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Review

Gender and psychiatric disorders in children with epilepsy. A meta-analysis

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ABSTRACT

Objective: The objective of the study was to assess the influence of gender on psychiatric disorders in children with epilepsy (CWE).
Method: A systematic review of the literature on risk factors for psychiatric disorder in CWE published between 2004 and June 2018 was undertaken. Studies including data on gender that permitted the calculation of a risk ratio (RR) were included in the meta-analysis. A meta-regression was conducted to examine the contribution of setting of the survey and the inclusion of learning disabilities.
Results: Thirty-nine papers were included in the review. The male/female RR in CWE for Attention Deficit Hyperactivity Disorder (ADHD) was 1.49 (Confidence Interval (CI): 1.24–1.79), autistic spectrum disorder (ASD) 1.67 (CI: 1.47 to 1.90), anxiety 1.00 (CI: 0.90–1.12), and depression 0.93 (CI 0.41–2.09). More boys than girls had ADHD and ASD, but in relative terms, the RR male/female was lower in CWE than the RR in the general population reported in other studies. Meta-regression indicated that the inclusion of children with intellectual disability (mental retardation) or the setting (community vs hospital) did not have a significant impact.
Conclusion: Compared with girls in the general population, girls with epilepsy seem to be at a higher risk of being diagnosed with ADHD/ASD as the gender ratio is more equal. This could be related to differences in the assessment of CWE and/or a shared pathogenesis between psychiatric conditions and epilepsy.

1. Introduction

The prevalence of some psychiatric disorders varies according to gender. In the epidemiological survey of mental health disorders in children and adolescents aged 5 to 16 years in Great Britain, the rate of psychiatric disorder was 11% in boys vs 8% in girls. Different disorders had different prevalence depending on gender: emotional disorder was slightly more frequent in girls than boys (4.3% girls vs 3.1% boys) whereas conduct disorders (CD), hyperkinetic disorder (HD), and autistic spectrum disorder (ASD) were more prevalent in boys (CD: 7.5% vs 3.9%; HD: 2.6% vs 0.4%; ASD: 1.4% vs 0.3%, respectively) [1]. This difference has been attributed to biological factors, case ascertainment, referral factors, and/or environmental issues.

For autism, a meta-analysis by Loomes et al. [2] found an odds ratio (OR) for boys/girls of 4.2, with better quality studies having an OR of 3.32. It has been proposed that there are different symptoms for boys and girls, which lead to an underdiagnosis of girls [2]. Alternatively, it has been proposed that autism is linked to chromosome X [3] and that females are protected by having two X chromosomes and hence, have a lower risk of the disorder.

Aside from the factors linked to differences in diagnostic rates between males and females, several factors have been associated with the relative risk of psychiatric disorders. For example, the presence/absence of an intellectual disability may affect the prevalence rates, including the ratio of males to females diagnosed. In a study including adults and children, Lai et al. [4] reported a male/female ratio for autism and ASD of 4/1 in individuals with intellectual disability and 5/1 at the high-functioning end. Similarly, the setting in which individuals are assessed may also affect the ratio of diagnosis between genders. Rucklidge [5] estimated that the worldwide-pooled prevalence rate for ADHD was 5.29%. Depending on the setting, the ratio of boys to girls varied from 2:1 to 9:1, with the rates being more equal in samples obtained from community settings. Finally, previous research has consistently shown that depression is more common in women than in men; however, the higher prevalence of depression in females starts to be apparent in adolescence, and in childhood, the rates are more equal [6]

Epilepsy is a neurological disorder. A recent study [7] reports a similar prevalence of active epilepsy in boys and girls (prevalence 0.39%

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based on a definition of epilepsy as having had seizures in the last 2 years). Epilepsy has a high rate of psychiatric comorbidity. In the UK, Davies et al. [8] found a prevalence of psychiatric disorder in 37% of children with epilepsy (CWE) vs 9% in the general population. A meta-analysis by Strasser et al. (2018) [9] found that the risk factors for ASD in people with epilepsy were intellectual disability, male gender, young age, and some specific epilepsy syndromes. In a population study among CWE aged 8–13 years, Alfstad et al. [10] looked at the effect of gender on psychiatric symptoms in CWE and found that girls had more emotional problems while boys had higher scores in peer relationship and hyperactivity/inattention problems. A study by Aaberg et al. [11] gives the different rates according to gender of psychiatric disorders and other medical conditions in CWE compared with the general population in Norway.

It would seem useful to look at the effect of gender on the prevalence of psychiatric disorder in CWE across different studies. If the ratio male/female of psychiatric disorder in CWE was more equal than in the general population of children, this could suggest that having epilepsy potentially overrides the factors influencing the different prevalence of psychiatric disorders according to gender in the general population or may suggest that epilepsy predisposes to/or has the same pathogenesis as various psychiatric disorders.

