Epilepsy & Behavior 92 (2019) 297–305

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Social outcomes for adults with a history of childhood-onset epilepsy: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 4 November 2018
Revised 7 January 2019
Accepted 7 January 2019
Available online 5 February 2019

Keywords:
Pediatric
Education
Employment
Income
Marital status
Psychosocial

ABSTRACT

Objectives: This review aimed to describe social outcomes in adulthood for people with a history of childhood-onset epilepsy and identify factors associated with these outcomes; focused on educational attainment, employment, income/financial status, independence/living arrangement, romantic relationships, parenthood, and friendships.

Methods: A comprehensive search of MEDLINE, EMBASE, and PsycINFO was conducted, as well as forward and backward citation tracking. A total of 45 articles met inclusion criteria. Random effects meta-analyses were conducted, and subgroup analyses evaluated outcomes for people with epilepsy (PWE) with good prognosis (e.g., normal intelligence, 'epilepsy-only') and poor prognosis (e.g., intellectual disability, Dravet syndrome), and those who underwent epilepsy surgery in childhood.

Results: Among all PWE, 73% (95% confidence interval [CI]: 64–82%) completed secondary school education, 63% (95%CI: 56–70%) were employed; 74% (95%CI: 68–81%) did not receive governmental financial assistance; 32% (95%CI: 25–39%) were in romantic relationships; 34% (95%CI: 24–45%) lived independently; 21% (95%CI:12–33%) had children, and 79% (95%CI: 71–87%) had close friend(s). People with epilepsy often fared worse relative to healthy controls. Among PWE with a good prognosis, a comparable number of studies reported similar/better outcomes relative to controls as reported poorer outcomes. The most consistent predictor of poorer outcomes was the presence of cognitive problems; results of studies evaluating seizure control were equivocal.

Conclusion: People with epilepsy with a good prognosis may show similar social outcomes as controls, though robust conclusions are difficult to make given the extant literature. Seizure control does not guarantee better outcomes. There is a need for more studies evaluating prognostic factors and studies with control groups to facilitate appropriate comparisons.

1. Introduction

Sixty percent of children with epilepsy attain seizure remission in the long-term and discontinue antiepileptic drug (AED) treatment [1,2], but comorbid cognitive and psychiatric problems may continue to persist. Furthermore, social outcomes in adulthood are often poor or unsatisfactory relative to controls in terms of educational attainment, employment, income, independence, romantic relationships, and friendships [3–8]. Although not all population-based studies find deficits in social outcomes, it is evident that childhood-onset epilepsy continues to have negative consequences in adulthood even when seizures remit [3,9]. Although neurological, cognitive, and psychiatric problems have been identified as key determinants, poor outcomes are also found among people with epilepsy (PWE) without such comorbidities [3,4]. A part from intellectual disability, it is not clear which factors, if any, are important in predicting social outcomes. Although a number of narrative reviews have described social outcomes [3,9], no study has systematically evaluated the literature to examine the overall extent of social deficits in adulthood and identify the factors associated with poor outcomes. This is particularly important in understanding the prognosis of childhood-onset epilepsy beyond seizure control, and thus, may aid in targeting supportive interventions and healthcare transition planning to foster optimal outcomes in adulthood, improve quality of life, and engender productive citizens.

The primary aim of this study was to systematically evaluate the literature and estimate the overall extent of social deficits in adults

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https://doi.org/10.1016/j.yebeh.2019.01.012
1525-5050/

Table 1
Characteristics of the articles included in this review.

