for relative advantage/disadvantage[16].

SGE symptomatic generalised epilepsy, IQR inter-quartile range

Table 2 - Lifetime and recent injury by age, sex, region, SEIFA, epilepsy duration and seizure frequency.

Confounder	Lifetime injuries* OR (95%CI)	Recent injuries* OR (95%CI)
age	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)
sex	1.04 (0.78, 1.37)	1.02 (0.67, 1.56)
region		
southern	1	1
northern	0.75 (0.53, 1.09)	0.84 (0.50, 1.42)
northwestern	1.39 (0.97, 1.99)	1.16 (0.72, 1.89)
SEIFA		
1	1	1
2	1.32 (0.85, 2.05)	1.13 (0.60, 2.12)
3	1.19 (0.76, 1.88)	1.10 (0.59, 2.06)
4	1.00 (0.65, 1.57)	0.97 (0.51, 1.86)
5	1.00 (0.64, 1.56)	1.12 (0.58, 2.20)
epilepsy duration	1.37 (1.16, 1.62)	0.69 (0.49, 0.96)
seizure		

frequency**		
any seizure in the last year	2.05 (1.48, 2.85)	8.19 (4.52, 14.82)
yearly convulsive seizures	1.72 (1.00, 2.93)	8.07 (3.12, 20.90)
< monthly convulsive seizures	3.50 (2.02, 6.07)	12.61 (5.40, 29.44)
> monthly convulsive seizures	11.89 (4.16, 33.98)	27.32 (10.78, 69.28)
< monthly focal seizures	1.43 (0.81, 2.51)	2.45 (0.78, 7.65)
monthly focal seizures	2.17 (1.22, 3.89)	1.29 (0.37, 4.48)
> monthly focal seizures	3.15 (1.93, 5.12)	6.80 (2.71, 17.07)
* N=819 (multiple imputation), OR (95% CI) odds ratio with 95% confidence intervals, ** baseline = no seizures		



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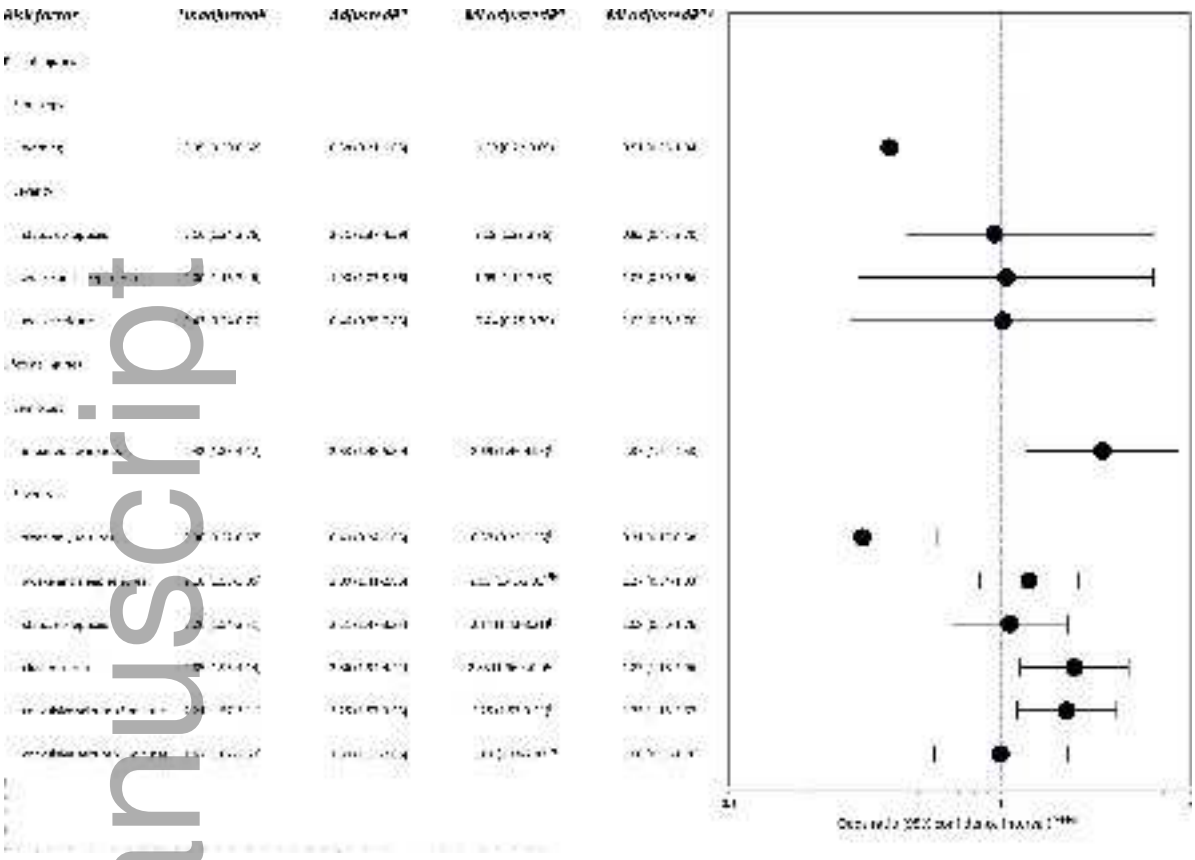

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