The aim of this study was to conduct a systematic review and meta-analysis of how gender influences the prevalence of psychiatric disorder in CWE, interpret the results in terms of study quality;, and assess the nature and source of heterogeneity of estimates through the assessment of potential moderating variables.

2. Method

Using published guidelines for the conduct of a meta-analysis [12], a systematic review of the literature looking at factors associated with psychiatric disorders in CWE was undertaken. The studies that included gender as a risk factor were included in the meta-analysis.

2.1. Search strategy

Electronic database searching and handsearching were used as methods to identify studies. A literature search of the following databases OvidMedline, PsycINFO, EMBASE, Cinahl, and Child Development was conducted to identify studies published between 2004 and June 2018. In 2004, Epilepsy& Behavior published a supplement that reviewed the available data on the psychiatric comorbidities in CWE [13], so 2004 was taken as the start date for this review.

The following keywords and Medical Subject Headings (MESH) headings were used in combination with the “AND” and “OR” Boolean operators: 1) epilep*; 2) behav* disorder or psych* disord* or mental health or mental illness or mental disord* or psych* co-morbidi* or psychopathology or emotional disord* or depression or anxiety or Post traumatic stress disorder or post-traumatic stress or attention deficit* or disruptive disord* or ADHD or ADD or Attention deficit or OCD or PTSD or psychos* or schizo* or affective disorder* or mood disord* or episodic dyscontrol or autis*or autistic dis* or ASD or child behavi* disord*; 3) prevalence or population risk or behavioral riskfactor surveillance system or risk factor* or attributable risk or risk or incidence or comorbidit* or prognosis or association or Epidemiology; 4) child* or Adoles* or teen* or infan*.

Additionally, review papers were handsearched for references as well as recent key articles. Reports from organizations specific to epilepsy were also examined to identify further papers.

2.2. Inclusion and exclusion criteria

To be included in the meta-analysis, studies were required to i) include only children (18 years or younger) in the sample or if they included children and adults, present the data separately for children, ii) use a standardized measures or assessment of psychological difficulties and/or psychiatric diagnosis, and iii) present data to enable the calculation of a risk ratio (RR), OR, correlation coefficient (Pearson's r), or the standardized mean difference as a measure of association between the risk factor and psychiatric diagnosis or psychological difficulty or gave the p value. Studies with the specific aim of assessing gender as a risk factor either for psychopathology in CWE or for a specific psychiatric disorder in CWE were included alongside studies that did not cite this as a main aim, providing the study met the above inclusion criteria and provided the required data to enable the comparison.

Studies were excluded from the review if they a) included adults and children without providing separate data for each population, b) were case study or case series with $n < 15$, c) focused on the effects or side effects of antiepileptic drugs (AEDs) or compared different AEDs, d) included a sample of children selected for epilepsy surgery, and e) were not published in either English or Spanish. Additionally, book chapters that did not contain the data from the original studies or review articles were not included.

Where different publications reported analyses from the same dataset, these were included so long as they provided estimates for different disorders and were checked to ensure that there was no duplication of data. Where data were duplicated, estimates from the largest sample or from the most comprehensive article were used.

2.3. Data extraction

Two of the authors (MTLP and VB) independently entered the relevant data on gender in a database and compared the results. If in case there was a discrepancy, the reviewers met and recalculated the prevalence rates. In addition, the sample origin (community or hospital) and inclusion of children with intellectual disability were coded.

2.4. Quality assessment

As eligible studies were all observational the ‘Quality Assessment Tool for observational cohort and cross-sectional studies’ (Retrieved from http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort) was used to assess study quality. This measure was initially devised by the National Institute of Health (USA) for cohort and observational studies on heart and blood disorders, but it has been used for other disorders since then. It consists of 14 items, each rated yes, no, or not applicable, with an overall rating of good, fair, and poor. The first author initially rated all the papers, with the second author examining the quality of papers independently. Where disagreement between ratings occurred, these were resolved via discussion.

2.5. Data analysis

To measure the strength of the association between gender and psychiatric disorder in CWE, the RR was used. The data extracted from papers were the total number of girls and boys in the sample of CWE and the total number of girls and boys with epilepsy having a psychiatric disorder. This gives the risks for ADHD, ASD and depression, anxiety, and psychopathology for boys with epilepsy compared with the risk for these disorders of girls with epilepsy.

A random effects meta-analysis was conducted to estimate the risk for various psychiatric disorders according to gender using STATA Version 14. I-squared was used to measure heterogeneity. Dichotomous data were entered directly into STATA to enable the calculation of a relative risk.

Where papers reported only a relative risk, this was included alongside an estimate of variance for the effect. Where papers failed to report sufficient data but included some information (such as textual description of no difference between the genders), these were included only in a sensitivity analysis to assess their impact on the findings. A conservative RR of 1 was used, with the standard error estimated from the other

included papers. The log RR and log of the standard error was then entered into the sensitivity analysis.

