Population-based incidence rates of 15 neuromuscular disorders: a nationwide capture-recapture study in the Netherlands

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A R T I C L E   I N F O

A B S T R A C T

Most neuromuscular disorders are rare, but as a group they are not. Nevertheless, epidemiological data of specific neuromuscular disorders are scarce, especially on the incidence. We applied a capture-recapture approach to a nationwide hospital-based dataset and a patients association-based dataset to estimate the annual incidence rates for fifteen neuromuscular disorders in the Netherlands.

The annual incidence rates per 100,000 population varied from 0.03/100,000 (95% CI 0.00 – 0.06) for glycogenosis type 5 to 0.9/100,000 (95% confidence interval 0.7 – 1.0) for myotonic dystrophy type 1. The summed annual incidence rate of these disorders was 4.1 per 100,000 per population. Nine of the provided incidence rates were previously unavailable, three rates were similar to the rates in the literature, and three rates were generally higher compared to previous findings but with overlapping confidence intervals.

This study provides nationwide incidence rates for fifteen neuromuscular disorders predominantly diagnosed in adult life, nine which were previously unavailable. The capture-recapture approach provided estimates of the total number of individuals with neuromuscular disorders. To complete the gaps in the knowledge of disease frequencies, there is a need for estimates from an automated, obligatory data collection system of diagnosed and newly diagnosed patients with neuromuscular disorders.

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1. Introduction

Individual neuromuscular disorders are rare, but as a group they are not [1]. The overall annual incidence rate of neuromuscular disorders is reported to be 122 per 100,000 population based on health insurance billing codes within administrative health databases in Ontario, Canada [2]. Despite the considerable size of the total group of patients with a neuromuscular disease, data regarding the epidemiology of the specific neuromuscular disorders are scarce, especially on incidence [1,3–6]. The few available frequency estimates are difficult to compare because of differences in ascertainment

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methods. Research that assesses the incidence of multiple neuromuscular disorders within one study, allowing for comparisons of the researched data, are also scarce. Furthermore, occurrence rates are often based on small geographical areas or limited-size populations [7,8].

Epidemiological data are highly relevant for clinical practice, patients, trial readiness, and health care policies in neuromuscular disorders. Incidence and prevalence rates are frequently used in the diagnostic process in personalized care and for etiological studies investigating risk factors in public health. As our understanding of various disease mechanisms swiftly advances and new treatments are being introduced, information on the epidemiology of specific neuromuscular disorders is needed for trial readiness and for approval and reimbursement of treatment options.

The epidemiological quantifiers prevalence, incidence and disease duration are closely related: the prevalence of a disease equals the incidence of the disease multiplied by the disease duration [9]. Thus, to define a disease in epidemiological terms, at least two of these quantifiers are needed.

Here, we present the results of a unique study providing population-based annual incidence rates for 15 neuromuscular disorders predominantly diagnosed in adults. The estimates are based on a hospital-based nationwide neuromuscular disorder registry and membership files from the Dutch Association for Neuromuscular Diseases in the Netherlands, a country with a well-organized health care system and excellent neuromuscular diagnostic and therapeutic services [10]. The Dutch neuromuscular expertise centers work in close collaboration and distances to the nearest center are limited throughout the country. By applying the capture-recapture method, we adjusted for the number of non-registered patients. This enabled us to use these extensive datasets to yield incidences rates formerly unavailable [11].

2. Patients and methods

2.1. Standard protocol approvals, registrations and patient consent

The project was discussed with the Medical Ethics Review Committee of the Radboud University Nijmegen Medical Centre (file no. 2011-397). Participant consent was not required for the use of the data described below for epidemiological analysis. Therefore this study was deemed not to fall within the scope of the Medical Research Involving Human Subjects Act.

2.2. Datasets

We used two nationwide datasets (see Table 1 for details). The first one is the Dutch *Computer Registry of All Myopathies and Polyneuropathies* database (CRAMP), which was initiated in 2004 to enable epidemiological studies and advance trial readiness [12]. Neurology departments of all eight university medical centers in the Netherlands with a neuromuscular service participated in the registry. Newly diagnosed patients were recorded using a classification system of 1400 diagnoses [13]. Diagnoses in CRAMP were based on the observations and examinations by neuromuscular neurologists from the participating centers according to the (then) current guidelines [14–17].

