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Comparison of neurodevelopmental, educational and adult socioeconomic outcomes in offspring of women with and without epilepsy: A systematic review and meta-analysis

Paolo Pierino Mazzone [a,f,g,*], Kirsty Mhairi Hogg [b], Christopher J. Weir [a,c], Jacqueline Stephen [c], Sohinee Bhattacharya [d], Simone Richer [e], Richard F.M. Chin [a,b,f,g]

[a] Muir Maxwell Epilepsy Centre, University of Edinburgh, Edinburgh, United Kingdom
[b] Royal Hospital for Children and Young People, Edinburgh, United Kingdom
[c] Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom
[d] Aberdeen Centre for Women's Health Research, The Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom
[e] The University of Edinburgh, Medical School, Edinburgh, United Kingdom
[f] Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom
[g] Child Life and Health, Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom

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ABSTRACT

Background: Adequate pre-pregnancy counselling and education planning are essential to improve outcomes for offspring of women with epilepsy (OWWE). The current systematic review and meta-analysis aimed to compare outcomes for OWWE and offspring of women without epilepsy (OWWoE).

Methods: We conducted a systematic review and meta-analysis. We searched MEDLINE, EMBASE, CINAHL, PsycINFO (database inception-1st January 2023), OpenGrey, GoogleScholar, and hand-searched journals and reference lists of included studies to identify eligible studies. We placed no language restrictions and included observational studies concerning OWWE and OWWoE. We followed the PRIMSA checklist for abstracting data. The Newcastle-Ottawa Scale for risk of bias assessment was conducted independently by two authors with mediation by a third. We report pooled unadjusted odds ratios (OR) or mean differences (MD) with 95% confidence intervals (95CI) from random (I^2>50%) or fixed (I^2<50%) effects meta-analyses. Outcomes of interest included offspring autism, attention deficit/hyperactive disorder, intellectual disability, epilepsy, developmental disorder, intelligence, educational, and adulthood socioeconomic outcomes.

Results: Of 10,928 articles identified, we included 21 in meta-analyses. OWWE had increased odds of autism (2 articles, 4,502,098 offspring) OR [95CI] 1·67 [1·54, 1·82], attention-deficit/hyperactivity disorder (3 articles, 957,581 offspring) 1·59 [1·44, 1·76], intellectual disability (2 articles, 4,501,786 children) 2·37 [2·13, 2·65], having special educational needs (3 articles, 1,308,919 children) 2·60 [1·07, 6·34]. OWWE had worse mean scores for full-scale intelligence (5 articles, 989 children) -6·05 [-10·31, -1·79]. No studies were identified that investigated adulthood socioeconomic outcomes.

Conclusions: Increased odds of poor outcomes are higher with greater anti-seizure medication burden including neurodevelopmental and educational outcomes. In fact, these two outcomes seem to be worse in OWWE compared to OWWoE, even if there was no ASM exposure during pregnancy, but further work is needed to take into account potential confounding factors.

1. Introduction

Most studies on outcomes of offspring of women with epilepsy (OWWE), are focused on neurodevelopmental outcome, but there is a paucity of data on educational and adulthood socioeconomic outcomes [1–4]. A Cochrane review in 2014 [2] found that prenatal (during pregnancy) anti-seizure medication (ASM) exposure was associated with an increased risk of neurodevelopmental disorders, but the review was restricted to randomised controlled trials and cohort studies. Other

* **Corresponding author**: Paolo Pierino Mazzone; Royal Hospital for Children and Young People, Edinburgh, EH16 4TJ
E-mail address: p.p.mazzone@sms.ed.ac.uk (P.P. Mazzone).

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Glossary

ASM	Anti-seizure medication
OWWE	Offspring of women with epilepsy
OWWoE	Offspring of women without epilepsy
OR	Odds ratio
MD	Mean difference
CI	Confidence interval
SUDEP	sudden unexpected death in epilepsy
PROSPERO	International Register of Systematic Review Protocols
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RD	Risk difference
ASD	autism spectrum disorder
ADHD	Attention-deficit/hyperactivity disorder
SEN	Attending special education needs/school for those with a learning disability
DQ	Developmental quotient
FSIQ	Full-scale intelligence quotient
VIQ	Verbal intelligence quotient
NVIQ	Non-verbal intelligence quotient
ID	Intellectual disability
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children.
ILAE	International League Against Epilepsy.

observational study types aside from cohort studies, such as case-control and or cross-sectional studies, can provide valuable data [4] and some major studies on the topic have been published since the Cochrane review [1,3,5-9].

Studies on outcomes of OWWE tend to focus solely on exposure to specific prenatal ASM, with some, such as valproate and topiramate, conferring higher risk [5–8]. However, there is evidence there may still be an increased risk for adverse offspring outcomes even if there is no prenatal ASM exposure [1,10,11]. A recent systematic review and meta-analysis of perinatal outcomes of women with epilepsy themselves, found that even when women with epilepsy were not on prenatal ASM, perinatal outcomes were still worse than women without epilepsy [4]. These data lead to the hypothesis that adverse neurodevelopmental outcomes experienced by OWWE are not due only to prenatal ASM exposure but there is a role played by the epilepsy itself. We also hypothesise that prenatal ASM burden in women with epilepsy contributes to adverse outcomes of their offspring. Although there is a body of evidence that generally points towards outcomes being worse in the OWWE compared to that of offspring of women without epilepsy (OWWoE), to our knowledge there is no recent systematic review nor meta-analysis to quantify risk on the neurodevelopmental, educational, and socioeconomic outcomes of OWWE.