To assess the impact of different variables on the analysis, meta-regression was performed using the metareg command in STATA version 14. Variables included in the meta-regression were prespecified (presence/absence of intellectual disability and setting of the research).

3. Results

The search elicited 6325 references. Following the removal of duplicates, 4947 papers remained. After inclusion and exclusion criteria were applied, 108 papers reported on risk factors and of these, 48 papers reported on the contribution of gender as a factor associated with psychiatric disorder or general psychopathology. Three papers were excluded as their results were contained in another more recent study, and six papers did not provide data that could be used in the meta-analysis. This left a total of 39 papers eligible for the main analysis.

The results of the search process are shown in the PRISMA flow diagram (see Fig. 1).

Of the 39 papers that reported on gender as a risk factor for psychiatric disorder included in the review, 32 used psychiatric diagnoses as outcome (ASD, ADHD, anxiety, depression, or internalizing disorders),

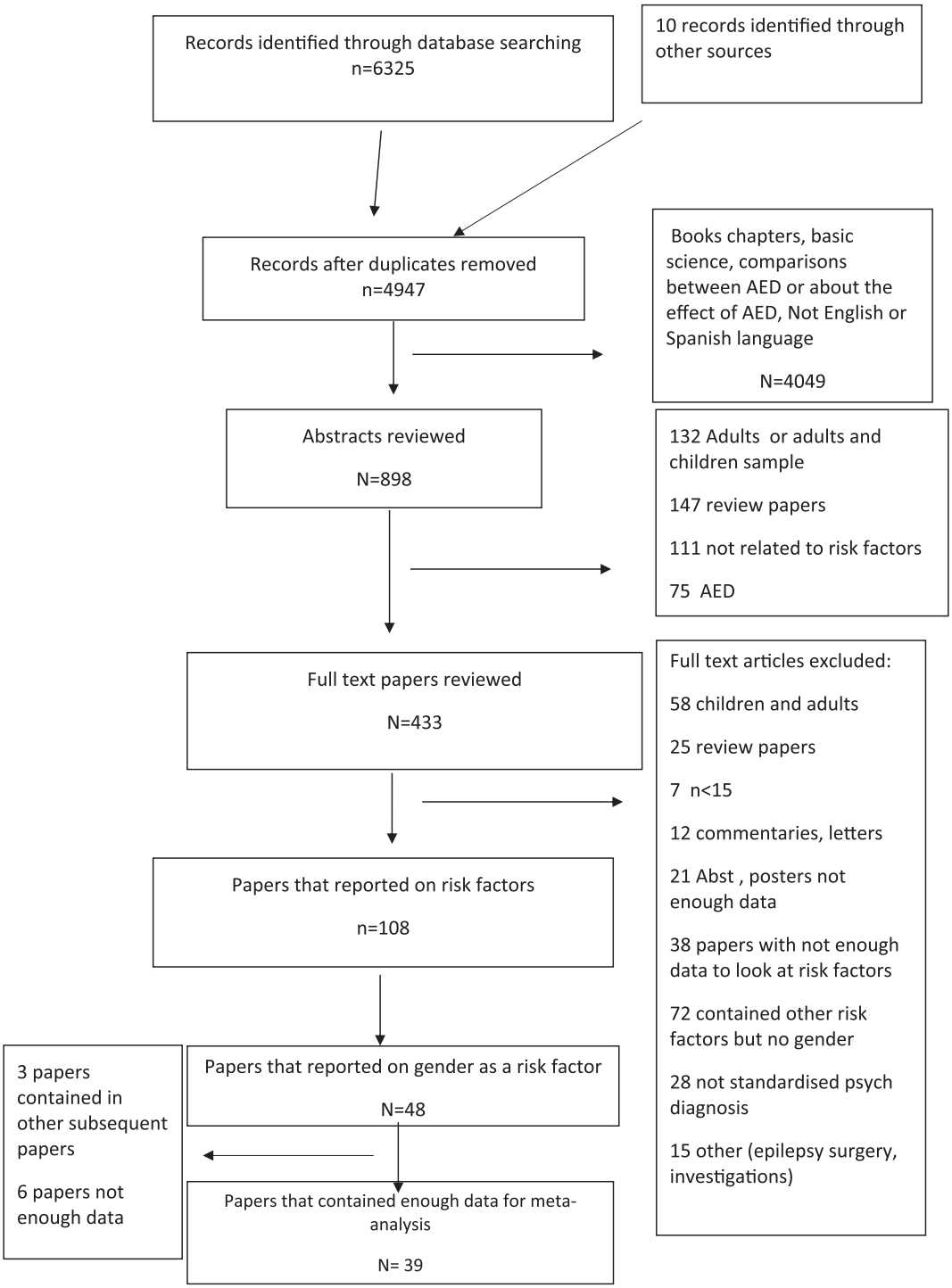

Fig. 1. PRISMA flow diagram.

