Systematic Review

Neuro
-epidemiology

Neuroepidemiology 2019;52:161–172
DOI: 10.1159/000494291

Received: April 16, 2018
Accepted: October 4, 2018
Published online: January 22, 2019

Incidence and Prevalence of Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Systematic Review and Meta-Analysis

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Keywords
Chronic inflammatory demyelinating polyradiculoneuropathy · Incidence · Prevalence · Systematic review · Meta-analysis

Abstract
Background: Prevalence and incidence rates of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are required to determine the impact of CIDP on society. We aimed to estimate the prevalence and incidence of CIDP worldwide and to determine the effect of diagnostic criteria on prevalence and incidence. ***Method:*** A systematic review was conducted for all published incidence and prevalence studies on CIDP until May 18, 2017. Methodological quality was assessed using the Methodological Evaluation of Observational Research checklist. We performed a random effect meta-analysis to estimate pooled prevalence and incidence rates. ***Results:*** Of the 907 studies, 11 were included in the systematic review, 5 in the meta-analysis of incidence (818 cases; 220,513,514 person-years) and 9 in the meta-analysis of prevalence (3,160 cases; 160,765,325 population). These studies had a moderate quality. The pooled crude incidence rate was 0.33 per 100,000 person-years (95% CI 0.21–0.53; I^2 = 95.7%) and the pooled prevalence rate was 2.81 per 100,000 (95% CI 1.58–4.39; I^2 = 99.1%). Substantial heterogeneity in incidence and prevalence across studies seems to be partly explained by using different diagnostic criteria. ***Conclusion:*** These findings provide a starting point to estimate the social burden of CIDP and demonstrate the need to reach consensus on diagnostic criteria for CIDP.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disorder of the peripheral nerves and nerve roots causing limb weakness and sensory deficits [1]. CIDP is considered an immune-mediated disorder although the pathogenesis and aetiology of CIDP remain elusive [2, 3].

The clinical presentation of CIDP is diverse and at least 15 sets of diagnostic criteria for CIDP have been developed to capture the full spectrum of CIDP and its variant forms [4–7]. The criteria from the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/

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PNS) from 2010 are based on a combination of clinical and electrodiagnostic characteristics and are currently the most widely accepted criteria to confirm the diagnosis of CIDP [4]. Proven effective treatments for CIDP are immunoglobulins, corticosteroids and plasmapheresis [8]. The clinical response to these treatments is usually only partial and transient. Most patients with CIDP require maintenance treatment for years or even decades [8]. CIDP is therefore a disabling disorder with a considerable impact on patients and patient-related health care costs [9–14]. However, the population-based burden and related health costs are unknown. To determine this, we need to estimate the incidence and prevalence of CIDP.

Previous reviews provided an overview of studies that investigated the incidence and prevalence of neuromuscular disorders, polyneuropathies and rare diseases in general [15–17]. However, these reviews were not performed to give an overview of the incidence and prevalence of CIDP in specific and no meta-analysis was conducted. Furthermore, the use of different sets of criteria to diagnose CIDP may affect the incidence and prevalence rates [18]. To better estimate the true frequencies, patient numbers of individual studies need to be combined and the incidence and prevalence of CIDP using different diagnostic criteria need to be compared.

Our aim was to conduct a systematic review and meta-analysis to estimate the incidence and prevalence of CIDP worldwide and to determine the effect of diagnostic criteria on reported incidence and prevalence rates.

Method

This systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines [19]. The protocol of this systematic review was registered (registration number 2017: CRD42017072270) in PROSPERO (International prospective register of systematic reviews) [20].

Data Sources and Search Strategy

One author (M.C.B.) and a biomedical information specialist (Gerdien B. de Jonge) searched in Embase, Medline Epub, Cochrane Central, Web of Science and Google Scholar for all published work until May 18, 2017 (online suppl. Appendix I; for all online suppl. material, see www.karger.com/doi/10.1159/000494291). We used a combination of disease-specific terms (CIDP, chronic inflammatory demyelinating polyneuropathy) and key words for incidence and prevalence (epidemiology, prevalence and incidence). Reference lists of obtained articles were reviewed for additional articles.

Study Selection

We included all studies that reported the prevalence and/or incidence of CIDP and met the following criteria: (1) English language, (2) population based, (3) cases were identified based on fulfilling general accepted diagnostic criteria for CIDP (e.g., 2010 EFNS/PNS criteria, American Academy of Neurology [AAN] criteria) and (4) original data (i.e., not a review or a duplicate of previously published data, and full text must have been published). There were no limitations regarding the study size and identified the number of CIDP cases. We excluded studies that identified cases not based on general accepted diagnostic criteria for CIDP (e.g., insurance administrative medical codes, patient reports, membership patient organization). Studies that reported the prevalence and/or incidence in specific disease groups (e.g., diabetic population) instead of the general population were excluded. Studies that reported age and gender-specific prevalence and/or incidence were included.

Eligibility of all articles was determined by one author (M.C.B.) and independently checked by another author (C.B.). Titles and abstracts of all articles identified by the initial search strategy were independently reviewed on relevance. Articles that obviously did not meet the inclusion criteria were excluded. The full text of the remaining articles was reviewed in detail to assess whether they met the inclusion criteria. In case of disagreement, a third author (B.C.J.) reviewed the article and consensus was reached through discussion.