The second database comprised data from the membership files of *Spierziekten Nederland* (SN), the Netherlands Patients Association of Neuromuscular Diseases, based on a classification system of 96 diagnoses [18]. The diagnoses recorded in SN were provided by the members themselves, or the members' parents, or partner. After matching the 1400 diagnoses in CRAMP with the 96 diagnoses in SN, 82 neuromuscular diagnoses were present in both databases.

By 2012, CRAMP contained over 18,000 individuals diagnosed with neuromuscular disorders and the SN dataset over 8000 individuals. We removed duplicate and incomplete records from the CRAMP dataset (the SN dataset was deduplicated by SN) and analyzed data from the period 2004–2011. The CRAMP dataset was not fully complete since pediatricians had no access to this registry, and because the registry process was only partially automated. The SN dataset was obviously not complete, since membership of a patients association is not mandatory. We combined both datasets for the application of the capture-recapture method, to accurately estimate neuromuscular disorder frequencies.

2.3. Capture-recapture method

Only mandatory registries with a specific incentive (for instance a payment system) are likely to approximate completeness. Therefore, most registries are not complete, but are often assumed to be. We made use of two datasets, which we combined to apply the capture-recapture method in order to estimate the number of unregistered patients to estimate incidences in a comprehensive way (Fig. 1) [11].

The capture-recapture method is based on four assumptions: a proper matching of subjects captured by the registries is achieved; the patient population under scrutiny is closed and stable, i.e., there are no new people entering or leaving the researched population during the researched period; the probability of being recorded in each registry is equal; and the two captures should be independent.

Individuals from the two datasets were first matched to identify those who were present in both datasets. As a unique identifier for the matching process (e.g., the citizen service number) was unavailable, we used a combination of four characteristics: date of birth, sex, diagnosis, and date of diagnosis. The first prerequisite for a match was a full match on date of birth and sex. Regarding diagnosis and date of diagnosis, these were deemed a match if they were completely identical. In addition, although a strategy that matches only if all four variables are identical may seem appropriate, this could yield mismatch of persons if variables differed slightly (e.g., day and month or year of diagnosis, but also subtypes of diagnosis or closely related diagnoses). Mismatch will cause inflation of the total number of affected individuals. Therefore, we applied a procedure wherein a possible match (i.e., not all variables completely identical) was also counted as a match, unless there was clear evidence of the contrary (for example, two very different diagnoses that are unlikely to be mixed up in the clinic). This process of matching in incomplete matches was performed by two of the researchers, an epidemiologist and a neurology resident experienced in neuromuscular disorders (JCWD and CGCH). When the date of diagnosis differed in otherwise matching individuals, we used the earliest date. If a difference in diagnosis between the databases was observed, the diagnosis recorded in CRAMP was retained. The matching process was carried out with a syntax written and executed in SAS statistical software for Windows version 9.2. All other calculations were done using Microsoft Excel 2013. Fig. 1 was made using MS Powerpoint, fig. 2 was plotted with Graphpad Prism 9.5.0.

2.4. Calculations

To calculate the incidence of the disorders, we used Chao's lower bound number estimate based on a binomial distribution sampling:

$$N = (m_2 + n_{10} + n_{01}) + \frac{(n_{10} + n_{01})^2}{4m_2}$$

Table 1

Characteristics of the CRAMP and SN datasets used for the capture-recapture calculations.