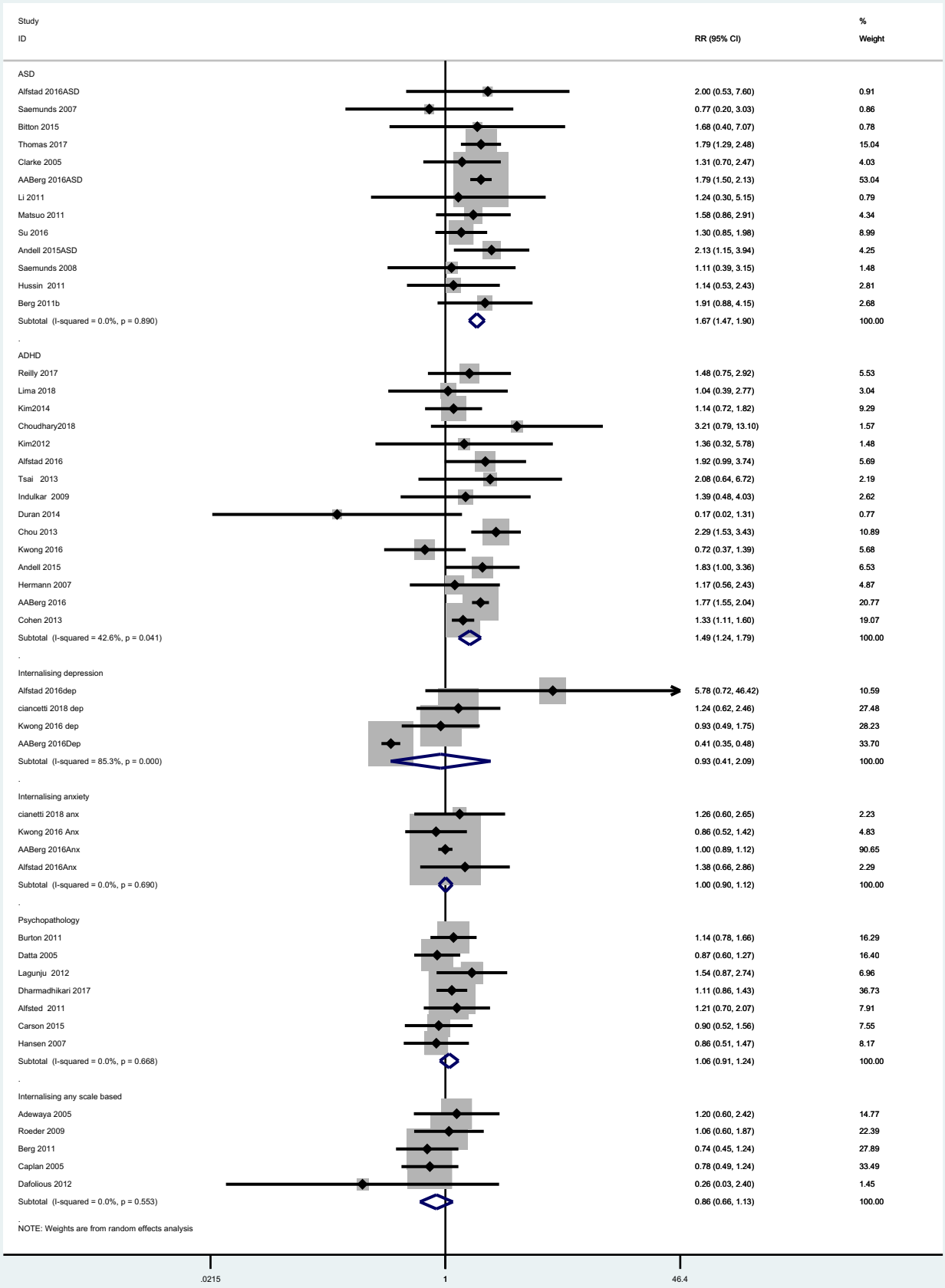

Fig. 2. Forest plot for all psychiatric diagnosis/psychopathology in CWE.

and 7 used scales in a dichotomous way as measures of general psychopathology. Five papers had diagnoses in more than one category [11,14–17]. Only one paper [14] mentioned in the title and abstract that studying the contribution of gender was an aim of the study.

The effect of gender was analyzed for each one of the psychiatric diagnoses and for the measures of general psychopathology.

3.1. Gender as a risk factor for psychiatric diagnosis in CWE

Thirteen papers had ASD diagnosis as an outcome measure [11,14,15,18–27]. Fifteen had the diagnosis of ADHD as an outcome [11,14,15,28–39]. Four papers [11,14,16,17] had the diagnoses of depression and anxiety as outcome measures; five papers [40–44] had internalizing disorder as an outcome.