Study	Country	Study design	Source of sample	Patient population	Sample size (n)	Sex n males (%)	Age at epilepsy onset Mean yrs. (SD) [range]	Current age Mean yrs. (SD) [range]	Seizure status at follow-up
POOR PROGNOSIS									
Riikonen 1996 [10]	Finland	RC	Hospital	West syndrome	147	~60%	~0.5 [0.8–1.9]	~50%: *20–25 yrs* 21%: *25–30 yrs* 29%: *30–35 yrs*	33% seizure-free >2 yrs
Wakamoto 2000 [8]	Japan	PC	Hospital (representative of population)	Intellectually disabled subgroup	49	~49%	~28%: <5 *yrs* 42%: *5–9 yrs* 30%: *10–16 yrs*	~26.0 (4.7) [20.0–38.0]	37% seizure-free >5 yrs
Szabo 2001 [11]	USA	PC	Clinic	Symptomatic/cryptogenic epilepsy	16	~48%	~9.5 ~[0.7–16.0]	>20.0	50% seizure-free
Kumagai 2001 [12]	Japan	RC	n/a	West syndrome	120	n/a	n/a	25.4 (4.5) [20.0–37.0]	~27% seizure-free
Michelsen 2006 [13]	Denmark	PC	Population	Cerebral Palsy	77	n/a	<6 years	[29–35]	n/a
Camfield 2008 [14]	Canada	PC	Population	Symptomatic epilepsy	52	30 (58%)	2.0 [0.8–12.0]	23.8 (3.5)	38% seizure-free >5 yrs
Beume 2010 [15]	Germany	RC	Hospital	Difficult to treat epilepsy syndromes	81	41 (51%)	~8.1 (5.2) [0.5–17.0]	n/a	26% seizure-free
Catarino 2011 [16]	Britain	RC	Hospital	Dravet syndrome	18	10 (56%)	7.9 (3.4) [3–15]	33.1 (10.7) [20–60]	0% seizure-free
Geerts 2011 [17]	Netherlands	PC	Hospital	Symptomatic/cryptogenic subgroup	99	~47%	~5.5 [0.8–15.5]	~[20–35]	~71% seizure-free ≥5 yrs
Chin 2011 [18]	Britain	PC	Population (birth cohort)	Symptomatic/cryptogenic subgroup	32	16 (50%)	44%: <*5 yrs* 56%: *5–16 yrs*	33.0	n/a
Seegmuller 2012 [19]	Switzerland & France	RC	Hospital	Continuous spikes and wave during sleep (CSWS)	7	5 (71%)	4.6 (1.3) [2.8–6.3]	24.7 (3.5) [20.0–29.0]	n/a
Takayama 2014 [20]	Japan	RC	Hospital	Dravet syndrome	64	30 (47%)	Median 0.4 [0.2–0.9]	Median 30 [19.0–45.0]	8% seizure-free ≥1 yr
Baca 2017 [21]	USA	PC	Community	'Complicated' epilepsy subgroup	70	40 (57%)	5.4 (4.1)	21.5 (3.8)	47% seizure-free >5 yrs
GOOD PROGNOSIS									
Olsson 1993 [22]	Sweden	RC	Population	Absence epilepsy; no intellectual disability	58	19 (33%)	71% <*12 yrs* 29% <*16 yrs*	22.5 [18.0–27.0]	43% seizure-free
Kleveland 1998 [23]	Norway	RC	Hospital	Juvenile myoclonic epilepsy	43	11 (26%)	15 (2.8)	29.0 (9.0) [17.0–57.0]	44% seizure-free >1 yr
Jalava 1997 [24]	Finland	PC	Population	Epilepsy-only‡	99	40 (40%)	<16	36.5 (4.8)	77% seizure-free >5 yrs
Wirrell 1997 [25]	Canada	PC	Population	Typical absence epilepsy	56	18 (32%)	7.4 [1–15]	23.1 [18–31]	n/a
Carran 1999 [26]	USA	RC	Hospital	No intellectual disability; surgical candidates	215	~54%	≤ 11 years	>18 years	0% seizure-free
Wakamoto 2000 [8]	Japan	PC	Hospital (representative of population)	Normal intelligence subgroup	99	~49%	~28%: <*5 yrs* 42%: *5–9 yrs* 30%:*10–16 yrs*	~26.0 (4.7) [20.0–38.0]	76% seizure-free >5 yrs
Pascalicchio 2007 [27]	Brazil	CS	Hospital	Juvenile myoclonic epilepsy	50	25 (50%)	n/a	26.2 (7.4) [17–53]	n/a
Koponen 2007 [28]	Finland	CS	Population	Epilepsy-only‡	69	~40%	<7	~[22–25]	~49% seizure-free >2 yrs
Chin 2011 [18]	Britain	PC	Population (birth cohort)	Idiopathic epilepsy subgroup	33	18 (55%)	36%: <*5 yrs* 64%: *5–16 yrs*	33	n/a
Marinas 2011 [29]	Spain	CS	Community	No intellectual disability	348	~48%	<15 yrs	~38.2 [18–65]	~38% seizure-free >1 yr
Geerts 2011 [17]	Netherlands	PC	Hospital	Idiopathic epilepsy subgroup	184	~47%	~5.5 [0.8–15.5]	~[20–35]	~71% seizure-free >5 yrs
Holtkamp 2014 [30]	Germany	RC	Clinic	Absence & juvenile myoclonic epilepsy	82	36 (44%)	n/a	60.9 (12.9) [30–87]	72% seizure-free >5 yrs
Schneider-von Podewils 2014 [31]	Germany	RC	Population	Juvenile myoclonic epilepsy & normal intelligence	30	11 (37%)	13.7 (3.9) [6–19]	52.1 (12.9) [33–77]	67% seizure-free
Syvertsen 2014 [32]	Norway	PC	Hospital	Juvenile myoclonic epilepsy	37	~40%	~16 (3.2)	~Median 47 [35–81]	53% seizure-free ≥5 yrs

Table 1 (*continued*)