|	CRAMP	SN (Spierziekten Nederland)
Origin of data	Registry for university medical centers with specific expertise in neuromuscular disorders	Data from the membership files of the Dutch patients association for neuromuscular diseases
Available information	Date of birth	Date of birth (sometimes only year and month)
	Sex	Sex
	Date of diagnosis	Date of diagnosis
	Two characters from the patients' name	Diagnosis (96-item list)
	Three-number part of local registration number	
	Which university medical center registered the diagnosis	
	Diagnosis (1400-item list), including certain neuromuscular features if a specific neuromuscular diagnosis lacked	
Details on date of diagnosis	Not prone to recall bias	Possibly prone to recall bias
	Sometimes returning patients were registered with incorrect, belated date of diagnosis	
Does information remain in the registry?	Once registered, persons stay in the registry unless they explicitly requested to be removed	If persons stop their membership, their information is removed, except if related family members are still a member (e.g. after a child or partner died)
Can non-patients be registered?	No	We received a list of patients; parents and other (family) members were removed beforehand by SN
Symptomatic patients or asymptomatic carrier	Symptomatic patients only	Symptomatic patients only
Date of diagnosis	Date as entered by the physician	Date as reported by the patient
What happened if patients were entered twice (by clinicians in different neuromuscular disorder centers)	Duplicates were removed before capture-recapture was applied	Not applicable, only one association, one dataset
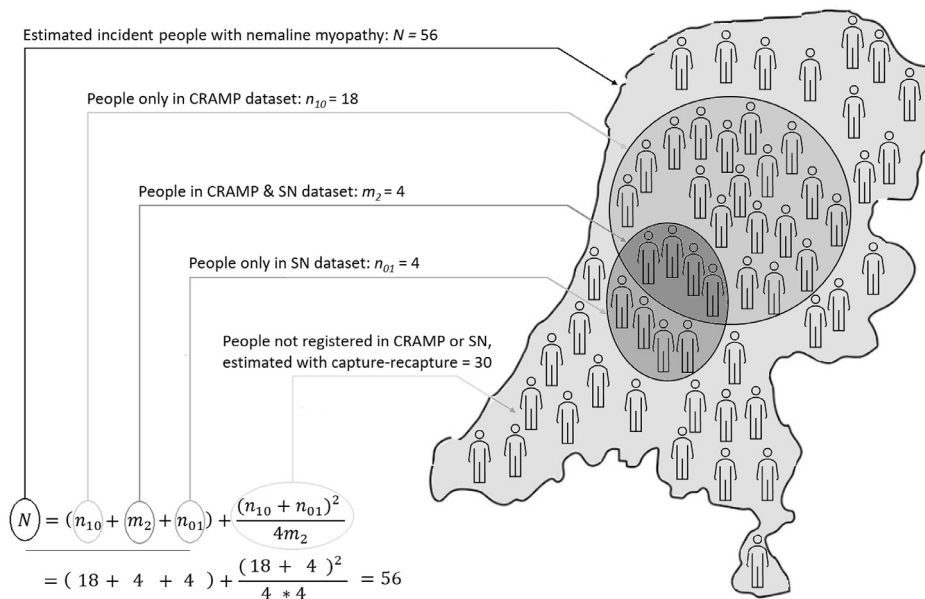
Fig 1. Graphical presentation of capture-recapture method using Chao's lower bound number estimate with our incidence findings for nemaline myopathy [19]. Two registries (CRAMP and SN) served as a "capture" and a "recapture"; based on the number of people with newly diagnosed nemaline myopathy in both registries and their overlap, we estimated the number of people with nemaline myopathy not present in CRAMP or SN to assess the total number (N) of people newly diagnosed with this disorder from 2004-2011. CRAMP: Computer Registry of All Myopathies and Polyneuropathies database; SN: Spierziekten Nederland, the Netherlands Patients Association of Neuromuscular Diseases.

The accompanied estimate of variance and associated Poisson-based 95% confidence interval (CI) were:

$$\text{Var}(N) = \frac{(n_{10} + n_{01})^2}{4m_2} \left(\frac{(n_{10} + n_{01})}{2m_2} + 1 \right)^2$$

95% CI for $N = N \pm 1.96\sqrt{\text{Var}(N)}$ where N = estimated patient population size, m_2 = number of persons present in both datasets (the overlap), n_{10} = number of persons only present in sample 1 (CRAMP), n_{01} = number of persons only present in sample 2 (SN), see Fig. 1 for example [19].