The current study aimed to investigate:

1. Neurodevelopmental, educational, and socioeconomic outcomes in offspring of women with compared to without epilepsy regardless of ASM exposure.
2. Effect of ASM burden on offspring outcomes through multiple comparisons each addressing a different level of ASM exposure:
   a. women with epilepsy not on prenatal ASM versus those of women without epilepsy;
   b. women with epilepsy on prenatal ASM versus those of women with epilepsy not on prenatal ASM;
   c. women with epilepsy on prenatal ASM polytherapy compared to those who were on prenatal ASM monotherapy

Assessing associations of individual ASMs or specific combinations was not an aim of the current study.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] (**Supplemental Material - PRISMA checklist**).

2.1. Search strategy and study selection

The review was registered on the International Register of Systematic Review Protocols (PROSPERO- www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42020221100). The search strategy is provided in **Supplemental Material, Appendix 1**. Study selection and analysis methods, including assessment of risk of bias have been previously described [4].

2.2. Outcomes of interest

Neurodevelopmental outcomes: Autism Spectrum Disorder, Attention Deficit/Hyperactive Disorder, Intellectual Disabilities, Epilepsy, Developmental disorder, Intelligence.

Educational outcomes: Special education needs, Educational achievement.

Adulthood socioeconomic outcomes: Socioeconomic status, Social class, Deprivation, Employment.

2.3. Data analysis

Studies similar in study design, outcomes investigated, and compared OWWE and OWWoE were combined in Review Manager 5 (RevMan) [13]. We applied the Mantel-Haenszel method to estimate pooled unadjusted odds ratio (OR) or mean difference (MD) with a 95% confidence interval (CI) for each outcome. The I^2 statistic was used to assess inter-study heterogeneity. We used a random-effects model for studies with $I^2 >= 50\%$ and a fixed-effects model for those $< 50\%$, with sensitivity analyses to determine the impact of model choice on effect estimates. If a study pooled data from individual studies, individual studies were not included to prevent double counting. Where articles used the same or overlapping time points assessing an outcome on the same participant population, we included the article with the largest total sample and longest time period in the meta-analysis (**Supplemental material, Appendix 2. eTable 1**). Where studies did not directly compare OWWE and OWWoE, but there were raw data available, they were included in a meta-analysis. Additional meta-analyses were performed to address the effect of ASM burden as detailed in our specific study aims. Subgroup analyses were used to investigate risk of bias on effect estimates. Unadjusted pooled risk differences (RD) with 95% CI were determined for all binary outcomes, using fixed or random effects meta-analysis according to the corresponding odds ratio (OR) analysis. When only one article was identified, unadjusted analysis was conducted.

3. Results

Of 10,928 potential articles identified, 21 studies were included. [1,3,5,7,8,14-29] (Fig. 1). Five were retrospective cohort [1,3,16,20,29], and 16 were prospective cohort studies [5,7,8,14,15,17-19,21-28]. All had low-risk of bias (1,3,5,7,8,14-30] using the Newcastle-Ottawa Scale [30] (**Supplemental Material, Appendix 3. eTable2**). No studies reported on adult socioeconomic outcomes. In the subgroup analyses to