Study	Country	Study design	Source of sample	Patient population	Sample size (n)	Sex n males (%)	Age at epilepsy onset Mean yrs. (SD) [range]	Current age Mean yrs. (SD) [range]	Seizure status at follow-up
Somayajula 2015 [33]	India	CS	Hospital	Juvenile myoclonic epilepsy & no intellectual disability	165	103 (62%)	n/a	25.35 (7.6) [16–54]	77% seizure-free ≥2 yrs
Camfield 2016 [34]	Canada	PC	Population	No intellectual disability	291	~54.6%	~6.0 (4.5) [0.08–16.0]	35.0 (6.4)	~63% in remission
Baca 2017 [21]	USA	PC	Community	'Uncomplicated' epilepsy subgroup	291	148 (51%)	6.4 (3.9)	~22.0 (3.4)	78% seizure-free >5 yrs
Mameniskiene 2017 [35]	Lithuania	CS	Hospital	No intellectual disability	253	91 (36%)	<18 yrs	~36.9 (12.7) [>18.0 yrs]	n/a
Leahy 2018 [36]	Ireland	CS	Hospital	Juvenile myoclonic epilepsy	12	5 (42%)	[12–20]	[18–27]	92% seizure-free >6 months
ALL PATIENTS OR NOT SPECIFIED									
Suzuki 1987 [37]	Japan	RC	Clinic	All patients/not specified	99	n/a	4.5 [0–10]	23 [20–39]	73% seizure-free >3 yrs
Sillanpaa 1990 [38]	Finland	PC	Population	All patients/not specified	178	85 (48%)	<16	48%: *23–29 yrs* 52%: *30–40 yrs*	76% seizure-free >3 yrs
Rwiza 1993 [39]	Tanzania	CS	Population	All patients/not specified	62	~45%	[0.8–18]	[19–86]	~47% have <5 seizures/year
Schupft 1994 [40]	USA	RC	Community	Idiopathic/cryptogenic epilepsy	1076	428 (40%)	[0–19]	~35.7 (0.6)	n/a
Kokkonen 1997 [41]	Finland	PC	Population	All patients/not specified	81	38 (47%)	20% <*2 yrs* 40% before school age	22.3 (1.9) [19–24]	95% seizure-free >1 yr
al-Saad 2001 [42]	Iraq	CS	Two clinics	All patients/not specified	55	~52%	38%: *0–9 yrs* 62%: *10–19 yrs*	≥18	~42% controlled seizures
Shackleton 2003 [43]	Netherlands	RC	Clinic	All patients/not specified	164	~(48%)	<18 yrs	~49.5 (11.2) [32–89]	~55% seizure-free >5 yrs
Varma 2007 [44]	India	CS	Clinic	All patients/not specified	51	~57%	<10 yrs	>18 years	~62% seizure-free >2 yrs
Wilson 2012 [45]	Australia	PC	Population	All patients/not specified	34	~39%	~6.0 (4.0) [0.2–15.0]	[19–30]	n/a
Jennum 2016 [5]	Denmark	PC	Population	All patients/not specified	11,589	5841 (50%)	12%: *0–5 yrs* 88%: *6–20 yrs*	30	n/a
Puka 2016 [6]	Canada	RC	Hospital	All patients/not specified; nonsurgical subgroup	27	10 (37%)	5.0 (4.3)	22.6 (2.6)	33% seizure-free >1 yr
RESECTIVE SURGERY				**Age at Surgery**					
Jarrar 2002 [46]	USA	RC	Hospital	14.4 [7–18]	32	17 (53%)	7.2 [1–16]	>18	53% seizure-free
Benifla 2008 [47]	Canada	RC	Hospital	Median 12.5 [0.67–18.8]	38	~22 (52%)	~Median: 3.5 [0.16–15.8]	>18	~67% seizure-free
Lach 2010 [48]	Canada	RC	Hospital	13.5 (3.7)	71	33 (46%)	5.8 (4.5)	22.3 (3.2)	54% seizure-free >1 yr
Puka 2016 [6]	Canada	RC	Hospital	15.21 (2.77) [7.2–18.8]	51	20 (39%)	6.86 (4.9)	22.27 (2.4)	53% seizure-free >1 yr
Ehrstedt 2017 [49]	Sweden	RC	Hospital	13.25 (4.58) [1.3–19.6]	20	11 (55%)	[0–18]	26.5 [18–35]	70% seizure-free
Hosoyama 2017 [50]	Japan	RC	Hospital	~9.8 (4.2) [1–15]	76	~66%	~4.0 (3.7) [0.2–15.0]	~27.0 (6.2) Work: [25–43] Marriage: [16–43]	~77% seizure-free
HEMISPHERECTOMY				**Age at Surgery**					
Althausen 2013 [51]	Germany	RC	Hospital	<16	15	~48%	~2.8 (3.7)	~24 (12.2) >19 yrs	~74% seizure-free

n/a: Not available; PC: Prospective cohort; RC: Retrospective cohort; CS: cross-sectional; yrs.: years; ‡"Epilepsy-only" refers to patients with normal neurologic examination, normal brain imaging, absence of intellectual disability, and no history of insults accounting for the epilepsy; ~approximate value (data from the subgroup of interest is not available).

with a history of childhood-onset epilepsy, and secondarily to identify factors associated with social outcomes. We focused on seven outcomes: 1) educational attainment, 2) employment, 3) income/financial status, 4) independence/living arrangement, 5) romantic relationships, 6) parenthood, and 7) friendships. These outcomes align with previous work suggesting that important markers of poor social outcomes include failure to complete high school, unemployment, living alone, poverty, pregnancy outside of a stable relationship, never in a romantic relationship >3 months, and depression or another psychiatric diagnosis [3]. Furthermore, given that PWE are a diverse group, a number of

authors have suggested that social outcomes should be considered separately for those with 'poor prognosis' and 'good prognosis' (e.g., PWE with and without intellectual disability) [3]. Therefore, subgroup analyses were planned a priori to address this heterogeneity.

2. Methods

2.1. Search strategy and article selection

A comprehensive search of MEDLINE (Ovid), EMBASE (Ovid), and PsycINFO was conducted on January 30, 2017 and consisted of a combination of keywords relating to 1) epilepsy, 2) childhood, 3) adult or long-term outcomes, and 4) the social outcomes of interest. Specifically, we searched (epilepsy) and (child* or pediatric or paediatric or adoles* or teen*) and (adult* or long-term) and (education* or employ* or unemploy* or work status or income or socioeconomic* or socio-economic* or socio* or poverty or marri* or divorce* or romanti* or spouse* or intimate or pregnan* or living arrangement or independence or friend* or social* or psychosocial*), and the search was limited to studies on humans, written in English, and published in or after 1987 (i.e., studies conducted in the past 30 years). To ensure no records were omitted, the reference lists of included articles (and articles excluded because they used the same patient sample as another article in this review) were manually searched (backward citation tracked), and publications citing these articles were searched, on February 22, 2018, using Web of Science and Scopus (forward citation tracking).