The Chao estimator is less biased, has a better confidence interval coverage and relaxes the independent source assumption compared to the more commonly used Chapman estimator [20]. As CRAMP registered incident cases of disease and ran for less than two decades, we provided incidence estimates and not prevalence estimates. Incidence rates were derived by dividing the absolute number of incident cases and its Poisson-based confidence intervals by the corresponding age- and sex-specific population numbers of the Dutch population available from Statistics Netherlands [21]. Rates per 100,000 population were rounded to the nearest significant digit, thus reporting order of magnitude rather than seemingly exact figures.
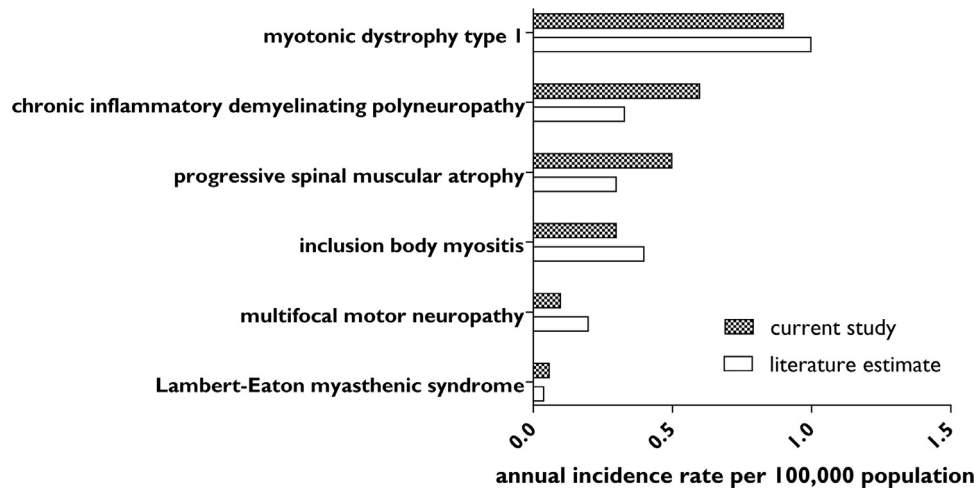
Fig 2. Comparison of capture-recapture results with findings from literature (unpublished results).

To enhance the validity of each incidence estimate, five criteria were formulated, arising from the capture-recapture specifics and characteristics of the used databases: the disorder is also diagnosed in adulthood; the disorder is chronic; the diagnosis is sufficiently specific; the SN patients association is findable by patients with the specific disorder; and the diagnosis is predominantly made or confirmed in university medical centers. Only estimates of the disorders that passed these five criteria were presented in this manuscript.

The data published in this article are available by request from any qualified investigator.

2.5. Neuromuscular disorder incidence rates for comparison

To evaluate whether the estimates were in line with the information available in literature, we searched for systematic reviews about incidence rates regarding the various disorders. If unavailable, we compared the annual incidence findings with rates in an updated version (unpublished results) of our overview article [1].

3. Results

After matching persons present in the CRAMP and SN datasets, sufficient data were available for the capture-recapture method in 49 of the 82 diagnostic categories. Fifteen diagnoses passed the five criteria to enhance validity and were deemed sufficiently accurate, see Table 2. These disorders comprised 1595 patients from the CRAMP dataset and 698 from the SN dataset; 264 persons were present in both datasets. The annual incidence rates ranged from 0.03/100,000 (95% CI 0.00 – 0.06) for glycogenosis type 5 to 0.9/100,000 (95% confidence interval 0.7 – 1.0) for myotonic dystrophy type 1, see Table 3. For 12 of the 15 diagnoses, data were available to calculate sex-specific incidence rates. When the incidence rates of these 15 disorders were added up, the resulted overall neuromuscular annual incidence rate was 4.1 per 100,000 population, which is approximately 1 in 2400 of the population.

Almost all identified systematic reviews and meta-analyses presented solely prevalence rates and did not mention pooled incidence rates of the specified neuromuscular disorders, except for one review including the incidence rate of chronic idiopathic demyelinating polyneuropathy [22]. It reported a pooled annual incidence rate of 0.33 per 100,000 population (95% CI 0.21-0.53). For comparison of the other findings, we made use of unpublished results.

4. Discussion

Based on two comprehensive datasets from the Netherlands, this study provided incidence rate estimates for fifteen neuromuscular disorders predominantly diagnosed in adult life, as well as separate and sex-specific incidence rates for these neuromuscular disorders. The estimates were adjusted for patients not registered in either of the two datasets, by applying a capture-recapture method. The summed annual incidence rate of these 15 disorders is 4.1 per 100,000 population. This was twice the incidence of presumably more common neurological disorders such as multiple sclerosis (2.1 per 100,000 population) [23].