Data Extraction

Data of included studies was initially extracted by a single author (M.C.B.) and independently checked by another author (C.B.). Discrepancies were resolved by discussion with a third author (B.C.J.). Extracted information included author, study design, study period, population (study region, population number, person-years, age, CIDP categories), diagnostic criteria used to identify CIDP cases, number of identified CIDP patients, gender ratio, reported incidence rates (crude, standardized, age- and sex adjusted) and reported prevalence rates (crude, standardized, age- en sex adjusted). When data needed for the meta-analysis (cases, population number and person-years) was missing, we asked the corresponding author to provide this additional information.

One author (M.C.B.) assessed the methodological quality and risk of bias of the included studies. The Methodological Evaluation of Observational Research (MORE) checklist [21] was used to verify methodological quality and risk of bias. This checklist was designed for quality and bias assessment in incidence or prevalence studies of chronic diseases, and was previously used in several systematic reviews [22–28]. Two authors (M.C.B., H.F.L.) modified the MORE checklist to provide an applicable checklist for quality and bias assessment of the included studies (online suppl. Appendix II). Based on the MORE checklist, general descriptive elements, internal validity and external validity items were judged and defined as "OK," "minor flaw," "major flaw" or "poor reporting." We used the statistical software IBM SPSS version 21 for descriptive analysis of quality and bias assessment.

Statistical Analysis

We performed a random effect meta-analysis to estimate pooled incidence and prevalence rates with 95% CI. Heterogeneity was assessed using the I^2 statistics and visualized using prediction intervals. Meta-analysis of the incidence rates was performed using a Poisson-normal model [29]. To estimate pooled prevalence rates we applied the Freeman-Tukey transformation and performed a random effect meta-analysis on the transformed scale

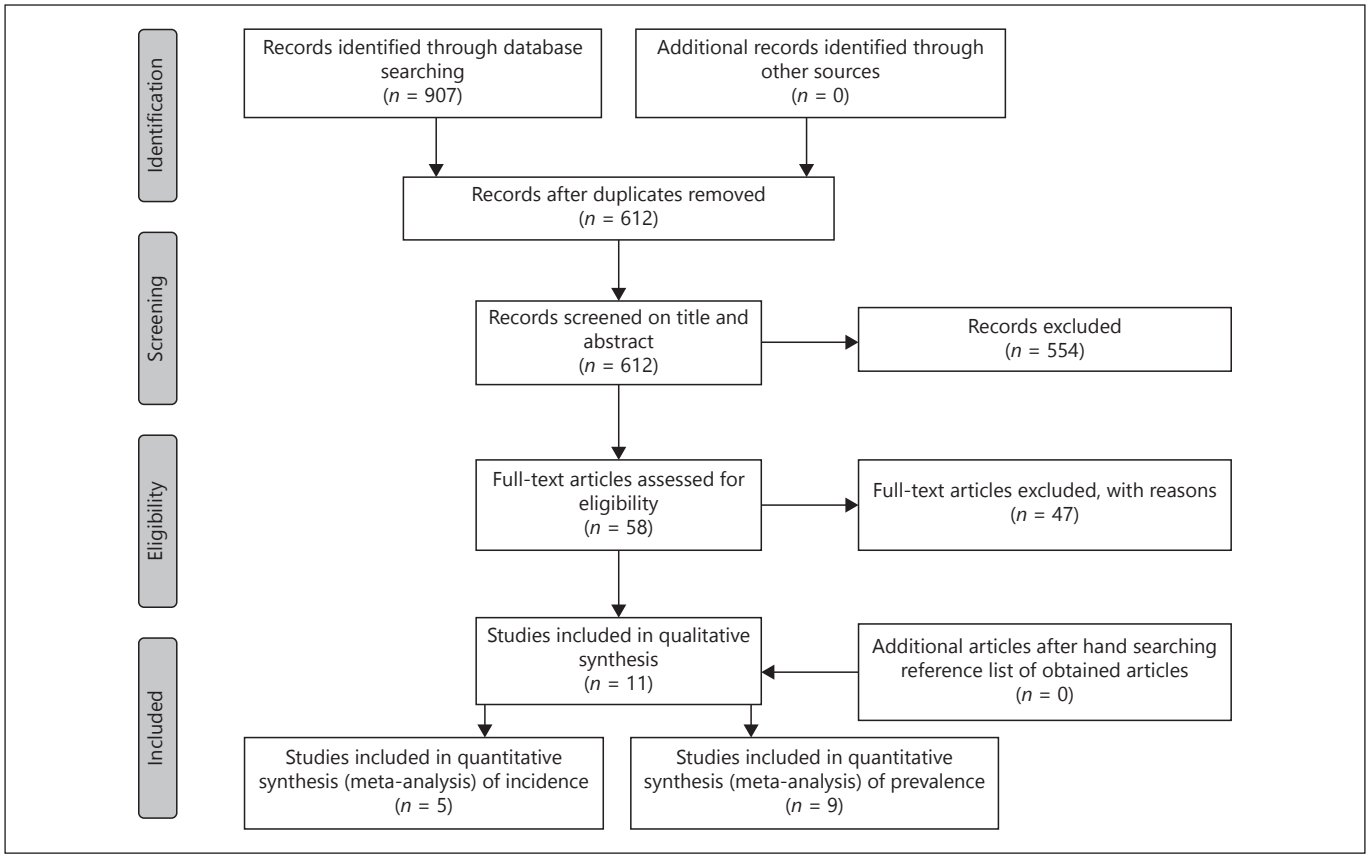

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the study selection process.