Articles were screened by two independent reviewers (KP & TPT) in two stages;: title and abstract screening, followed by full-text screening. Any disagreements were discussed and resolved by consensus. Articles were included if they presented data on any of the seven social outcomes of interest for adults (≥18 years of age) with childhood-onset (<18 years of age) epilepsy. Among studies evaluating surgical outcomes, surgery had to be completed in childhood (<18 years of age). As the age criterion for adulthood is somewhat arbitrary, studies that included some PWE who were slightly younger or older than 18 years were also included. Review articles and case reports were excluded. We also excluded studies whose inclusion or exclusion criteria included any of the seven social outcomes of interest, since our aim was to estimate the prevalence of these outcomes (e.g., studies recruiting PWE residing in group homes or other institutions). To avoid double counting data, articles reporting on the same patient group were closely evaluated and the article providing the most complete information for this review was included. Table 1 presents articles included in this review, and Table S1 presents the articles excluded to avoid double counting of data.

2.2. Quality assessment

All included articles were evaluated by two independent reviewers (KP & TPT) using a modified quality assessment checklist (Tables S2 and S3). The checklist was modeled after a critical appraisal tool developed for studies addressing questions of prevalence [52]. Questions irrelevant for the topic of this review were removed, and items pertaining to reporting quality were added (as has been suggested [53]) from the Downs and Black checklist [54]. In addition, we included a question pertaining to the presence of controls groups, and a question to determine whether evaluating social outcomes of adults with childhood-onset epilepsy was a primary objective of the article.

2.3. Data extraction and consolidation

Data describing clinical and demographic characteristics, social outcomes, and factors associated with each social outcome were extracted by one reviewer (KP) and verified by a second independent reviewer (TPT). When methodological questions arose or more detailed data were required, corresponding authors were contacted. All data relating to social outcomes were recorded, and after inspecting the available data, it was determined that data would be best presented in a binary format indicating the proportion of PWE meeting certain criteria. These criteria included the proportion of PWE who were/had: 1) secondary school education (i.e., high school), 2) any postsecondary school education, 3) college or university level education, 4) currently employed, 5) receiving government financial assistance, 6) living independently, 7) married or in a romantic relationship, 8) had children, and 9) had close friends. A detailed list of the definitions used in this review is presented in Table S4.

Given that PWE are a diverse group, we anticipated heterogeneity would be high, and decided a priori that subgroup analyses would be used. Whenever possible, data were extracted and presented on subgroups of PWE separately, while being careful to avoid double counting data in producing the overall estimates. The a priori subgroups were: 'good prognosis' (e.g., normal intelligence, epilepsy-only), 'poor prognosis' (e.g., intellectual disability, Dravet syndrome), 'not specified' (i.e., studies including all PWE), and PWE who underwent epilepsy surgery. Table 1 details the patient samples and their categorization into these subgroups.

2.4. Meta-analyses

The proportion of individuals meeting each criterion was meta-analyzed to obtain an average prevalence estimate and 95% confidence interval (CI). Meta-analyses were conducted in Stata 13.0 using the *metaprop* command, exact CIs, the Freeman–Tukey double arcsine transformation when proportions were close to 0 or 1, and random effect models to account for methodological and clinical heterogeneity [55]. Statistical heterogeneity was assessed using the I^2 statistic [56]. Lastly, publication bias was evaluated using funnel plots for proportions

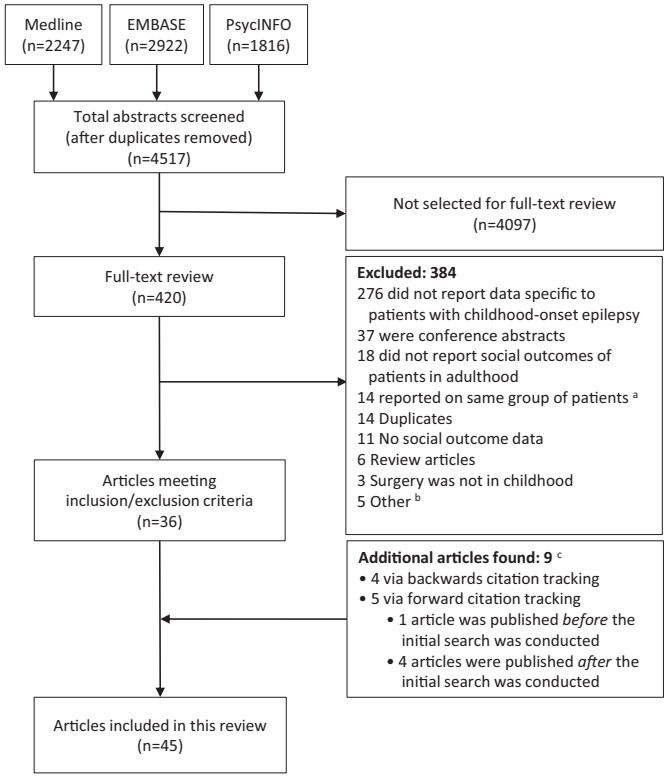

Fig. 1. Flow chart of article selection. [a]Table S1 provides a list of these articles, excluded to avoid double counting of participant data [b]Other includes 2 articles whose inclusion/exclusion criteria included the social outcomes of interest; 2 articles from which no data could be extracted (i.e., merged results of multiple social outcomes, or did not provide the number of patients); 1 case study [c]Two additional studies were found, but were not included because they reported on the same group of patients (see Table S1).

in SAS 9.4, when there were at least ten studies in the meta-analysis [57]. Specifically, plots were visually inspected for asymmetry around the average proportion [58].