Of the fifteen calculated rates, only six could be compared with information from the literature (Fig. 2 and Table 3). The incidence for myotonic dystrophy type 1, multifocal motor neuropathy and inclusion body myositis found in this study agreed with or was close to the mean incidence estimate from the studies referenced in Table 3. The incidence estimates found for chronic inflammatory demyelinating polyneuropathy, progressive (spinal) muscular atrophy and Lambert-Eaton myasthenic syndrome were moderately higher compared with information in the literature. This may be due to the application of the capture-recapture method, which estimates the number of individuals not registered in either dataset into account. Still, the 95% CI, and if the CI were unavailable the range of the findings, overlapped for all disorders. For hereditary motor and sensory neuropathy type 1 and 2, proximal (spinal) muscular atrophy, glycogenosis types 2 and 5, Becker muscular dystrophy, myotonic dystrophy type 2, oculopharyngeal muscular dystrophy and nemaline myopathy, we found no previous information regarding incidence rates in the literature.

The capture-recapture method is based on several assumptions (see Patients and methods section). As in any epidemiological study using capture-recapture, some of these are difficult to address. Possible detrimental effects of not meeting the assumptions were controlled for by several measures. By limiting the observation period, for example, the influence of a non-closed population was restricted. A constructed variable was used as a unique identifier for the matching procedure, enabling correct matching. In addition, the application of a not-too-conservative matching strategy guarded against matching issues, which otherwise could have resulted in overestimation of the incidence. Next, we applied Chao's estimator, which, in case the independency assumption is not fully met, presents a proper lower limit for the number of cases. Furthermore, dependency between

Table 2

Validity assessment of the capture-recapture estimates for specific neuromuscular disorders based on five criteria, listed in alphabetical order.

Disorder	Diagnosis (also) in adults[1]	Chronic nature[2]	Specific disorder[3]	SN Findable[4]	UMC based[5]	Fulfilling all criteria
Amyotrophic lateral sclerosis	+	-	+	+	-	
Becker myotonia	+	+	+	-	+	
Bethlem disease	+	+	+	-	+	
Becker muscular dystrophy	+	+	+	+	+	+
Central core disease	+	+	+	-	+	
Chronic idiopathic axonal polyneuropathy	+	+	+	+	-	
Chronic inflammatory demyelinating polyneuropathy	+	+	+	+	+	+
Congenital muscular dystrophy	-	+	-	+	+	
Congenital myasthenia gravis	+	+	+	-	+	
Congenital myopathies not specified	+	+	-	-	+	
Dermatomyositis	+	+	+	+	-	
Distal spinal muscular atrophy	+	+	+	-	+	
Duchenne muscular dystrophy	-	+	+	+	+	
Eulenberg myotonia	+	+	+	-	+	
Friedreich ataxia	+	+	-	+	+	
Focal spinal muscular dystrophy	+	+	+	-	+	
Facioscapulohumeral muscular dystrophy	+	+	+	+	+	+
Guillain Barré syndrome	+	-	+	+	-	
Glycogenosis type 2	+	+	+	+	+	+
Glycogenosis type 5	+	+	+	+	+	+
Hereditary motor and sensory neuropathy not specified	+	+	-	+	-	
Hereditary motor and sensory neuropathy type 1	+	+	+	+	+	+
Hereditary motor and sensory neuropathy type 2	+	+	+	+	+	+
Hereditary neuropathy with liability to pressure palsies	+	+	+	+	-	
Hereditary sensory and autonomic neuropathy	+	+	+	-	+	
Inclusion body myositis	+	+	+	+	+	+
Lambert-Eaton myasthenic syndrome	+	+	+	+	+	+
Limb girdle muscular dystrophy	+	+	-	+	+	
Myotonic dystrophy type 1	+	+	+	+	+	+
Myotonic dystrophy type 2	+	+	+	+	+	+
Metabolic myopathies	+	+	-	+	+	
Myasthenia gravis	+	+	+	+	-	
Monoclonal gammopathy of unknown significance with neuropathy	+	+	-	-	+	
Miller-Fisher syndrome	+	-	+	-	+	
Other mitochondrial myopathies	+	+	-	+	+	
Multifocal motor neuropathy	+	+	+	+	+	+
Other myasthenic syndrome	+	+	-	+	+	
Other myopathies	+	+	-	-	+	
Myositis not specified	+	+	-	+	+	
Myotonia not specified	+	+	-	-	+	
Myotubular and centrotubular myopathies	+	+	+	-	+	
Neuralgic amyotrophy	+	-	+	+	-	
Nemaline myopathy	+	+	+	+	+	+
Oculopharyngeal muscular dystrophy	+	+	+	+	+	+
Polymyositis	+	+	+	+	-	
Post-polio syndrome	+	+	+	+	-	
Progressive spinal muscular atrophy	+	+	+	+	+	+
Spinal muscular atrophy not specified	+	+	-	+	+	
Spinal muscular atrophy type 1	-	-	+	+	+	
Spinal muscular atrophy type 2	-	+	+	+	+	