[30]. This transformation was necessary, since prevalence rates were close to zero. All statistical analyses were performed using R version 3.4.1., with the Metafor package version 2.0–0 used to perform the meta-analysis [31].

Results

We identified 907 articles in the initial search of which 295 duplicates were removed. Based on the title and abstract, 554 articles were excluded. After reviewing the full text of the remaining articles, 47 articles did not fulfil the following inclusion criteria: English language ($n = 6$), full text available ($n = 3$), reporting prevalence and/or incidence rates ($n = 6$), fulfilment of general accepted diagnostic criteria for CIDP ($n = 3$), original data ($n = 28$) and no duplication ($n = 1$). We contacted the corresponding authors of 2 studies because of missing data for conducting a meta-analysis; one author provided the required information (crude incidence rate, number of cases and person-years) [32]; one author could not provide the required information [33]. Finally, we included 11 publications for this systematic review of which 9 studies were sufficient for meta-analysis of prevalence [9–13, 18, 34–36] and 5 studies [11, 13, 18, 32, 34] for meta-analysis of incidence (Fig. 1). One study determined prevalence and incidence twice by using different diagnostic criteria [18]. Of this study, only prevalence and incidence rates based on the EFNS/PNS 2006 criteria were included in the meta-analysis.

Characteristics of Studies

Most studies were conducted in Europe ($n = 7$) including the United Kingdom ($n = 3$), Republic of Ireland ($n = 1$), Italy ($n = 1$), Iceland ($n = 1$) and Norway ($n = 1$; Table 1). The remaining studies were conducted in Australia ($n = 1$), Japan ($n = 2$) and the United States of America ($n = 1$). The population size in the studies varied between 135,802 and 127,655,000 patients. Person-years varied between 2,857,143 and 127,655,000. Six studies used the AAN criteria to define CIDP cases. In 4 studies, the EFNS/PNS criteria were used to confirm the diagno-

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Table 1. Study characteristics

Study author, reference number, and year	Study design	Prevalence year or period	Incidence period	Study region	Case ascertainment	Included ages	Included CIDP categories	Population number	Person-years
Lefter et al. [36], 2017	Retrospective and prospective	December 31, 2013	NA	Republic of Ireland	EFNS/PNS 2010 criteria	≥18 years	NR	3,439,565	NA
Hafsteinsdottir and Olafsson [32], 2016	NR	NA	January 1, 1991 – December 31, 2011	Iceland	EFNS/PNS 2010 criteria	All ages	Definite and probable	284,082	5,996,021*
Mahdi-Rogers and Hughes [9], 2014	NR	January 1, 2008	NA	Southeast England	EFNS/PNS 2006 criteria	NR	Definite, probable and possible	3,557,352	NA
Rajabally et al. [18], 2009	NR	May 1, 2008	2005–2007	UK, Leicestershire, Rutland	EFNS/PNS 2006 criteria, AAN criteria	All ages	Definite, probable and possible	963,600	2,857,143†
Laughlin et al. [33], 2009	NR	January 1, 2000	January 1, 1982 – December 31, 2001	USA, Olmsted County	Dyck et al. [62], 1975	All ages	Definite, probable	NR	NR
Iijima et al. [34], 2008	NR	September 2004 – August 2005	September 2004 – August 2005	Japan	AAN criteria, Saperstein's modified criteria, INCAT, other criteria	All ages	NA	127,655,000	127,655,000†
Chiò et al. [11], 2007	NR	December 31, 2001	1995–2001	Italy, Piemonte and Valle d'Aosta	AAN criteria	All ages	Definite, probable and possible	4,334,225	26,005,350†
Mygland and Monstad [10], 2001	Prospective	October 31, 1999	NA	Norway, Vest-Agder	Albers and Kelly criteria	All ages	NA	155,464	NA
McLeod et al. [13], 1999	NR	August 6, 1996	1986–1995	Australia, New South Wales	AAN criteria, Dyck et al. [61], 1993	All ages	Definite, probable and possible	5,995,544	58,000,000
Lunn et al. [12], 1999	NR	January 1, 1995	NA	England, Four Thames health regions	AAN criteria	NR	Definite, probable and possible	14,049,850	NA
Kusumi et al. [35], 1995	Retrospective	December 31, 1992	NA	Japan, Tottori prefecture	AAN criteria	NR	NR	614,725†	NA

Case definition: Albers and Kelly [60]; AAN criteria, American Academy of Neurology criteria [6]; Dyck et al. [61], 1993; Dyck et al. [62], 1975; EFNS/PNS 2006 criteria [49]; EFNS/PNS 2010 criteria [4]; INCAT, inflammatory neuropathy cause and treatment [5]; Saperstein›s modified criteria [63]; other criteria [64].

† Calculated, * provided by author of corresponding study.

NA, not applicable.