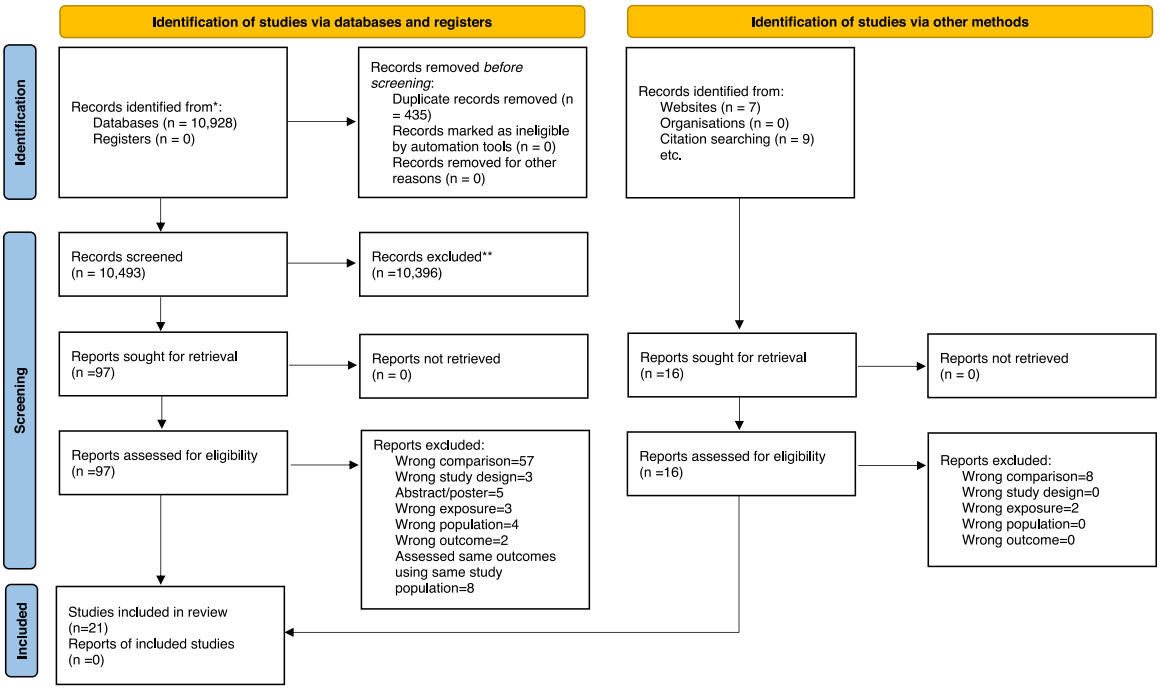

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 Flow Diagram for New Systematic Reviews That Included Searches of Databases, Registers, and Other Sources"
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

assess the effect of ASM burden, there were instances in which no studies with attention-deficit hyperactive disorder (ADHD) data or developmental quotient (DQ) measured by specific psychometric instruments were identified. In the results text below, we report on available data and indicate in Tables 1 and 2, absence of data for specific comparisons.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

3.1. Key

Wrong comparison - Did not compare Offspring of Women With Epilepsy (OWWE) and Offspring of Women Without Epilepsy (OWWoE); or OWWE not on anti-seizure medication (ASM) and OWWoE; or OWWE on ASM and OWWE not on ASM; or OWWE on ASM polytherapy and OWWE on ASM monotherapy.

Wrong outcome - Did not assess an outcome specified in the protocol.
Wrong population - The exposed cohort did not comprise OWWE only.
Wrong exposure - Did not have maternal epilepsy as the primary exposure.
Wrong study design - A study designs that was excluded as per the protocol.

Table 1
Pooled unadjusted meta-analyses of neurodevelopmental and educational outcomes in OWWE compared to OWWoE.

		OWWE		OWWoE					
Outcomes	Studies	Events	Offspring	Events	Offspring	Pooled OR [95 CI]	p-value	I^2 (%)	Pooled RD [95 CI]
ASD	2	548	38,005	38,441	4,464,093	1·67 [1·54, 1·82]	<0·001	0	0·01 [0·00, 0·01]
ADHD	3	402	8,114	30,803	949,467	1·59 [1·44, 1·76]	<0·001	35	0·02 [0·01, 0·02]
Childhood epilepsy	2	26	1,003	656	124,752	3·48 [0·91, 13·33]	0·07	82	0·02 [-0·02, 0·07]
ID	2	330	37,858	16,384	4,463,928	2·37 [2·13, 2·65]	<0·001	0	0·01 [0·00, 0·01]
SEN and Educational attainment	3	119	1,569	36,548	1,307,350	2·60 [1·07, 6·34]	<0·001	78	0·07 [-0·02, 0·15]
Outcomes	**Studies**	**Events**	**Offspring**	**Events**	**Offspring**	**Pooled MD [95 CI]**	**p-value**	**I^2 (%)**	**Pooled RD [95 CI]**
FSIQ	5	n/a	544	n/a	445	-6·05 [-10·31, -1·79]	0·005	81	n/a
VIQ	5	n/a	425	n/a	497	-4·14 [-7·74, -0·55]	0·02	67	n/a
NVIQ	5	n/a	425	n/a	497	-6·77 [-11·73, -1·81]	0·007	80	n/a
DQ – Bayley MDI	3	n/a	105	n/a	116	-6·05 [-9·47, -2·63]	<0·001	44	n/a
DQ – Bayley PDI	3	n/a	103	n/a	115	-1·36 [-5·35, 2·62]	0·50	0	n/a

Abbreviations: OWWE: Offspring of women with epilepsy; OWWoE: Offspring of women without epilepsy; ASD: Autism spectrum disorder/autism; ADHD: Attention deficit/hyperactivity disorder; ID: Intellectual disability; SEN: Special educational needs; FSIQ: Full-scale intelligence quotient; VIQ: Visual intelligence quotient; NVIQ: Non-verbal intelligence quotient; DQ: Development quotient; MDI: Mental development index; PDI: Psychomotor development index; OR: Odds ratio; MD: Mean difference; RD: Risk difference; 95CI: 95% confidence interval·

Table 2
Pooled unadjusted effect estimates and p-values for all outcomes under each comparison from meta-analyses and single studies*