[1] the disorder is (also) diagnosed in adulthood;
[2] the disorder is chronic;
[3] the diagnosis is sufficiently specific;
[4] the SN patients association is findable by patients with the specific disorder;
[5] the diagnosis is predominantly made or confirmed in university medical centers.

Table 3

Capture-recapture based numbers of neuromuscular disorders and sex-specific incidence rates with related information from literature, ordered by incidence rate from high to low rate.

Neuromuscular disorder	Capture-recapture information from period 2004-2011				Annual incidence rate per 100,000 population (95% CI)			Updated version of overview per 100,000 population	
	Persons only in CRAMP	Persons only in SN	Overlap CRAMP and SN	Estimated total number	Total population*	Men	Women	Mean incidence rate	Range
Myotonic dystrophy type 1	315	98	64	1143	0.9 (0.7-1.0)	1.0 (0.7-1.3)	0.8 (0.6-1.0)	1	0.20-2.061 [43-45]
Chronic inflammatory demyelinating polyneuropathy	188	44	28	741	0.6 (0.4-0.7)	0.7 (0.5-1.0)	0.4 (0.2-0.7)	0.33 **	0.21-0.53 [22]
Hereditary motor and sensory neuropathy type 1	72	49	7	651	0.5 (0.2-0.8)	0.3 (0.1-0.6)	0.7 (0.0-1.4)	-	-
Progressive spinal muscular atrophy	212	40	42	672	0.5 (0.4-0.6)	0.6 (0.5-0.8)	0.4 (0.2-0.6)	0.3	- [46]
Facioscapulohumeral muscular dystrophy	149	33	26	527	0.4 (0.3-0.5)	0.5 (0.3-0.8)	0.3 (0.2-0.4)	- ***	-
Hereditary motor and sensory neuropathy type 2	57	47	11	361	0.3 (0.1-0.4)	0.6 (0.1-1.1)	0.1 (0.1-0.2)	-	-
Inclusion body myositis	122	39	35	381	0.3 (0.2-0.4)	0.4 (0.2-0.5)	0.2 (0.1-0.3)	0.4	0.09-0.76 [47-51]
Glycogenosis type 2	59	28	15	228	0.2 (0.1-0.2)	0.2 (0.1-0.4)	0.1 (0.1-0.2)	-	-
Multifocal motor neuropathy	28	19	6	145	0.1 (0-0.2)	0.2 (0-0.3)	0.1 (0-0.1)	0.2	- [52]
Becker muscular dystrophy	17	17	9	75	-	0.1 (0-0.2)	-	-	-
Myotonic dystrophy type 2	21	3	1	169	0.1 (0.0-0.4)	-	-	-	-
Oculopharyngeal muscular dystrophy	32	8	8	98	0.07 (0.04-0.1)	0.06 (0.03-0.09)	0.1 (0-0.2)	-	-
Lambert-Eaton myasthenic syndrome	29	4	6	84	0.06 (0.03-0.1)	0.07 (0.01-0.1)	0.06 (0.01-0.1)	0.04	0.030 – 0.048 [16,53]
Nemaline myopathy	18	4	4	56	0.04 (0.01-0.07)	0.04 (0-0.08)	0.05 (0-0.1)	-	-
Glycogenosis type 5	12	1	2	36	0.03 (0-0.06)	-	-	-	-