Table 2. Quality and bias assessment of included studies using MORE checklist

	OK *n* (%)	Minor flaws *n* (%)	Major flaws *n* (%)	Poor reporting *n* (%)	Total *n*
General descriptive elements					
Aim of study					
Incidence	5 (83.3)	0 (0)	0 (0)	1 (16.7)	6
Prevalence	9 (90)	0 (0)	0 (0)	1 (10)	10
Study design	7 (63.6)	0 (0)	0 (0)	4 (36.4)	11
Funding of study	7 (63.6)	0 (0)	0 (0)	4 (36.4)	11
Conflict of interest	4 (36.4)	2 (18.2)	0 (0)	5 (45.5)	11
Ethical approval	5 (45.5)	2 (18.2)	0 (0)	4 (36.4)	11
External validity					
Sampling	3 (27.3)	8 (72.7)	0 (0)	0 (0)	11
Assessment of sampling bias	0 (0)	1 (9.1)	1 (9.1)	9 (81.8)	11
Estimate bias					
Response rate	2 (50)	1 (25)	0 (0)	1 (25)	4
Exclusion rate	0 (0)	0 (0)	1 (9.1)	10 (90.9)	11
Addressment of sampling bias	4 (36.4)	0 (0)	0 (0)	7 (63.6)	11
Internal Validity					
Source of data	4 (36.4)	7 (63.6)	0 (0)	0 (0)	11
Validation	11 (100)	0 (0)	0 (0)	0 (0)	11
Incidence					
Type of incidence	6 (100)	0 (0)	0 (0)	0 (0)	6
Type of estimation	3 (50)	3 (50)	0 (0)	0 (0)	6
Reference period	6 (100)	0 (0)	0 (0)	0 (0)	6
Precision of estimate	4 (66.7)	0 (0)	0 (0)	2 (33.3)	6
Prevalence					
Type of prevalence	1 (10)	9 (90)	0 (0)	0 (0)	10
Type of estimation	3 (30)	7 (70)	0 (0)	0 (0)	10
Precision of estimate	5 (50)	0 (0)	0 (0)	5 (50)	10

MORE checklist, methodological evaluation of observational research.

sis of CIDP; 2 studies used the EFNS/PNS 2006 criteria and the other 2 studies used the EFNS/PNS 2010 criteria. Most studies included all CIDP categories (definite, probable and possible CIDP), while 2 studies only included definite and probable CIDP. Years for which incidence rates were available varied from 1982 to 2011. Years for which the prevalence rates were available varied from 1992 to 2013.

Methodological Quality of Studies

Methodological quality varied between studies (Table 2). Measurement of incidence and prevalence rates was validated in all studies. We found minor flaws in the source of data due to crude incidence and prevalence rates and assessment of sampling bias ($n = 1$). We found major flaws in assessment of sampling bias ($n = 1$) and exclusion rate ($n = 1$). Poor reporting for assessment of sampling bias (81.8%), addressment of sampling bias (63.6%) and exclusion rate (90.9%) were found in most studies. No studies were excluded from the review based on insufficient methodological quality.

Incidence

We included 5 incidence studies in the meta-analysis of incidence [11, 13, 18, 32, 34]. In the meta-analysis of incidence, 818 cases and 220,513,514 person-years were included. Crude incidence rates varied between 0.15 and 0.70 cases per 100,000 person-years (Table 3). The pooled crude incidence rate for the total population is 0.33 per 100,000 person-years (95% CI 0.21–0.53, $I^2 = 95.7\%$; prediction interval 0.11–0.98; Fig. 2). If we had included the estimated incidence based on the AAN criteria instead of based on the EFNS/PNS 2006 criteria of one study [18], the pooled incidence rate would have been 0.29 per 100,000 (95% 0.20–0.43, $I^2 = 93.3\%$; prediction interval 0.12–0.71). The pooled crude incidence rate for studies

Table 3. Incidence rates

Study author, year, and reference number	Number of cases	Number of male	Number of female	Gender rate ratio cases, male/female	Total incidence per 100,000 population (95% CI)*	Male incidence per 100,000 population (95% CI)*	Female incidence per 100,000 population (95% CI)*	Gender rate ratio incidence, male/female
Hafsteinsdottir and Olafsson [32], 2016	15[#]	NR	NR	NR	0.25[#] 0.3 (0.04–2.47)***	NR	NR	NR
Rajabally et al. [18], 2009								
EFNS/PNS 2006 criteria	20	13	7	1.9[†]	0.70 (0.43–1.08)	0.92 (0.49–1.58)	0.48 (0.19–0.99)	1.9[†]
AAN criteria	10[†]	NR	NR	NR	0.35 (0.17–0.64)	0.56 (0.24–1.10)	0.14 (0.02–0.50)	4.0[†]
Laughlin et al. [33], 2009	NR	NR	NR	NR	1.4 (0.8–2.0)[!, ***] 1.6 (0.9–2.2)***	NR	NR	NR
Iijima et al. [34], 2008	601	354	247	1.4[†]	0.48	0.58	0.38	1.5[†]
Chiò et al. [11], 2007	95	NR	NR	NR	0.36 (0.29–0.44) 0.34 (0.28–0.42)**	0.51 (0.39–0.65)	0.22 (0.15–0.31)	2.3[†]
McLeod et al. [13], 1999	87	NR	NR	NR	0.15	NR	NR	NR

[†] Calculated; * crude rate, if not specified otherwise; ** standardized rate; *** age- and sex-adjusted rate; [!] excluding MGUS; [#] provided by author of corresponding study.