	OWWE vs OWWoE			OWWE not on ASM vs OWWoE			OWWE on ASM vs OWWE not on ASM			OWWE polytherapy vs monotherapy		
Outcomes	Pooled OR [95 CI]	p-value	Sample size (Studies)	Pooled OR [95 CI]	p-value	Sample size [Studies]	Pooled OR [95 CI]	p-value	Sample size [Studies]	Pooled OR [95 CI]	p-value	Sample size [Studies]
ASD	1·67 [1·54, 1·82]	<0·001	4,502,098 [2,1,15]	1·44 [1·27, 1·62]	<0·001	4,485,753 [2,1,15]	1·38 [1·16, 1·63]	<0·001	37,735 [2, 1,15]	1·71 [0·64, 4·56]	0·29	314 [2,15, 28]
ADHD	1·59 [1·44, 1·76]	<0·001	957,581 [3,3,15,28]	1·50 [1·35, 1·67]	<0·001	956,586 [2, 3,28]	*2·29 [0·67, 7·78]	0·18	293 [1,28]	1·55 [0·41, 5·91]	0·52	314 [2,15, 28]
Childhood epilepsy	3·48 [0·91, 13·33]	0·07	125,755 [2, 20,29]	*7·14 [3·01, 16·95]	<0·001	1,934 [1, 20]	*0·90 [0·37, 2·19]	0·82	440 [1,20]	*1·15 [0·24, 5·47]	0·86	262 [1,20]
ID	2·37 [2·13, 2·65]	<0·001	4,501,786 [2,1,26]	1·77 [1·50, 2·09]	<0·001	4,485,575 [2,1,26]	1·80 [1·44, 2·24]	<0·001	37,871 [2, 1,26]	*10·76 [0·53, 219·29]	0·12	54 [1,26]
SEN and Educational attainment	2·60 [1·07, 6·34]	<0·001	1,308,919 [3,5,16,27]	1·84 [1·03, 3·31]	0·04	1,261,785 [3,5,16,27]	1·24 [0·68, 2·24]	0·48	1,397 [3,5, 16,27]	2·17 [1·30, 3·61]	<0·001	1,051 [2, 16,27]
Outcomes	**Pooled MD [95 CI]**	**p-value**	**Sample size [Studies]**	**Pooled MD [95 CI]**	**p-value**	**Sample size [Studies]**	**Pooled MD [95 CI]**	**p-value**	**Sample size [Studies]**	**Pooled MD [95 CI]**	**p-value**	**Sample size [Studies]**
FSIQ	-6·05 [-10·31, -1·79]	0·005	989 [5,7,8, 17-19]	-2·41 [-7·70, 2·89]	0·37	248 [2,17, 19]	-0·81 [-6·05, 4·42]	0·76	294 [2,17, 19]	-8·20 [-12·94, -3·46]	<0·001	191 [2,17, 19]
VIQ	-4·14 [-7·74, -0·55]	0·02	922 [5,8, 17-19,25]	-0·99 [-5·91, 3·93]	0·69	248 [2] [17,19]	-2·49 [-7·59, 2·61]	0·34	249 [2] [17,19]	-8·57 [-13·26, -3·88]	<0·001	191 [2,17, 19]
NVIQ	-6·77 [-11·73, -1·81]	0·007	922 [5,8, 17-19,25]	-4·68 [-10·16, 0·81]	0·09	248 [2] [17,19]	1·43 [-4·13, 6·99]	0·61	249 [2] [17,19]	-5·79 [-10·96, -0·62]	0·03	191 [2] [17,19]
DQ – Bayley MDI	-6·05 [-9·47, -2·63]	<0·001	221 [3, 21-23]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
DQ – Bayley PDI	-1·36 [-5·35, 2·62]	0·50	218 [3, 21-23]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
DQ – Griffiths total	*-3·31 [-5·99, -0·63]	0·02	424 [1,14]	*4·00 [0·11, 7·89]	0·04	257 [1,14]	*-8·49 [-12·83, -4·15]	<0·001	194 [1,14]	*-1·84 [-10·09, 6·41]	0·66	167 [1,14]

* Unadjusted OR/MD (95 CI) calculated from single-study raw data.

Abbreviations: OWWE: Offspring of women with epilepsy; OWWoE: Offspring of women without epilepsy; ASM: Anti-seizure medication; ASD: Autism spectrum disorder/autism; ADHD: Attention deficit/hyperactivity disorder; ID: Intellectual disability; SEN: Special educational needs; FSIQ: Full-scale intelligence quotient; VIQ: Visual intelligence quotient; NVIQ: Non-verbal intelligence quotient; DQ: Development quotient; MDI: Mental development index; PDI: Psychomotor development index; OR: Odds ratio; MD: Mean difference; RD: Risk difference; 95CI: 95% confidence interval·

4. Offspring of women with epilepsy vs Offspring of women without epilepsy

4.1. Meta-analysis

OWWE had increased odds of having autism spectrum disorder (ASD) [1,15], attention-deficit/hyperactivity disorder (ADHD) [3,15, 28], ID [1,26], special education needs (SEN)/lower educational attainment [5,16,27]. They also had lower mean developmental quotient (DQ) on the Bayley Infant Development Scales Mental Development Index [21–23], full-scale intelligence quotient (FSIQ) [7,8,17-19], verbal intelligence quotient (VIQ) [8,17-19,25], and non-verbal intelligence quotient (NVIQ) [8,17-19,25] on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) or Wechsler Intelligence Scale for Children (WISC). However, there were no statistically significant differences in DQ measured by the Bayley Infant Development Scales Psychomotor Development Index [21–23], or in odds of childhood epilepsy [20,29] (Figs. 2-3 and Tables 1-2**; Supplemental Material Appendix 4**).