Comparisons of outcomes for PWE and healthy controls were summarized qualitatively because relatively few studies included controls. Some studies had adjusted for multiple comparisons or utilized more complicated statistical methods when comparing PWE to controls; to ensure consistency among studies, we simply used the proportion of individuals in each group and compared them using chi-square and Fishers' exact tests. In evaluating the factors associated with social outcomes, there was considerable heterogeneity in the operationalization of the factors, analyses used, and data reported that did not allow for a meta-analysis; these results were summarized qualitatively for factors that were evaluated by at least two studies. We focused on univariable associations to allow comparisons among studies; comparison of multivariable models is not possible given that different studies include different variables in their models, and thereby control for different factors.

3. Results

3.1. Search results and study characteristics

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [59]. The search strategy identified 4517 records; 420 articles underwent full-text screening, identifying 36 articles that met inclusion/exclusion criteria (see Fig. 1). Nine additional articles were found through backward and forward citation tracking. Therefore, a total of 45 articles were included in this review. Funnel plots for proportions did not suggest publication bias, although a small number of studies were available for some outcomes.

Table 1 presents a summary of the study and patient characteristics. The articles included were very diverse; studies were conducted in a variety of countries, included PWE ranging from young adulthood to the elderly, and included PWE with varying outcomes for seizure control, ranging from 0% to 95% attaining seizure freedom.

The results of the quality assessment are presented in Table S3 and show that 56% of the articles included specifically focused on the social outcomes of adults with childhood-onset epilepsy, and only 36% included a control group (primarily comprised of healthy volunteer participants (8 out of 16 studies with controls) or population-based statistics data (5 out of 16 studies with controls)). Reporting quality was generally good (89% clearly described their objectives/hypotheses; 98% clearly described their outcomes; 69% clearly defined the social outcomes evaluated, and 87% clearly described their participants and the setting). Participants were not recruited from a single tertiary care center in 67% of articles. Lastly, 58% of articles evaluated subgroups or potential confounding factors for social outcomes.

Summary of Findings	# studies	n	B/S/W*	Forest plot	Estimated Proportion (95%CI)	I^2	Range of Proportions
OVERALL (Non-surgical + Surgical)**				Proportion 0 0.25 0.5 0.75 1			
Secondary school education or higher	17	13,069	0/3/7		0.73 (0.64, 0.82)	96.9%	0.04 - 1.00
Post secondary education	11	12,240	1/2/2		0.45 (0.29, 0.61)	99.0%	0.02 - 0.97
College/University	16	12,715	0/2/5		0.21 (0.17, 0.26)	86.4%	0.00 - 0.41
Employed or student	31	14,416	0/6/5		0.63 (0.56, 0.70)	96.0%	0.00 - 0.93
Not on government financial assistance	11	12,258	0/1/5		0.74 (0.68, 0.81)	89.4%	0.40 - 0.93
In a romantic relationship	26	15,132	0/1/9		0.32 (0.25, 0.39)	97.1%	0.02 - 0.73
Living Independently	12	1,373	0/1/3		0.34 (0.24, 0.45)	92.9%	0.00 - 0.74
Has Children	15	2,525	0/1/4		0.21 (0.12, 0.33)	96.7%	0.00 - 0.70
Has Close Friend(s)	7	589	0/1/1		0.79 (0.71, 0.87)	83.2%	0.29 - 0.93
GOOD PROGNOSIS (Nonsurgical only)							
Secondary school education or higher	9	987	0/3/2		0.77 (0.63, 0.88)	94.7%	0.36 - 0.97
Post secondary education	4	267	1/0/1		0.64 (0.37, 0.91)	97.0%	0.35 - 0.97
College/University	7	618	0/1/2		0.34 (0.29, 0.39)	31.2%	0.17 - 0.41
Employed or student	12	1,537	0/2/2		0.82 (0.74, 0.89)	91.9%	0.59 - 0.93
Not on government financial assistance	6	279	0/1/1		0.79 (0.69, 0.89)	81.7%	0.60- 0.93
In a romantic relationship	12	1,455	0/1/4		0.44 (0.34, 0.54)	92.9%	0.15 - 0.73
Living Independently	4	724	0/1/1		0.49 (0.23, 0.75)	98.0%	0.15 - 0.74
Has Children	7	812	0/1/2		0.44 (0.26, 0.62)	96.0%	0.10 - 0.70
Has Close Friend(s)	5	548	0/1/1		0.83 (0.75, 0.90)	81.7%	0.66 - 0.93
POOR PROGNOSIS (Nonsurgical only)							
Secondary school education or higher	4	158	0/0/3		0.39 (0.08, 0.76)	95.3%	0.04 - 0.81
Post secondary education	3	247	0/0/0		0.10 (0.01, 0.19)	-	0.02 - 0.19
College/University	3	97	0/0/1		0.11 (0.00, 0.38)	-	0.00 - 0.31
Employed or student	8	433	0/1/2		0.29 (0.12, 0.51)	94.5%	0.00 - 0.79
Not on government financial assistance	3	111	0/0/1		0.55 (0.30, 0.79)	-	0.40 - 0.79
In a romantic relationship	8	537	0/0/3		0.15 (0.05, 0.29)	91.8%	0.02 - 0.66
Living Independently	6	319	0/0/1		0.18 (0.06, 0.34)	87.8%	0.00 - 0.38
Has Children	6	315	0/0/2		0.07 (0.00, 0.22)	90.7%	0.00 - 0.53
Has Close Friend(s)	2	59	0/0/0		0.74 (0.63, 0.84)	-	0.29 - 0.79
RESECTIVE SURGERY							
Secondary school education or higher	3	142	0/0/0		0.98 (0.86, 1.00)	-	0.80 - 1.00
Post secondary education	3	142	0/1/0		0.45 (0.25, 0.64)	-	0.30 - 0.57
College/University	3	142	0/0/0		0.19 (0.09, 0.32)	-	0.11 - 0.35
Employed or student	6	254	0/1/0		0.75 (0.69, 0.81)	7.4%	0.67 - 0.84
Not on government financial assistance	0	-	-		-	-	-
In a romantic relationship	4	215	0/0/0		0.29 (0.11, 0.52)	90.7%	0.07 - 0.45
Living Independently	1	51	0/0/0		0.29 (0.17, 0.44)	-	0.29
Has Children	2	71	0/0/0		0.07 (0.02, 0.15)	-	0.04 - 0.20
Has Close Friend(s)	0	-	-		-	-	-
				0 0.25 0.5 0.75 1 Proportion			