NR, not reported; AAN, American Academy of Neurology [6]; EFNS/PNS criteria 2006 [49].

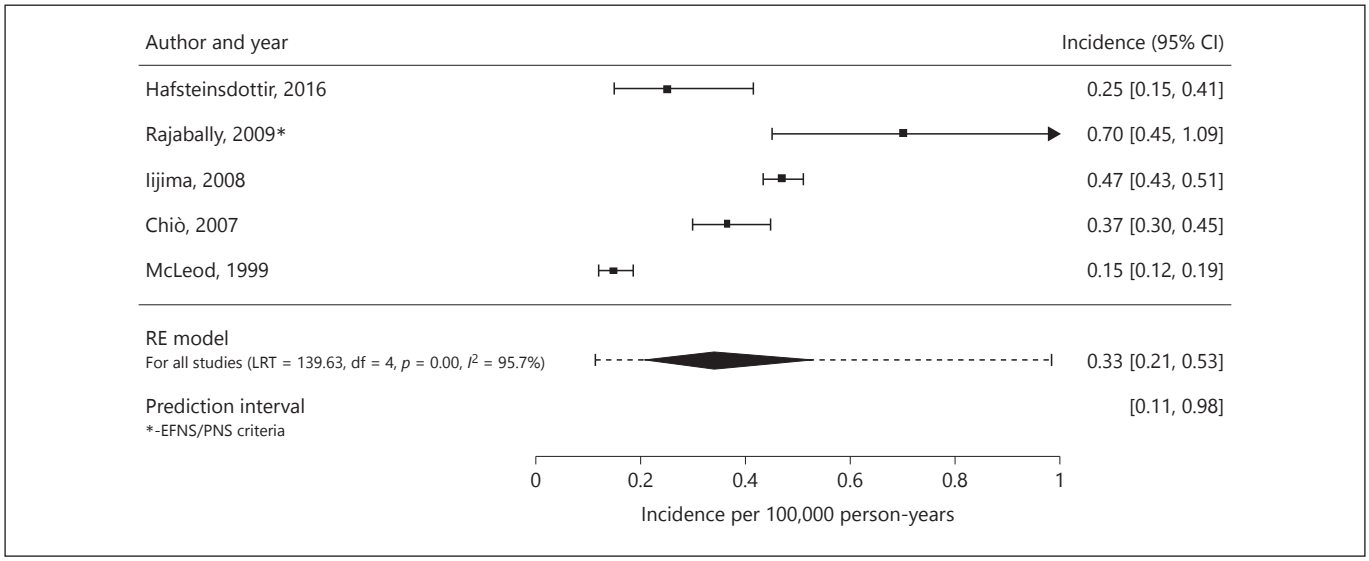

Fig. 2. Pooled crude incidence rate using the random-effects model. RE model, random-effects model.

using the AAN criteria is 0.36 per 100,000 person-years (95% CI 0.30–0.44, I^2 = 0.0%; prediction interval 0.30–0.44). Data of studies using the EFNS/PNS 2006 and EFNS/PNS 2010 criteria was insufficient to conduct a crude pooled estimate for these criteria. Overall, the prediction intervals were substantially wider, thereby reflecting the observed heterogeneity between studies. In general, the reported crude incidence rates were higher in males than females (gender rate ratios varied between 1.5 and 4.0; Table 3). One study determined age-specific incidence rates [34]. The crude incidence rate in the age group of 15 years and older was 0.54 per 100,000 person-years (0.40 per 100,000 person-years in age-group of 15–55 years and 0.73 per 100,000 person-years in the age-group older than 55 years) compared to a crude incidence rate of 0.06 per 100,000 person-years in age-group 0–15 years.

Table 4. Prevalence rates

Study author, year and reference number	Number of cases	Number of male	Number of female	Gender ratio cases, male/female	Total prevalence per 100,000 population (95% CI)*	Male prevalence per 100,000 population (95% CI)*	Female prevalence per 100,000 population (95% CI)*	Gender ratio prevalence, male/female
Lefter et al. [36], 2017	202	NR	NR	NR	5.87 (5.06–6.68)#	NR	NR	NR
Mahdi-Rogers and Hughes [9], 2014	101	66	35	1.9†	2.84 (2.31–3.45) 2.92 (2.39–3.56)**	3.84 (2.97–4.89)	1.90 (1.32–2.65)	2.0†
Rajabally et al. [18], 2009								
EFNS/PNS 2006 criteria	46	34	12	2.8†	4.77 (3.49–6.37)	6.73 (4.60–9.50)	2.87 (1.57–4.81)	2.3†
AAN criteria	19	14	5	2.8†	1.97 (1.19–3.08)	2.94 (1.61–4.94)	1.02 (0.33–2.39)	2.9†
Laughlin et al. [33], 2009	11	NR	NR	NR	10.3 (4.2–16.4)***	NR	NR	NR
Iijima et al. [34], 2008	2,433	1,495	938	1.6†	1.61	2.01	1.23	1.6†
Chiò et al. [11], 2007	155	105	50	2.1†	3.58 (3.02–4.20) 3.41 (2.92–3.98)**	5.02 (4.13–6.10)	2.23 (1.65–2.94)	2.3†
Mygland and Monstad [10], 2001	12	NR	NR	NR	7.7 (3.2–12.2)	NR	NR	NR
McLeod et al. [13], 1999	112	64	48	1.3†	1.9 (1.5–2.2)	2.2 (1.7–2.8)	1.6 (1.2–2.1)	1.4†
Lunn et al. [12], 1999	94	NR	NR	NR	0.67	NR	NR	NR
Kusumi et al. [35], 1995	5	4	1	4.0†	0.81	1.36	0.31	4.4†

† Calculated; * crude rate; if not specified otherwise; ** standardized rate; *** age- and sex-adjusted rate; # prevalence rates is expressed as case/100,000 adults. NR, not reported; AAN criteria, American Academy of Neurology criteria [6]; EFNS/PNS 2006 criteria [49].