4.2. Single-study analysis

OWWE had lower mean DQ scores on the Griffiths Mental Development Scale [14] (Figs. 2-3 and Tables 1-2; **Supplemental Material Appendix 5**).

5. Offspring of women with epilepsy not on prenatal ASM vs Offspring of women without epilepsy

5.1. Meta-analysis

Compared to OWWE, OWWoE who were not on prenatal ASM had increased odds of having ASD [1,15], ADHD [3,28], ID [1,26], and SEN [5,16,27]. The point estimates for mean FSIQ [17,19], VIQ [17,19], or NVIQ [17,19] using the WPPSI or WISC were consistently lower in those whose mothers were not on prenatal ASM but the differences were not statistically significant (Figs. 2-3 and Table 2**; Supplemental Material Appendix 4**).

5.2. Single-study analysis

OWWE who were not on prenatal ASM were still at increased odds of

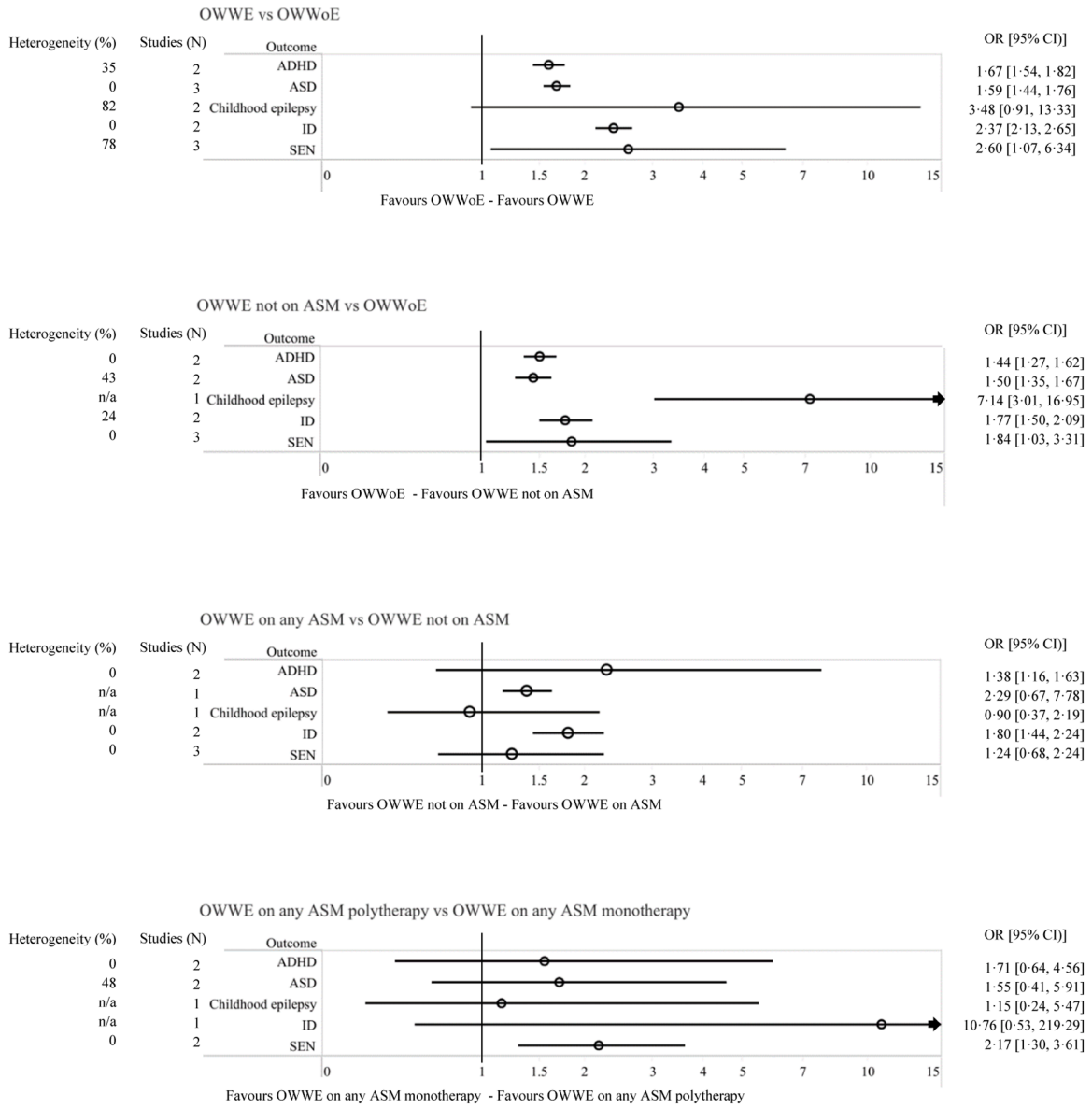

Figure 2. Summary of findings from meta-analyses of ADHD, ASD, childhood epilepsy, intellectual disability, and SEN in offspring: Pooled Unadjusted Odds Ratio (OR) and 95% Confidence Interval (CI).
Abbreviations
OWWE: Offspring of Women With Epilepsy; OWWoE: Offspring of Women Without Epilepsy; SEN: Special Educational Needs; ID: Intellectual Disability; ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder.