I^2: heterogeneity statistic; CI: confidence interval; Range of proportions: specifies the lowest and highest proportion found by the included studies
*Number of studies finding that the epilepsy group was better (B), similar (S), or worse (W) in comparison to the control group
**Includes studies for which the patient population was heterogenous/not specified (ie. could not be categorized into good or poor prognosis)

Fig. 2. Summary of meta-analyses results.

3.2. Social outcomes

Fig. 2 presents a summary of all results and Tables S5 to S13 present detailed results for each outcome. For brevity, outcomes of all PWE and of PWE with good prognosis are primarily summarized in the results below;, though all pertinent information for the other groups is presented in the tables.

Among all PWE, we found that 73% (95% CI: 64–82%) completed high school, vocational training, college, or university; 45% (95% CI: 29–61%) completed vocational training, college, or university; 21% (95% CI: 17–26%) completed college or university; 63% (95% CI: 56–70%) were employed; 74% (95% CI: 68–81%) did not receive government financial assistance; 32% (95% CI: 25–39%) were in romantic relationships; 34% (95% CI: 24–45%) lived independently; 21% (95% CI: 12–33%) had children, and 79% (95% CI: 71–87%) had close friend(s). There was considerable heterogeneity in these results ($I^2 = 83.2$ to 99.0%). Studies comparing results with healthy controls or population data found that PWE fared worse with respect to secondary school education, college or university education, financial status, romantic relationships, living arrangement, and parenthood. Inconsistent results were found with respect to postsecondary school education, employment, and friendships, with an approximately equal number of studies reporting worse and similar/better outcomes relative to controls.

Among PWE with a good prognosis, we found that 77% (95% CI: 63–88%) completed high school, vocational training, college, or university; 64% (95%CI: 37–91%) completed vocational training, college, or university; 34% (95%CI: 29–39%) completed college or university; 82% (95% CI: 74–89%) were employed; 79% (95% CI: 69–89%) did not receive government financial assistance; 44% (95% CI: 34–54%) were in romantic relationships; 49% (95% CI: 23–75%) lived independently; 44% (95% CI: 26–62%) had children, and 83% (95% CI: 75–90%) had close friend(s). There was considerable heterogeneity in these results ($I^2 = 31.2$ to 98.0%). The few studies that compared results with healthy controls or population data found that PWE with good prognosis fared worse with respect to romantic relationships. Inconsistent results were found for educational attainment, employment, financial status, living arrangement, parenthood, and friendships, with an approximately equal number of studies reporting worse and similar/better outcomes relative to controls.

Among PWE with a poor prognosis, we found that 39% (95% CI: 8–76%) completed high school, vocational training, college, or university; 29% (95% CI: 12–51%) were employed; 55% (95% CI: 30–79%) did not receive government financial assistance; 15% (95% CI: 5–29%) were in romantic relationships; 18% (95% CI: 6–34%) lived independently; 7% (95% CI: 0–22%) had children, and 74% (95% CI: 63–84%) had close friend(s).

Among PWE who had undergone epilepsy surgery in childhood, we found that 98% (95% CI: 86–100%) completed high school, vocational training, college, or university; 75% (95% CI: 69–81%) were employed; 29% (95% CI: 11–52%) were in romantic relationships; 29% (95% CI: 17–44%) lived independently, and 7% (95% CI: 2–15%) had children.

Some aspects of the social outcomes of interest were not evaluated consistently across studies, and thus are summarized qualitatively. With respect to parenthood, Sillanpaa [38] found that of their 46/175 (26%) PWE with children, 53% had one child; 36% had two, and 11% had three. Only two articles evaluated pregnancy outside a stable relationship, reporting an occurrence of 91/272 (33%) [34] and 1/30 (3%) [31] among PWE with a good prognosis. Lastly, income/financial status was measured in a number of different ways, including financial dependency (47/52 [90%] of PWE with poor prognosis) [14];, insufficient income (18/42 [43%] for PWE with good prognosis) [30];, poverty (107/290 [37%] for PWE with good prognosis) [34];, poor and adequate financial situation (10/142 [7%] and 36/142 [25%], respectively, of all PWE) [38];, earning less than CAD $20,000 annually (35/51 [69%] for PWE who underwent resective epilepsy surgery) [48];, earning less than CAD $10,000 annually (38/51 [75%] of PWE who underwent resective epilepsy surgery) [6];, earning less than €4800 annually (12/13 [92%] for PWE who underwent a hemispherectomy) [51];, and earning an average of €26,218 (PWE with onset ≤5 years) and €28,918 (PWE with onset >5 years) annually [5].