Prevalence

We included 9 studies in the meta-analysis of prevalence rates [9–13, 18, 34–36]. In total, 3,160 cases and a population size of 160,765,325 were included in the meta-analysis of prevalence. The crude prevalence rate varied between 0.67 and 7.7 cases per 100,000 persons (Table 4). The pooled crude prevalence rate for the total population is 2.81 per 100,000 (95% CI 1.58–4.39, I^2 = 99.1%; prediction interval 0.12–8.78; Fig. 3). If we had included the estimated prevalence based on the AAN criteria instead of based on the EFNS/PNS 2006 criteria of one study [18], the pooled prevalence rate would have been 2.52 per 100,000 (95% 1.41–3.95, I^2 = 99.0%; prediction interval 0.10–7.91). The pooled crude prevalence rate for studies using the AAN criteria is 1.59 per 100,000 (95% CI 0.57–3.11, I^2 = 96.7%; prediction interval 0.01–5.52). The pooled crude prevalence rate for studies using the EFNS/PNS 2006 criteria is 3.67 per 100,000 (95% CI 2.01–5.83, I^2 = 87.2%; prediction interval 1.18–7.52). While we find that studies using the EFNS/PNS 2006 criteria obtain higher prevalence rates than studies using the AAN criteria, the difference between the 2 estimates is not significant (p = 0.11). One study described prevalence using the EFNS/PNS 2010 criteria (5.87 per 100,000) [36]. Overall, the prediction intervals were substantially wider, thereby reflecting the observed heterogeneity between studies. In general, reported crude prevalence rates were higher in males than in females (gender rate ratios varied between 1.4 and 4.4; Table 4). Five studies determined age-specific prevalence rates [9, 11, 13, 18, 34]. Reported age-groups varied between studies. Overall, the prevalence increased with age (Table 5).

Discussion

Our meta-analysis provides a pooled crude incidence rate for CIDP of 0.33 per 100,000 (95% CI 0.21–0.53; prediction interval 0.11–0.98) person-years and a pooled crude prevalence rate of 2.81 per 100,000 (95% CI 1.58–4.39; prediction interval 0.12–8.78) persons. Reported incidence and prevalence of CIDP showed substantial heterogeneity across studies. This heterogeneity may partly be explained by the use of different diagnostic criteria. Most CIDP patients were male and the incidence and prevalence of CIDP increased with age. We observed no evident geographical variation in the incidence or prevalence rates.