childhood epilepsy [20] compared to those whose mothers did not have epilepsy. In one study, there was a non-statistically significant higher point estimate of mean DQ scores on the Griffiths Mental Development Scale in OWWE who were not on prenatal ASM [14] **(**Figs. 2-3 and Table 2; **Supplemental Material Appendix 5).**

6. Offspring of women with epilepsy on prenatal ASM vs Offspring of women with epilepsy not on prenatal ASM

6.1. Meta-analysis

OWWE who were on prenatal ASM had increased odds of having ASD [1,15], ID [1,26], and SEN [5,16,27]. There were no statistically significant differences in mean FSIQ, VIQ, or NVIQ scores [17,19] measured using the WPPSI or WISC (Figs. 2-3 and Table 2; **Supplemental Material Appendix 4)**

6.2. Single-study analysis

Single studies found that OWWE who were on prenatal ASM did not have significantly increased odds of ADHD [28] or childhood epilepsy [20]. Another reported a significantly lower mean Griffiths Mental Development Scale score [14] (Figs. 2-3 and Table 2; **Supplemental Material Appendix 5)**.

7. Offspring of women with epilepsy on prenatal ASM polytherapy vs Offspring of women with epilepsy on prenatal ASM monotherapy

7.1. Meta-analysis

OWWE who were on prenatal ASM polytherapy had increased odds of having SEN [16,27] compared to those whose mothers were only on monotherapy. They also had reduced mean FSIQ, VIQ, and NVIQ scores