The RR for ASD male/female in CWE is 1.67 (CI: 1.47 to 1.90) meaning, the risk of boys with epilepsy having ASD is 1.67 times greater than the risk for girls. The I-squared of 0% indicated a lack of statistical heterogeneity. For ADHD, the RR male/female for CWE is RR = 1.49 (CI: 1.24–1.79), I-squared = 42.6% indicating moderate heterogeneity. Both of these findings were statistically significant. For depression, RR = 0.93 (CI: 0.41–2.09), I-squared = 85% indicating high heterogeneity; for anxiety, RR = 1.00 (CI: 0.90–1.12), I-squared = 0.0% indicating lack of heterogeneity. For internalizing disorder, RR = 0.86 (CI: 0.66–1.13), I-squared = 0.0% indicating lack of heterogeneity. None of these findings were statistically significant.

3.2. Gender as a risk factor when the outcome is general psychopathology

There were six papers [45–49] that used scales to measure outcome and provided useable data for the meta-analysis. All of the papers used parent-rated measures (Child Behavior Checklist (CBCL), Strengths and difficulties questionnaire (SDQ), Rutter scales parent rated, Child Behavior Questionnaire for Parents (CBQFP)); additionally, one paper [50] used overall psychiatric diagnosis from care notes but did not classify the type of disorder, so it was, therefore, included within the general psychopathology outcomes.

Male/female RR for psychopathology in CWE = 1.06 (CI: 0.91–1.24), I-squared = 0% indicating no heterogeneity. Three papers [51–53] reported that gender did not have a significant effect but did not give enough data to be included in the meta-analysis. In this case, these papers were included in a sensitivity analysis to assess the effect of these papers on the RR. Results of the sensitivity analysis indicated that the inclusion of these papers did not change the overall conclusion.

Forest plot giving the RR has been used to summarize the data (Fig. 2).

3.3. Risk of publication bias

Given that there were papers that did not provide useable data for the meta-analysis, we also examined the risk of publication bias. A funnel plot (Fig. 3) indicates that there is some limited evidence of small study bias, such that the small studies included in the meta-analysis show a positive effect, with small studies showing a negative effect absent from the plot. The funnel plot is also influenced by one study which is an outlier RR nearly 6.

3.4. Moderators

A meta-regression was conducted to examine the impact of intellectual disability and setting on the effect of gender. Given the small number of papers, meta-regression was only conducted for ADHD and ASD. Papers were coded regarding whether the sample included children with intellectual disability or excluded them and whether the sample was recruited from the community, a hospital setting, or a mixed setting. Neither the presence of intellectual disabilities nor the study setting had any significant impact on the results.

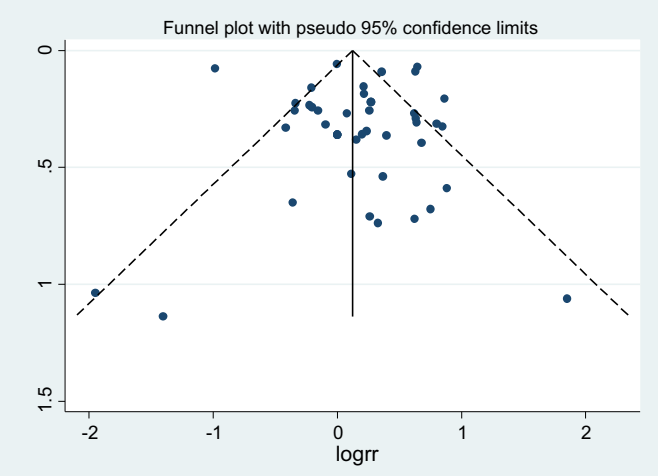

Fig. 3. Funnel plot – risk for publication bias.

3.5. Quality analysis

The 39 papers included in the meta-analysis were observational studies, either cross-sectional or cohort studies. Studies varied in their quality and focus. The measure used for assessment of quality and the summary of the quality rankings is available as supplementary information. Across the 39 papers, 28 were considered good, 9 fair, 1 poor, and 1 (poor/fair).

The two reviewers agreed on the rating of 38 out of 39 papers. In one paper, one of the reviewers considered the paper poor and the other reviewer fair. The quality ratings have been provided as supplementary information.

4. Discussion

The risk for ADHD and ASD is higher for CWE than in children in the general population [8,9]. Within the systematic review and meta-analysis, we indicated that the risk for these disorders is slightly higher for boys with epilepsy than for girls with epilepsy. Girls with epilepsy are at a much higher risk for being diagnosed with these disorders than girls within the general population; for example Meltzer et al. [54] found that in children in Great Britain, the male/female rate for HD was 2.4/0.4, 0.5/0.1 for pervasive developmental disorder, and 11.4/7.6 for anxiety. The results of a recent population study conducted in Norway by Aaberg et al. [11] are in the same direction. They found an OR of male/female for ADHD for CWE as 1.6, which compares to an OR of 2.5 in the general children population. For autism, the same authors found an OR of 1.6 in CWE compared with 3.7 in the general children population, anxiety OR of 1.1 in CWE compared with 0.7 for the general children population, and for depression, the OR is 0.4, the same for CWE and for children in the general population