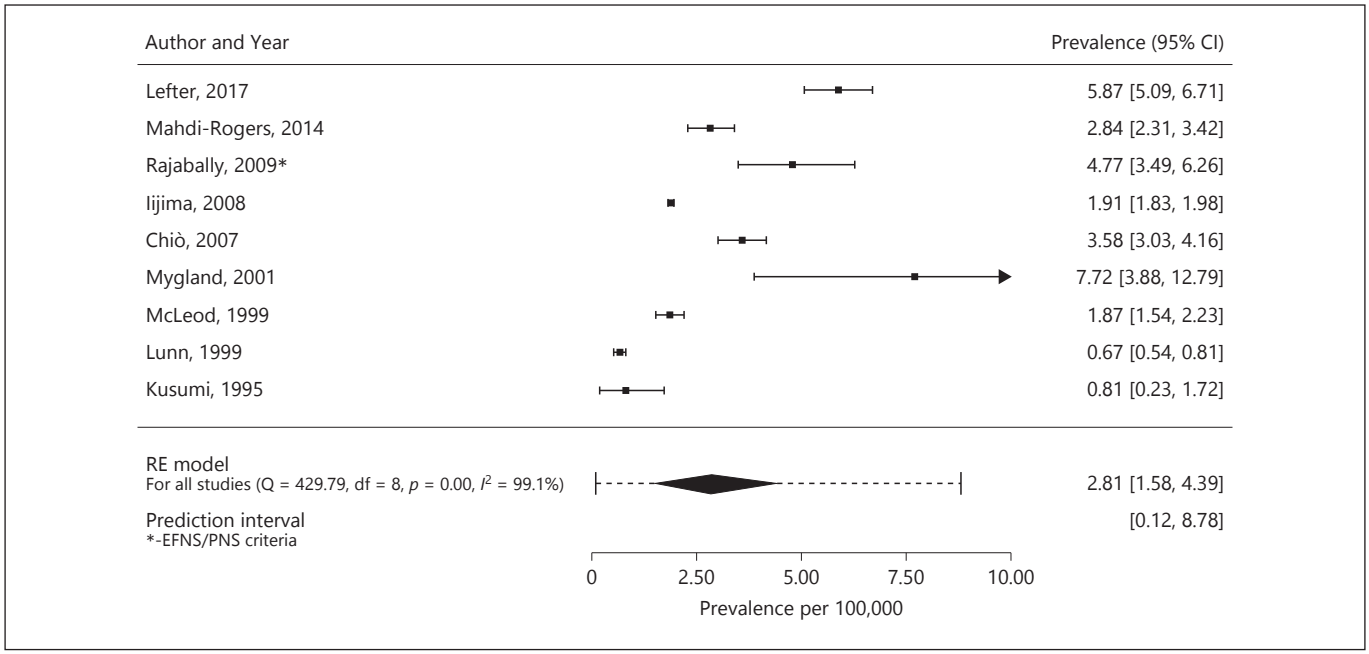

Fig. 3. Pooled crude prevalence rate using the random-effects model. RE model, random-effects model.

Interestingly, males are also overrepresented in other immune-mediated neuropathies including the Guillain-Barré syndrome (GBS) and multifocal motor neuropathy [9, 37–40]. The male predominance in these immune-mediated neuropathies is unexplained and deviates from female predominance in many classic autoimmune disorders [41–43]. A male predominance has also been suggested for other forms of polyneuropathies, suggesting that males are more at risk to develop a polyneuropathy [44, 45]. However, a recent comprehensive overview of the literature indicated that polyneuropathies in general are more common in females [15]. Older people seem to be more at risk to develop CIDP. An increasing incidence with age has also been demonstrated for GBS and polyneuropathies in general [39, 44].

The pooled incidence and prevalence rates should be read cautiously because of the substantial heterogeneity between the included studies. A critical determinant in these studies is the used case definition, since more than 15 different sets of diagnostic criteria for CIDP have been proposed in literature. Our meta-analysis suggests that studies using the AAN criteria found lower incidence and prevalence rates than studies using the EFNS/PNS 2006 criteria, and lower prevalence rates than studies using the EFNS/PNS 2010 criteria. One study determined prevalence and incidence rates for the AAN en EFNS/PNS 2006 criteria in the same population and found significantly (McNemar's exact test; $p < 0.0001$) higher rates when using the EFNS/PNS 2006 criteria for prevalence (1.97 vs. 4.77 per 100,000) and incidence (0.35 vs. 0.70 per 100,000) [18]. These differences are likely related to the variation in sensitivity and specificity of these diagnostic criteria. The AAN criteria are considered most specific but are less sensitive presumably due to requirement of electrophysiological evidence of a minimum of 5 or 6 demyelinating findings in 2 nerves, and of abnormalities in cerebrospinal fluid and/or nerve biopsy studies for a diagnosis of definite CIDP [6, 46–48]. Overall, EFNS/PNS criteria have a higher sensitivity, likely because in contrast to the AAN criteria, only 1 or 2 demyelinating findings are required to diagnose CIDP, with or without additional testing, but are still highly specific presumably due to the higher thresholds for demyelinating features [6, 46–49]. The higher specificity and lower sensitivity of de AAN criteria seem to explain the reason behind the lower incidence and prevalence rates when using the AAN criteria. However, in our study, the difference between the pooled estimate using the AAN criteria and the pooled estimate using the EFNS/PNS 2006 criteria for prevalence was not significant, presumably due to the low number of prevalence studies using these criteria. The number of incidence studies using the AAN, EFNS/PNS 2006 and EFNS/

PNS 2010 criteria was insufficient to determine significance between studies using different criteria. Only one incidence study used the most recent EFNS/PNS criteria (2010) to confirm the diagnosis of CIDP. In contrast, this study found a lower incidence rate compared to studies using the AAN criteria, which may be explained by the exclusion of the category of patients with a "possible" CIDP in this study [32]. Of one study, we included estimates based on the EFNS/PNS 2006 criteria and excluded estimates based on the AAN criteria in the meta-analysis to avoid overrepresentation of this study in our sample [18]. We found no large differences in the pooled prevalence and incidence between only including estimates based on the AAN criteria or only including estimates based on the EFNS/PNS 2006 criteria of this study. The reported incidence and prevalence rates are also influenced by differences in inclusion and exclusion criteria between the studies. Particularly relevant is whether patients are included with additional diabetes mellitus or monoclonal gammopathy of undetermined significance. In addition, not all studies included the full range of ages of patient with CIDP. One study excluding patients younger than 18 years observed a relatively highly prevalence rate (5.87 per 100,000 adults; 95% CI 5.06–6.68), that is probably explained by the increase of CIDP with age [36]. In conclusion, the use of different diagnostic criteria seems to affect the observed incidence and prevalence rates of CIDP but also differences in the use of other inclusion criteria seem to play a role. However, this should be read cautiously because significance between diagnostic criteria could not be demonstrated.

The prevalence of a disease depends on the disease duration. In clinical practice, it may be difficult to discriminate between patients with active disease and patients with residual nerve damage but inactive disease. The CIDP Disease Activity Status tool has been developed to define long-term outcomes in CIDP and to classify patients as cured if they have a stable neurological examination (either normal or abnormal) and are off all treatment for 5 or more years [50]. However, the concept of being cured in CIDP is questionable, because patients may relapse even years after the disease became inactive [50, 51]. Most studies in our meta-analysis did not define the disease activity status or whether "cured" patients were excluded and this could have influenced the reported prevalence of CIDP. Long-term follow-up studies recording the disease activity status are needed to more accurately estimate the prevalence.