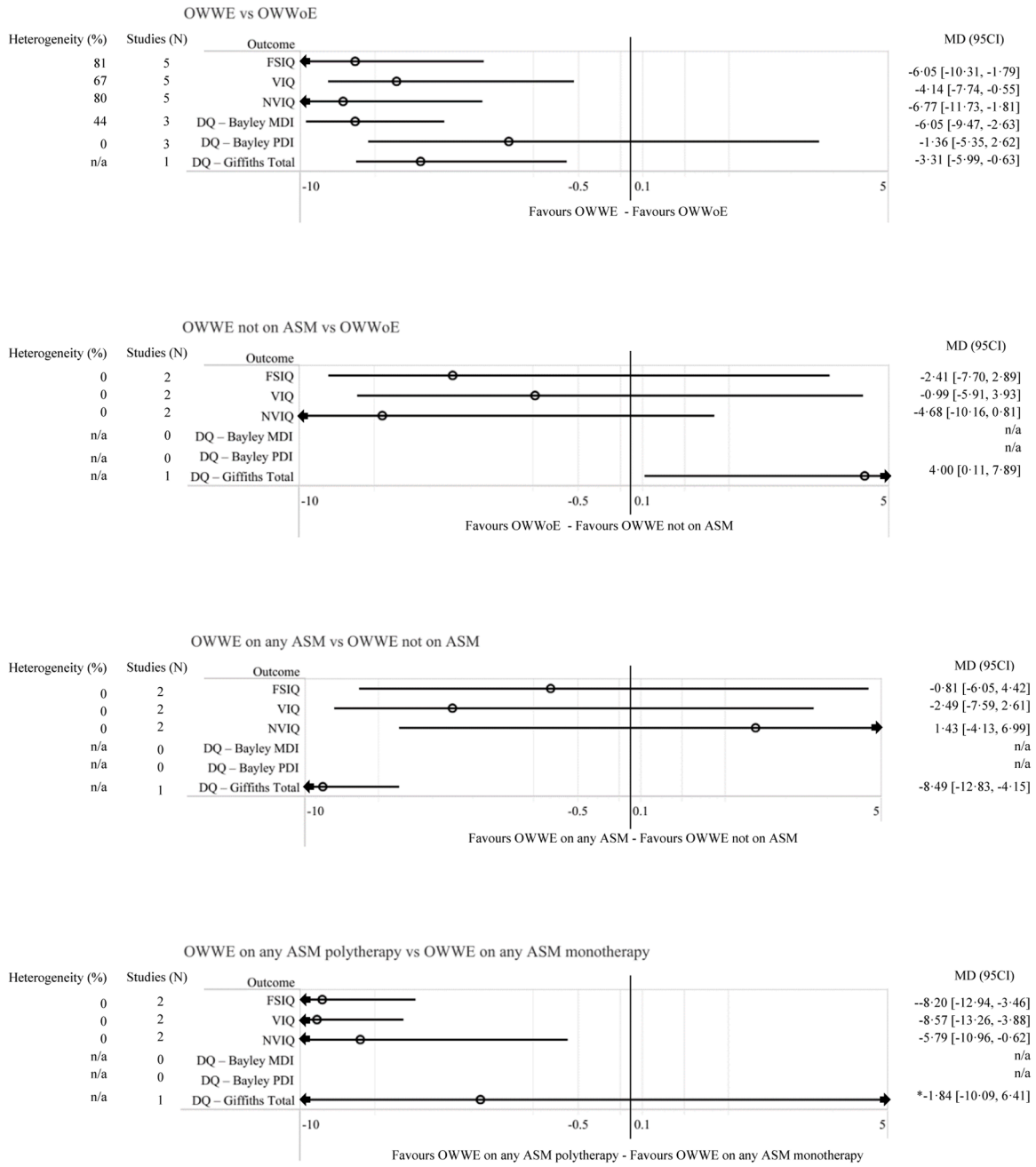

Figure 3. Summary of findings from meta-analyses of intelligence and developmental quotients in offspring: Pooled Unadjusted Mean Difference (MD) and 95% Confidence Interval (CI).
Abbreviations
OWWE: Offspring of Women With Epilepsy; OWWoE: Offspring of Women Without Epilepsy; DQ: Development Quotient; FSIQ: Full-Scale Intelligence Quotient; VIQ: Verbal Intelligence Quotient; NVIQ: Non-Verbal Intelligence Quotient; MDI: Mental Development Index; PDI: Psychomotor Development Index.

[17,19] (Figs. 2-3 and Table 2; **Supplemental Material Appendix 4**.

7.2. Single-study analysis

OWWE who were on prenatal polytherapy had similar odds of childhood epilepsy [20], ID [26], and mean DQ scores on the Griffiths Mental Development Scale [14] as those whose mothers were on monotherapy (Figs. 2-3 and Table 2; **Supplemental Material Appendix 5**).

8. Discussion

For ethical reasons, assessment of the outcomes of OWWE compared to the OWWoE and the role of ASM burden must rest on observational studies rather than randomised trials. Therefore, the findings of this systematic review and meta-analysis of the neurodevelopmental, educational, and socioeconomic outcomes of the OWWE were restricted to observational studies and complement and supplement our recent systematic review and meta-analysis of the perinatal outcomes of women with epilepsy [4]. Our main findings in the current study are [1] there is a paucity of information on the topic with some outcomes having no reported studies or only single studies, and in some instances, only a few studies with modest sample sizes thereby limiting confidence on study findings; [2] OWWE seem to have higher unadjusted odds of autism spectrum disorders, attention deficit/hyperactivity disorder,

intellectual disability and special educational needs and have reduced mean intelligence and development quotients compared to OWWoE, but further work is needed adjusting for potential confounders; [3] generally, there is an impression that outcomes are worse with greater prenatal ASM burden. Individual ASMs were not investigated, and it is possible that ASMs with a known higher risk for poor outcomes, such as sodium valproate and or topiramate, could be inflating these negative outcomes.

8.1. OWWE compared to OWWoE

We acknowledge there may be questions surrounding our finding that OWWE have worse outcomes compared to those of women without epilepsy. This is because in our unadjusted pooled estimates we were unable to adjust for potential epilepsy and social confounders such as epilepsy aetiology and prenatal smoking [31–33]. Notwithstanding, the finding of increased odds of ASD and ID is mainly from data from a large comprehensive cohort study of combined health data on 4.5 million children from Nordic countries between 1996 and 2017(1). In that study, increased odds remained even after adjustment for a large number of potential confounders (1). Similarly, the finding of increased odds of ADHD is mainly from data from one large Danish study [3] with 10 million person-years of observation, and the increased odds remained after adjusting for potential confounders including maternal epilepsy, maternal age, maternal psychiatric history, maternal diabetes, sex of the child, birth year, and parity. Thus, although neither of these two high quality studies were able to adjust for epilepsy characteristics aside from whether any prenatal ASM was used, their data suggest there is a true increased odds of worse outcome in the OWWE compared to OWWoE. The limited available data outside the Nordic region highlights the need for further research. Our finding that OWWE had lower DQ on the MDI domain but not on the PDI domain of the Bayley Infant Development Scale points towards differences in cognitive versus motor development, rather than a global effect on development. Further research is needed to determine whether this is related to the epilepsy itself or to ASM exposure including to specific individual medications, combination therapy and or dosage.