* The summed annual incidence rate was 4.1 per 100,000, which is approximately 1 in 2400 of the population;
** Pooled crude incidence rate per 100,000 person-years and 95% CI from meta-analysis;
*** the only other estimate available was based on partly the same data [24].

datasets hampering the correct estimation of numbers can never be ruled out in any capture-recapture method. However, in a previous study on the incidence of facioscapulohumeral muscular dystrophy, three sources were available, including the CRAMP and SN datasets we used here [24]. This enabled the assessment of dependency between sources to a considerable extent, which turned out to be mostly non-significant.

When we first looked into applying a capture-recapture method, we anticipated large overlaps between the datasets and large dependencies among them. This was because newly diagnosed patients are very often encouraged to become a member of the patients association. However, the findings from the 3-source capture-recapture pilot for facioscapulohumeral muscular dystrophy showed that dependencies were small or absent, and overlap between CRAMP and SN was smaller than expected. Our current findings showed overlap that varied between 4% and 21% of the total group of patients (in CRAMP, SN and in both datasets), with a mean and median of 13%. This was also less than expected and gives rise to higher capture-recapture-based incidence estimates compared to data in literature. Furthermore, even though patients are encouraged to join the patient advocacy association, they often do not. When we compared our overlaps to those of a number of other 2-source capture-recapture based studies, the overlaps of 17 estimates from 13 studies were found to vary between 1% and 62%, with a mean value of 29% and median of 15% [25–37].

Whether the differences between our observations and the scarcely published literature reflect true differences, or whether these differences are due to residual methodological issues, remains open for debate. These limitations call for a nationwide automated system based on an existing healthcare registry with an intrinsic incentive for data collection, similar to the Belgian Neuromuscular Diseases Registry and the French national research program on rare disease cohorts [38,39]. Such a system will provide more accurate incidence estimates if set up correctly and in due time prevalence estimates of rare diseases as well.

To what extent these findings will be usable outside the Netherlands, is an interesting yet unanswerable question. Some NMD are known for their gradient or latitude-based occurrence such as inflammatory myopathies [40]. Other disorders such as myotonic dystrophy may exhibit a founder effect in specific countries [41,42]. More research on epidemiological key estimates is highly needed. Meanwhile, using estimates from a geographically different area is the next-best option.

Research reports usually start with a short summary of the disease at hand with epidemiological key figures, such as incidence, prevalence, mortality and age at onset or diagnosis. To properly describe a disease in epidemiological terms, two out of three of these frequency measures should be available [9]. As disease duration is an epidemiological quantifier difficult to obtain, incidence rates are just as necessary as prevalence rates. For many diseases, prevalence data are more abundantly available and incidence rates are often lacking, which hampers a complete description of the epidemiological aspects of the disease. Also, the use of incidence rates rather than prevalence rates may even be more appropriate (unpublished results). Even so, incidence rates are generally "underrated" and underrepresented.

5. Conclusions

With this study we added incidence rates for several neuromuscular disorders and have thus contributed to the epidemiological body of knowledge. The capture-recapture approach provided a method to accurately estimate the total number of individuals with these 15 neuromuscular disorders in the Netherlands. The summed annual incidence rate of these specific neuromuscular disorders predominantly diagnosed in adults was twice the incidence of presumably more common neurological disorders such as multiple sclerosis. This illustrates that it is not uncommon to have a rare neuromuscular disorder. To fill in the gaps in the epidemiological knowledge, we need estimates from preferably automated, obligatory data

collection system of diagnosed and newly diagnosed patients with neuromuscular disorders. This can provide an up-to-date and complete basis to derive valid prevalence and incidence estimates highly needed in all fields of individual as well as public health care.

Abbreviations

CRAMP: *Computer Registry of All Myopathies and Polyneuropathies* database; SN: *Spierziekten Nederland*, the Netherlands Patients Association of Neuromuscular Diseases; N = estimated patient population size, m_2 = number of persons present in both datasets (the overlap), n_{10} = number of persons only present in sample 1 (CRAMP), n_{01} = number of persons only present in sample 2 (SN); CI: confidence interval

Declaration of competing interest

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