The observed incidence and prevalence rates may seem to increase in more recent studies, but no statistical

Table 5. Age group specific prevalence rates

	Mahdi-Rogers and Hughes [9], 2014		Rajabally et al. [18], 2009 EFNS/PNS 2006 criteria [49]		Rajabally et al. [18], 2009 AAN criteria [6]		Iijima et al. [34], 2008		Chiò et al. [11], 2007		McLeod et al. [13], 1999	
Juvenile prevalence per 100,000 population (95% CI)*	0–9 years	0.00	0–19 years	1.26 (0.26–3.69)	0–19 years	0.42 (0.01–2.34)	0–15 years	0.23	0–19 years	0.57 (0.22–1.24)	0–9 years	0.23
	10–19 years	0.46									10–19 years	0.48
Adult prevalence per 100,000 population (95% CI)*	20–29 years	0.21	20–59 years	2.51 (1.34–4.30)	20–59 years	1.16 (0.43–2.52)	15+ years	1.83	20–39 years	0.43 (0.16–0.94)	20–29 years	0.57
	30–39 years	0.51	60+ years	14.37 (9.69–20.51)	60+ years	5.74 (2.97–10.04)	15–55 years	1.50	40–59 years	2.99 (2.19–3.98)	30–39 years	1.27
	40–49 years	3.01					55+ years	2.31	60–79 years	9.45 (7.88–11.25)	40–49 years	2.45
	50–59 years	2.61							80 ≥ years	8.78 (5.68–13.00)	50–59 years	1.81
	60–69 years	8.90									60–69 years	6.10
	70–79 years	11.60									70–79 years	6.69
	80–89 years	8.85									80–89 years	2.74
	≥90 years	0.00									≥90 years	–

* Crude rate, if not specified otherwise.

significant trend in time for incidence is found [32, 33]. Although the pathogenesis and aetiology of CIDP is far from understood, previous studies reported infections and vaccinations preceding the onset of CIDP symptoms [52–56]. Our pooled estimates of incidence and prevalence of CIDP can be used to assess changes of CIDP incidence following infections, vaccinations or other potential causal exposures, and to demonstrate a causal relation between preceding events and CIDP.

Strength and Limitations

A comprehensive literature search was performed by a biomedical information specialist and a medical doctor to ensure that most relevant published articles were captured. We used an evidence-based tool (Preferred Reporting Items for Systematic reviews and Meta-Analyses checklist) [19] to optimize the reporting of title, abstract, introduction, methods, results, discussion and funding of this systematic review and meta-analysis. To reduce diagnostic uncertainty, we excluded studies based on health insurance administrative claims (prevalence of 5.9 per 100,000) and not widely accepted diagnostic criteria (prevalence of 3–12 per 100,000; incidence of 2 per 100,000) for CIDP [57–59]. Overall, the quality of the included studies is moderate. Most studies reported a good internal validity. External validity and the quality of general descriptive elements could be improved. More attention to avoid sampling bias is needed in further incidence and prevalence of CIDP studies.

This systematic review and meta-analysis have some limitations. Most studies were performed in European countries. However, we found no difference in incidence and prevalence rates between European and non-European countries. Most studies used the former (2006) EFNS/PNS criteria. In addition, at present, the currently used EFNS/PNS (2010) criteria are being revised. The number of studies was too limited to conduct a proper comparison in phenotypes of CIDP between regions. We could not include one study (age- and sex-adjusted incidence 1.6 per 100,000 person-years; age- and sex-adjusted prevalence rate 10.3 per 100,000 persons) for meta-analysis because crude rates were not provided [33]. Including this study may have increased the pooled prevalence and incidence rates. In our meta-analysis, confidence intervals of the included studies sometimes differ from published CIs presumably due to different preferred calculation of confidence intervals. We may have missed relevant articles because we excluded non-English papers (n = 6), including studies conducted in France (n = 3), Germany (n = 1), Switzerland (n = 1) and Brazil (n = 1).

Conclusion

Our meta-analysis provides an estimate of the prevalence and incidence of CIDP and a starting point to better assess the social burden due to CIDP and to identify risk factors for developing CIDP, such as infections and vaccinations preceding the onset of CIDP symptoms. However, the observed heterogeneity between studies limits the application for future risk factor assessments. The use of different diagnostic criteria seems to explain in part the variation in reported prevalence and incidence rates and indicates the need to reach consensus of diagnostic criteria for CIDP. More high-quality studies are required to explain the heterogeneity, and to better estimate the prevalence and incidence of CIDP using the revised EFNS/PNS criteria.

Acknowledgements

We would like to thank Gerdien B. de Jonge, Biomedical Information Specialist at the Medical Library Erasmus MC, University Medical Center Rotterdam for her help in the literature search.

Funding Sources and Disclosure Statement

We would like to thank the Dutch Prinses Beatrix Spierfonds for funding (grant application number: W.OR16–18). B.C.J. has received unrestricted financial support for research from the Prinses Beatrix Spierfonds, GBS-CIDP Foundation International, Baxter Biopharmaceutics, CSL-Behring, Grifols and Annexon.

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