8.2. ASM burden

The finding that OWWE who were not on prenatal ASM were still at increased odds of having ASD, ADHD, and ID suggests that prenatal ASM exposure may not be the sole factor associated with these worse outcomes; other factors need to be considered. We could not determine whether women with epilepsy had been taking ASM pre-pregnancy and if so, for what duration and or dose. This is relevant given evidence of a potential transgenerational association between some ASMs, such as sodium valproate, and neurodevelopmental disorders [1,34,35]. Potential epilepsy confounding/effect-modifying factors could be a further alternative explanation but we were unable to account for these. For example, individuals with epilepsy are significantly more likely to have autism, ADHD and cognitive difficulties which on their own could put their children at higher risk for such conditions [36,37]. Future studies trying to tease out the effect of ASM would benefit from intergroup comparisons amongst women without epilepsy on prenatal ASM (e.g. women on valproate for mood stabilisation rather than anti-seizure effects), women with epilepsy on ASM, and women without any underlying neurological condition and not on ASMs. Further, studies adjusting for potential confounders such as those mentioned above, epilepsy severity and maternal history of learning and or behavioural problems would clarify risk factors that could be targets for intervention.

Lack of analysis on specific prenatal ASM exposure is a major limitation of the current study. It is the most likely explanation for the finding of no differences in offspring IQs whilst in the same intergroup comparison there was an increased odds of intellectual disability. The two studies that contributed to IQ analyses had modest sample sizes [17,19], they were older studies and did not include valproate or topiramate which are two of the most well-known prenatal ASMs associated with worse outcomes. The increased odds of ID were largely based on the recent combined Nordic study mentioned above [1] that included analyses on a large number of ASMs including the “bad actors” valproate and topiramate. In the Nordic study, prenatal carbamazepine was not associated with offspring ID, which would be more in keeping with the normal IQ found in the studies analysed. Future work on the effect of individual and combination prenatal ASM, especially the newer ASMs, is urgently needed.

8.3. Strengths and Limitations

This review was based on an a priori protocol, broad search terms, and stringent inclusion and exclusion criteria. We conducted a quality assessment of the included articles and have provided up-to-date ORs and MDs with 95CIs, complementing a Cochrane review on the topic [2]. We also provide novel data on outcomes of OWWE not on ASM in pregnancy and have identified substantial gaps in the literature. We undertook meta-analyses to provide objective and statistical estimates of effect, rather than to provide narrative synthesis which would have relied on subjective interpretation [38]. Studies which met inclusion criteria but did not have full data available for meta-analysis or could not be combined in meta-analysis for other reason(s), for example, Meador et al. (2021) [39], were thus, excluded. Despite the comprehensive nature of the current study, there are other limitations besides those already mentioned. ASM use in many of the included studies is based on prescription redeeming and do not account for adherence; moreover, these studies do not always exclude other possible teratogenic medications. Given that the International League Against Epilepsy (ILAE) have stated that most women with epilepsy should be on ASMs [40], the frequency of those not on ASMs raises concern for misclassification, reporting error, or under treatment. Most of the studies included in analyses were published over a decade ago; prescriber practices, including potentially teratogenic drugs and folic acid, have since changed [41], and neurodevelopmental outcomes for OWWE today may be different [39].

It must be noted that women with epilepsy not exposed to ASMs most likely either do not have epilepsy or are undertreated based on the ILAE’s 2014 "practical definition of epilepsy" [40]. These possibilities could confound any conclusions. When considering exposure to polytherapy vs monotherapy there is the likelihood of differences in epilepsy severity and, therefore, that seizures in the polytherapy group are less likely to be controlled. Ongoing seizures during pregnancy would be expected to be associated with worse outcomes in the offspring. It is, therefore, not possible to determine if increased odds are driven by ASM burden or epilepsy and/or seizure severity.

A limited number of articles are included in some meta-analyses and limited sample sizes for some comparisons, which means that results for some comparisons are highly influenced by a single or small number of studies.

9. Conclusion

Clinicians and pregnant people with epilepsy who are considering or capable of having children should consider the findings of the current study and pay close attention to the UK national guideline [42] that pre-pregnancy counselling should be provided at the time of epilepsy diagnosis and regularly during epilepsy management. This includes preconception counselling on the risks of ASM use during pregnancy to offspring. These current guidelines are understandably aimed at adult people with epilepsy capable of pregnancy, but it may be worth considering revising and extending the need for such discussions to children with epilepsy who would be capable of pregnancy.

9.1. Key Points

Anti-seizure medication burden increases risk of neurodevelopmental disorders and special educational needs in offspring of women with epilepsy.

Offspring of women with epilepsy may have worse developmental and or educational outcomes than offspring of women without epilepsy, even if there was no ASM exposure during pregnancy but further work is needed.

Women with epilepsy should receive pre-pregnancy counselling soon after diagnosis and regularly during management.

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CRediT authorship contribution statement

Paolo Pierino Mazzone: Conceptualization, Project administration, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft. **Kirsty Mhairi Hogg:** Formal analysis, Investigation, Validation, Visualization. **Christopher J. Weir:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Resources, Visualization, Writing – review & editing, Supervision. **Jacqueline Stephen:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Resources, Visualization, Writing – review & editing, Supervision. **Sohinee Bhattacharya:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Resources, Visualization, Writing – review & editing, Supervision. **Simone Richer:** Formal analysis, Visualization, Writing – review & editing. **Richard F. M. Chin:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Resources, Visualization, Writing – review & editing, Supervision.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2024.02.014.

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