3.3. Predictors of social outcomes

Table 2 presents a qualitative summary of the association between each social outcome and the factors evaluated by at least two studies. Table S14 presents detailed results specifying the associations reported in each article. The association between seizure control with employment and living arrangement was inconsistent, and no association was found between seizure control with educational attainment, financial situation, romantic relationships, parenthood, and friendships. Cognitive functioning was the most consistent predictor of better social outcomes and was associated with better educational attainment [4,6,18,38], employment [4,6,18,38], financial situation [6,38], and romantic relationships [6,10,18,38], but not associated with living independently or parenthood. Women with epilepsy were found to have more children relative to males [4,35,40], although this sex difference was not found in two studies [18,31]. Older PWE and PWE with an older age of epilepsy onset were more likely to be in romantic relationships [4,5,33,48] and have more children [4,40]. An absence of psychiatric problems was associated with better educational attainment [4,18,38], and higher parental education was associated with higher educational attainment in PWE, better employment, and having fewer children [4,34]. Lastly,

Table 2
Summary of bivariate relationships between social outcomes and factors evaluated in at least two studies. The number of studies finding each association is presented below.

	Higher education		Greater employment		No social security/ financial aid		More likely to be married/cohabitating		Living independently from parents		Has more children		More friends	
	Overall	+/−/x	Overall	+/−/x	Overall	+/−/x	Overall	+/−/x	Overall	+/−/x	Overall	+/−/x	Overall	+/−/x
Sex (ref = male)	x	1/0/2	x	0/0/3	x	0/0/2	?	3/1/4	?	1/0/1	+	3/0/2	x	0/0/2
Older age at onset	x	0/0/5	x	1/0/5	x	1/0/3	+	4/0/1			+	2/0/1	x	0/0/3
Idiopathic etiology	?	1/0/1	x	1/0/2	?	1/0/1								
Older current age							+	2/0/1			?	1/0/1		
Seizure control	x	3/0/7	?	6/0/5	x	1/0/4	x	0/1/7	?	2/0/2	x	0/1/4	x	0/0/5
Shorter duration of epilepsy							?	1/1/0						
No cognitive problems	+	4/0/0	+	4/0/0	+	2/0/0	+	4/0/1	?	1/0/1	x	1/0/2		
No psychiatric problems	+	3/0/1	x	2/0/2			?	2/0/2			x	0/0/2		
Better childhood SES	?	1/0/1	?	1/0/1							?	0/1/1		
Higher parental education	+	2/0/0	+	2/0/0					?	1/1/0	−	0/2/0		
Had surgery	x	0/0/2	x	0/0/2			x	0/0/2					x	0/0/2
Higher patient education							?	1/0/1						

+ positive relationship; − negative relationship; ? direction of relationship unclear; x no significant relationship ($p > .05$).
SES: socioeconomic status.

results suggested that 1) age of seizure onset was not associated with educational attainment, employment, receiving social security, and friendships, and 2) sex was not associated with employment. Although other factors have been reported to be associated with social outcomes, results have been inconsistent or evaluated by few studies (see Table 2). Results remained similar when articles focusing on PWE with poor prognosis were removed (Table S14).

4. Discussion

The long-term prognosis of childhood-onset epilepsy is favorable in terms of seizure control; however, poor social outcomes have been widely documented, but never systematically reviewed. In an effort to identify areas of future research, provide clinicians and families with a holistic overview of expected long-term outcomes, and allow for targeted interventions and healthcare transition planning, we conducted a systematic review and meta-analyses of social outcomes for adults with a history of childhood-onset epilepsy. Not surprisingly, there was considerable heterogeneity in study results given the diverse patient samples, operationalization of outcomes, and cultural and societal expectations in different countries. Among all PWE, social outcomes were often poorer relative to healthy controls. Among PWE with a good prognosis (e.g., normal intelligence, 'epilepsy-only'), however, a comparable number of studies reported similar/better outcomes relative to controls as reported poorer outcomes. Presence of cognitive problems was the most consistent predictor of poorer outcomes, and seizure control did not guarantee better social outcomes. Few studies evaluated predictors of social functioning, and few studies compared results with healthy controls. Future research on social outcomes requires a more detailed evaluation of social outcomes and the complex process of person–environment interactions that influence youth's experiences and opportunities, and ultimately their social outcomes [60].

4.1. Social outcomes

We calculated the average prevalence for each social outcome for all PWE and provided subgroup estimates for PWE with good prognosis, poor prognosis, and PWE who had undergone epilepsy surgery in childhood. In evaluating all PWE relative to controls, PWE fared worse on nearly all social outcomes, with the exception of postsecondary school education, employment, and friendships, which showed inconsistent results. However, among PWE with a good prognosis, a comparable number of studies reported similar/better outcomes across most domains as reported poorer outcomes (the only exception being romantic relationships). Given the heterogeneity in patient samples and relative lack of studies utilizing healthy controls, it is difficult to characterize the extent of social difficulties faced by PWE. However, it is clear that childhood-onset epilepsy, even in the absence of other neurological deficits or comorbidities, continues to have a lasting effect in adulthood. This message is echoed by the large community-based studies that are often referenced in this area [8,17,18,21,34,38].