The reason why the rate between boys and girls for ADHD and ASD is more equal for CWE than for the general population is unclear. It could be that having epilepsy predisposes to ADHD and ASD because seizures may damage the neurological pathways for social recognition or attention [55] or that there is a common genetic predisposition or common pathophysiology for neuropsychiatric disorders and epilepsy. Support for this last hypothesis may come from family studies that have found higher rates of ADHD in first degree relatives of CWE [56]. Another reason could be that there is a better identification of symptoms in CWE than in children in the general population because CWE are seen by specialists: Some researchers have reported gender differences in ADHD symptoms, girls with ADHD have fewer problems with attention, impulsivity, hyperactivity, and externalizing problems than boys [57]

making their identification more difficult. It could be that girls with epilepsy who are seen in specialist centers are more thoroughly assessed, and this leads to better identification of ASD and ADHD.

4.1. Strengths and limitations

This is the first systematic review and meta-analysis examining the effects of gender on psychiatric diagnosis in CWE and indicates that more equal RR for males and females (by comparison with the total population) persists across different countries and studies. However, the results must be interpreted with caution. Within the meta-analysis, there was a mixture of papers, including two that were rated as poor quality, and it was considered that excluding these papers would add a bias and therefore were included. The meta-analysis for papers of depression showed high heterogeneity, suggesting caution with the interpretation of the data, as the level of heterogeneity may represent differences in either the clinical populations included or the study methods. Some of the studies, which used scales as an indicator or general psychopathology, indicated that the contribution of gender was "nonsignificant" but did not provide useable data for the meta-analysis. Although this may add bias to the results, these studies were included within a sensitivity analysis that indicated that their inclusion did not change the results of the main analysis. Unfortunately, because of limitations on the number of variables that can be analyzed, we are unable to say whether other factors, such as the onset/duration of seizures or the time between diagnosis of epilepsy and psychiatric disorder, have a wearing on the gender ratio. Finally, only one of the papers included in the review was specifically focused on gender as a risk factor, in all other papers, data were extracted for gender without being the main aim of the investigation.

5. Conclusions

Children with epilepsy have a higher rate of psychiatric disorders compared with children in the general population. Children with epilepsy should be comprehensively assessed for all psychiatric conditions but particularly for ASD and ADHD. Children with slight symptoms (particularly girls) may be unrecognized. Standardized assessment protocols across settings could ensure that children receive a thorough assessment and treatment. The frequency of neuropsychiatric disorders seems to be increased in girls with epilepsy compared with girls in the general population. The nature of the relationship between ASD, ADHD, and epilepsy, and the impact that gender can have on this relationship continue to be a challenge and further research studies will be needed to ascertain the nature of the relationship.

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Disclosure of conflicts of interest

ET is a trustee of Autistica, which funds and disseminates research on autism spectrum disorders; no other author has any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.02.014.