Similar findings of poorer social outcomes in adulthood have been reported for youth with various disabilities, including autism spectrum disorder, mental illness, developmental disorders, and physical impairments [60]. With respect to employment, results among those with disabilities were similar to our findings in that some studies report poorer rates of employment relative to peers and others report similar rates [60,61]. Notably, among the studies finding similar employment rates, the types of employment differed, with individuals with disabilities more often employed part-time or through temporary contracts [60,61]. Research on social outcomes among individuals with other disabilities is also limited, making it difficult to determine whether PWE differ from those with other disabilities [60]. In childhood, those with epilepsy have been found to fare worse with respect to social relationships relative to youth with some other conditions (e.g., congenital heart disease, bronchial asthma, type 1 diabetes mellitus), and fare better relative to youth with other conditions (e.g., cerebral palsy, attention-deficit hyperactivity disorder) [62]. However, there is a need for future studies to evaluate the social outcomes of PWE relative to those with other disabilities, particularly among adults with disabilities diagnosed in childhood.

4.2. Factors associated with social outcomes

We found that seizure control in adulthood was not necessarily associated with better social outcomes. Six articles found that seizure control was associated with better employment, and five did not find a significant association. We consistently found that seizure control was not associated with government financial assistance, romantic relationships, or friendships. Absence of cognitive problems was the most persistent predictor of better outcomes, across most social domains. Other consistent findings included the following: 1) older age of onset associated with greater likelihood of being married, 2) absence of psychiatric problems associated with greater educational attainment, 3) no association between age at seizure onset and educational attainment, employment, government financial assistance, and friendships, and 4) no association between sex and employment. With respect to the other factors evaluated, strong conclusions could not be deduced, due to the relative lack of studies evaluating factors associated with social outcomes. It is important to note that with respect to other outcomes in the long-term, such as health-related quality of life, factors such as seizure control and AED use have been found to be associated with better outcomes [63,64].

Research with other disorders suggests that the condition/impairment is only one small factor in the developmental trajectory and social outcome for youth with disabilities [60]. It has been suggested that social outcomes may be better understood as a developmental process, whereby the person, environment, and person–environment interactions affect youth's opportunities, social relationships, and experiences, which in turn affect social outcomes [60,65]. Person–environment interactions are most important at transition points (especially the transition into adulthood), where youth with disabilities may experience a 'narrowing' of social pathways and opportunities (e.g., becoming more isolated), as opposed to widening social experiences as typically experienced by healthy controls [60,66]. Notably, studies of PWE have not typically focused on environmental factors nor utilized more sophisticated study designs and analyses, such as longitudinal designs or mediation and moderation analyses; future studies employing these methods are warranted.

4.3. Limitations of past research and opportunities for improvement

The findings of this systematic review and meta-analysis must be considered in the context of the limitations of the included articles. There is a need for longitudinal and methodologically robust studies to evaluate the potential interactions among predictors of social outcomes and compare outcomes with healthy controls and individuals with other disorders. The utilization of comparison groups would reduce heterogeneity in estimates by addressing the cultural and societal context. Existing studies have also evaluated PWE at only one time point in adulthood, with one exception that focused on employment [7]. Another limitation is the lack of consistent operationalization and lack of rich detail available for social outcomes. For example, in terms of employment, few studies report on whether employment was full or part-time, whether PWE were underemployed, and the type of employment with respect to the educational or skill level required. In terms of other outcomes, only two articles reported on pregnancy outside of a stable relationship [34], and few studies indicated whether PWE lived with their parents by choice or because of cognitive, financial, or other limitations.

4.4. Limitations of current study

Limitations of this systematic review and meta-analysis include a small number of studies for some outcomes and analyses. The results of the meta-analyses showed considerable heterogeneity, and therefore, the estimated proportions should be interpreted with caution and demonstrate that more work is needed to identify outcomes of specific patient subgroups. We attempted to parse the heterogeneity in patient samples using subgroup analyses; metaregression was not used because we generally did not have the suggested minimum of ten studies [57]. The available literature did not allow us to control for a number of factors that could in part determine long-term social outcomes, such as seizure frequency, AED use, whether seizures were controlled in childhood, access to transportation or driving, family environment, mental health problems, extent of perceived and/or enacted stigma, and external vs. internal locus of control. A further limitation was that we could only compare bivariate relationships; we could not compare multivariable analyses given that studies invariably include different variables in their multivariable models. We attempted to categorize patient subgroups and broadly defined 'good' and 'poor' prognosis based on the patient population of each study, and thus the possibility of misclassification error exists. Quality assessment tools for prevalence data are limited, and our adapted quality assessment tool has not been validated, making it difficult to assess the quality of evidence. A number of studies of PWE with severe impairments did not report on some social outcomes (e.g., educational attainment, employment), presumably because patients were too impaired to attain such outcomes. Therefore, the estimated proportions for PWE with poor prognosis may be overestimated. Lastly, although our search strategy was extensive and included forward and backward citation tracking, we may have missed some articles whose primary objective was not to evaluate social outcomes and therefore would not have mentioned social outcomes in their title, abstract, or keywords.

4.5. Conclusion

It is clear that childhood-onset epilepsy, even in the absence of other neurological deficits or comorbidities, continues to have a lasting effect in adulthood. Given the heterogeneity in methodology and results of the current literature, robust conclusions of the extent of social difficulties could not be made. People with epilepsy with good prognoses may show similar social outcomes with controls, though results are inconsistent. The most consistent predictor of poorer outcomes across domains is the presence of cognitive problems, whereas seizure control is not consistently associated with social outcomes. Further research utilizing longitudinal designs is needed to compare outcomes in adults with a history of childhood-onset epilepsy with controls, and identify prognostic factors, especially environmental factors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.01.012.

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