References

[1] Green H, McGinnity A, Meltzer H, Ford T, Goodman R. Mental health of children and young people in Great Britain, 2004. London: ONS; 2005.
[2] Loomes R, Hull L, Mandy WPL. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. J Am Acad Child Adoles Psychiatry 2017;56:466–74.
[3] Skuse DH. Imprinting the X-chromosome, and the male brain: explaining sex differences in the liability to autism. Pediatr Res 2000;47:9–16.
[4] Lai MC, Baron-Cohen S, Buxbaum JD. Understanding autism in the light of sex/gender. Mol Autism 2015;6:2040–392.
[5] Rucklidge JJ. Gender differences in attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2010;33:357–73.
[6] Avenevoli S, Knight C, Kessler RC, Merikangas KR. Epidemiology of depression in children and adolescents. In: Abela JRZ, Hankin BL, editors. Handbook of depression in children and adolescents. New York: Guilford Press; 2008. p. 6–32.
[7] Aaberg KM, Gunnes N, Bakken IJ, Lund Soraas C, Berntsen A, Magnus P, et al. Incidence and prevalence of childhood epilepsy: a nationwide cohort study. Pediatrics 2017;139(5):e20163908.
[8] Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. Dev Med Child Neurol 2003;45:292–5.
[9] Strasser L, Downes M, Kung J, Cross JH, De Haan M. Prevalence and risk factors for autism spectrum disorder in epilepsy: a systematic review and meta-analysis. Dev Med Child Neurology 2018;60(1):19–29.
[10] Alfstad KÅ, Clench-Aas J, Van Roy B, Mowinckel P, Gjerstad L, Lossius MI. Psychiatric symptoms in Norwegian children with epilepsy aged 8–13 years: effects of age and gender? Epilepsia 2011;52(7):1231–8.
[11] Aaberg K, Bakken I, Lossius M, Lund Søraas C, Håberg SE, Stoltenberg C, et al. Comorbidity and childhood epilepsy: a nationwide registry study. Pediatrics 2016;183(3):e20160921.
[12] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[13] Pellock JM, editor. Psychiatric and behavioral comorbidity in children and adolescents with epilepsy, Epilepsy Behav 2004;5(Suppl. 3):s3–46.
[14] Alfstad KÅ, Torgersen H, Van Roy B, Hessen E, Hansen BH, Henning O, et al. Psychiatric comorbidity in children and youth with epilepsy: an association with executive dysfunction? Epilepsy Behav 2016;56:88–94.
[15] Andell E, Tomson T, Carlsson S, Hellebro E, Andersson T, Adelöw C, et al. The incidence of unprovoked seizures and occurrence of neurodevelopmental comorbidities in children at the time of their first epileptic seizure and during the subsequent six months. Epilepsy Res 2015;113:140.
[16] Cianchetti C, Bianchi E, Guerrini R, Baglietto MG, Briguglio M, Cappelletti S, et al. Symptoms of anxiety and depression and family's quality of life in children and adolescents with epilepsy. Epilepsy Behav 2018;79:146–53.
[17] Kwong KL, Lam D, Tsui S, Ngan M, Tsang B, Lai TS, et al. Self-esteem in adolescents with epilepsy: psychosocial and seizure-related correlates. Epilepsy Behav 2016;63:118–22.
[18] Saemundsen E, Ludvigsson P, Hilmarsdottir I, Rafnsson V. Autism spectrum disorders in children with seizures in the first year of life — a population-based study. Epilepsia 2007;48:1724–30.
[19] Bitton JY, Demos M, Elkouby K, Connolly M, Weiss SK, Donner EJ, et al. Does treatment have an impact on incidence and risk factors for autism spectrum disorders in children with infantile spasms? Epilepsia 2015;56:856–63.
[20] Thomas S, Hovinga ME, Rai D, Lee BK. Brief report: prevalence of co-occurring epilepsy and autism spectrum disorder: the U.S. National Survey of Children's Health 2011–2012. J Autism Dev Disord 2017;47:224–9.
[21] Clarke DF, Roberts W, Daraksan M, Dupuis A, McCabe J, Wood H, et al. The prevalence of autistic spectrum disorder in children surveyed in a tertiary care epilepsy clinic. Epilepsia 2005;46:1970–7.
[22] Li B-M, Liu X-R, Yi Y-H, Deng YH, Su T, Zou X, et al. Autism in Dravet syndrome: prevalence, features, and relationship to the clinical characteristics of epilepsy and mental retardation. Epilepsy Behav 2011;21(3):291.
[23] Su CC, Chi MH, Lin SH, Yang YK. Bidirectional association between autism spectrum disorder and epilepsy in child and adolescent patients: a population-based cohort study. Eur Child Adolesc Psychiatry 2016;25:979.
[24] Matsuo M, Maeda T, Sasaki K, Ishii K, Hamasaki Y. Frequent association of autism spectrum disorder in patients with childhood onset epilepsy. Brain Dev 2010;32:759–63.
[25] Saemundsen E, Ludvigsson P, Rafnsson V. Risk of autism spectrum disorders after infantile spasms: a population-based study nested in a cohort with seizures in the first year of life. Epilepsia 2008;49:1865–70.
[26] Hussin RA, Abdel Ghani AAM. Autistic spectrum disorders and hyperactivity in epileptic children. Egypt J Neurol Psychiatry Neurosurg 2011;48(1):11–7.
[27] Berg AT, Plioplys S, Tuchman R. Risk and correlates of autism spectrum disorder in children with epilepsy: a community-based study. J Child Neurol 2011;26(5):540–7 [ha].
[28] Reilly C, Atkinson P, Das KB, RFM Chin, Aylett SE, Burch V, et al. Parent- and teacher-reported symptoms of ADHD in school-aged children with active epilepsy: a population-based study. J Atten Disord 2017;21(11):887–97.
[29] Lima EM, Rzezak P, Dos Santos B, Gentil L, Montenegro MA, Guerreiro MM, et al. The relevance of attention deficit hyperactivity disorder in self-limited childhood epilepsy with centrotemporal spikes. Epilepsy Behav 2018;82:164–9.
[30] Kim EH, Yum MS, Kim HW, Ko TS. Attention-deficit/hyperactivity disorder and attention impairment in children with benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav 2014;37:54–8.
[31] Choudhary A, Gulati S, Sagar R, Sankhyan N, Sripada K. Childhood epilepsy and ADHD comorbidity in an Indian tertiary medical center outpatient population. Sci Rep 2018;8(1):2670. https://doi.org/10.1038/s41598-018-20676-8 [Published 2018 Feb 8].
[32] Kim GH, Kim JY, Byeon GH, Eun BL, Rhie YJ, Seo WH, et al. Attention deficit hyperactivity disorder in epileptic children. J Korean Med Sci 2012;27(10):1229–32.

[33] Tsai FJ, Liu ST, Lee CM, Lee WT, Fan PC, Lin WS, et al. ADHD-related symptoms, emotional/behavioral problems, and physical conditions in Taiwanese children with epilepsy. J Formos Med Assoc 2013;112(7):396–405.
[34] Indulkar S, Le ND, Sarkis R, Burgess R, Loddenkemper T. Comorbidities in children with benign focal epilepsy of childhood. Epilepsia 2009;50(Suppl. 11) [2.170 Abstract].
[35] Duran MH, Guimarães CA, Montenegro MA, Neri ML, Guerreiro MM. ADHD in idiopathic epilepsy. Arq Neuropsiquiatr 2014;72:12–6.
[36] Chou IC, Chang YT, Chin ZN, Muo CH, Sung FC, Kuo HT, et al. Correlation between epilepsy and attention deficit hyperactivity disorder: a population-based cohort study. PLoS One 2013;8(3):e57926.
[37] Kwong KL, Lam D, Tsui S, Ngang M, Tsang B, Lam SM. Attention deficit hyperactivity disorder in adolescents with epilepsy. Pediatr Neurol 2016;57:56–63.
[38] Hermann B, Jones J, Dabbs K, Allen CA, Sheth R, Fine J, et al. The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy. Brain 2007;130:3135–48.
[39] Cohen R, Senecky Y, Shuper A, Inbar D, Chodick G, Shalev V, et al. Prevalence of epilepsy and attention-deficit hyperactivity (ADHD) disorder: a population-based study. J Child Neurol 2013;28:120–3.
[40] Adewuya AO, Ola BA. Prevalence of and risk factors for anxiety and depressive disorders in Nigerian adolescents with epilepsy. Epilepsy Behav 2005;6(3):342–7.
[41] Roeder R, Roeder K, Asano E, Chugani HT. Depression and mental health help-seeking behaviors in a predominantly African American population of children and adolescents with epilepsy. Epilepsia 2009;50:1943–52.
[42] Berg AT, Caplan R, Hesdorffer DC. Psychiatric and neurodevelopmental disorders in childhood-onset epilepsy. Epilepsy Behav 2011;20(3):550–5.
[43] Caplan R, Siddarth P, Gurbani S, Hanson R, Sankar R, Shields WD. Depression and anxiety disorders in pediatric epilepsy. Epilepsia 2005;46(5):720–30.
[44] Dafoulis V, Kalyva E. Factors associated with behavioural problems in children with idiopathic epilepsy. Epilepsy Res 2012;100:104–12.
[45] Burton K, Rogathe J, Hunter E, Burton M, Swai M, Todd J, et al. Behavioural comorbidity in Tanzanian children with epilepsy: a community-based case–control study. Dev Med Child Neurol 2011;53:1135–42.
[46] Datta SS, Premkumar TS, Chandy S, Kumar S, Kirubakaran C, Gnanamuthu C, et al. Behaviour problems in children and adolescents with seizure disorder: associations and risk factors. Seizure 2005;14:190–7.
[47] Lagunju I, Bella-Awusah T, Takon I, Omigbodun O. Mental health problems in Nigerian children with epilepsy: associations and risk factors. Epilepsy Behav 2012;25(2):214–8.
[48] Carson J, Weir A, McLellan A, Chin RF. Socioeconomic deprivation is an independent risk factor for behavioural problems in children with epilepsy. Epilepsy Behav 2015;45:105–9.
[49] Hanssen-Bauer K, Heyerdahl S, Eriksson AS. Mental health problems in children and adolescents referred to a national epilepsy center. Epilepsy Behav 2007;10:255–62.
[50] Austin JK, Perkins SM, Johnson CS. Behavior problems in children at time of first recognized seizure and changes over the following 3 years. Epilepsy Behav 2011;21:373–81.
[51] Dharmadhikari AS, Sinha VK. Psychiatric comorbidity in children with epilepsy: a cross-sectional 5 years rural prevalence study. J Neurosci Rural Pract 2017;8(2):179–84.
[52] Caplan R, Siddarth P, Gurbani S, Ott D, Sankar R, Shields WD. Psychopathology and pediatric complex partial seizures: seizure related, cognitive, and linguistic variables. Epilepsia 2004;45:1273–81.
[53] Freilinger M, Reisel B, Reiter E, Zelenko M, Hauser E, Seidl R. Behavioural and emotional problems in children with epilepsy. J Child Neurol 2006;21:939–45.
[54] Meltzer H, Gatward R, Goodman R, Ford T. Mental health of children and adolescents in Great Britain. Int Rev Psychiatry 2003;15:185–7.
[55] Brooks-Kayal A. Epilepsy and autism spectrum disorders: are there common developmental mechanisms? Brain Dev 2010;32:731–8.
[56] Bennett-Back O, Keren A, Zelnik N. Attention-deficit hyperactivity disorder in children with benign epilepsy and their siblings. Pediatr Neurol 2011;44:187–92.
[57] Gershon J. A meta-analytic review of gender differences in ADHD. J Atten Disord 2002;5:143–54.