An Epidemiological Perspective On Neuromuscular Disorders

– nationwide registries in practice –

Hanneke Deenen

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– nationwide registries in practice –

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Chapter 1

Introduction

The group of neuromuscular disorders (NMDs) comprises a range of different and individually rare diseases. Many of these disorders are characterised as disabling and often require specialised care. Until a few decades ago, factual knowledge about the frequency of the NMDs was based on hospital-based tallies and scarce literature on a few specific disorders, mainly case series. This situation changed when NMD registries were launched. In this introduction, the trajectories of two nationwide registries are outlined: one on multiple neuromuscular disorders and the other solely on facioscapulohumeral muscular dystrophy (FSHD). These registries aim to obtain valid epidemiological information and to provide a framework for future clinical research into NMDs.

NEUROMUSCULAR DISORDERS

The main focus of the presented studies in this thesis is on the epidemiological characteristics of neuromuscular disorders. The term 'neuromuscular disorders' includes a heterogeneous group of disorders that affect the function of skeletal muscles due to abnormalities in the motor neuron, nerve, neuromuscular junction, or the muscle itself. Most commonly, the disorders manifest by difficulties in voluntary skeletal muscles, often resulting in weakness of the upper and lower limbs, the trunk, the face and the respiration. Smooth muscles and the autonomic or the central nervous system may also be involved, since neuromuscular disorders can be a part of a generalised systemic disorder.

There are more than 600 different neuromuscular disorders, that differ from each other in many ways:

- there are inherited disorders as well as acquired disorders
- most are chronic, but there are also conditions from which individuals can partially or fully recover
- some are stable, but many are progressive
- the age of onset may vary from prenatal to older age
- symptoms may involve muscle weakness, sensory problems, but other organ systems with a variety of associated symptoms can also be involved
- apart from these symptoms, patients will often experience pain, fatigue and varying degrees of physical disability, as well as psychological complaints
- even within a specific disorder, the time of onset, symptoms, severity, and level of disability can vary widely.

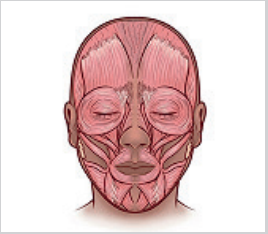
The term 'disorder' refers to a condition of the body that prevents some parts of it from functioning properly. In this thesis, we use the term 'disorder' interchangeably with 'disease', which is the disorder seen from the physician's perspective. In contrast, 'illness' (the way the patient experiences his or her disorder) or 'sickness' (the disorder seen from the perspective of society) are not used [1]. To illustrate what it means to have a neuromuscular disorder, Box 1 below represents an informal conversation with Nynke, who was diagnosed with facioscapulohumeral muscular dystrophy (FSHD).

Many neuromuscular disorders have a high burden of disease for both patients and society, and require extensive health care. Even with the limited information available, this group of patients is firmly among the top five diseases of the health care burden worldwide [2-4]. This is due to the extensive and lifelong disability of the diseases and the lack of effective treatments [2].

In the past decades, there has been a tremendous development in understanding the specific genetic, immunological and other disease mechanisms of many of the neuromuscular disorders. In addition to providing diagnostic aid, this knowledge gives insight into treatment options, either curative or symptomatic. This in turn calls for trial readiness, with a need to find a large group of well-defined and correctly diagnosed patients in a relatively short period of time. It poses a major challenge, as almost all neuromuscular disorders appear to be rare or very rare. The word 'rare' literally means 'not found in large numbers' or 'not occurring very often' [5].In Europe, a disease is considered rare, if it affects 1 person in 2,000 or 50 persons in 100,000 [6].

Box 1 - An introduction to FSHD by a conversation with Nynke about the effects of the disorder

This is Nynke, who was diagnosed with FSHD at the age of 8. FSHD is a hereditary muscle disease that is initially most noticeable in the muscles of the face (facies), shoulder blades (scapula), and upper arms (humerus). Later, the muscles of the abdomen and legs are also affected. The first symptoms and signs often occur between the age of ten and twenty, but this can vary from toddler age to over 50 years. The severity of the symptoms and course of FSHD differ from person to person and range from mild to severe; people may end up in a wheelchair.



Upper image:
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Lower image:
Muscles of the face

Muscles are located throughout the body, including the face. Muscle diseases not only lead to muscle weakness, but also to fatigue, pain and problems with facial expressions. The mouth and eyes are sphincter muscles and in Nynke's face these muscles are weakened.

What features does a clinician notice? A beautiful woman, with facial abnormalities: large eyes due to drooping of the lower eyelids, an asymmetrical mouth, slightly opened on the right side, thin lips, and a limited facial expression. Her facial expression does not tell you how she feels. People often fill this gap with their own interpretation, which causes a lot of issues in everyday life. Frequently observed compensation mechanisms for the restriction in facial expression are: speaking with hands, nodding the head, explicitly stating emotions.

Nynke, what does it mean for you to have FSHD?

"I have so-called early onset FSHD. My parents saw the first signs when I was still a toddler. This means that I have had to deal with this muscle disease from a very young age. My condition has deteriorated considerably ever since. Nowadays I use an electric wheelchair and I need assistance from others for many things.

What FSHD means to me is that I am almost always dependent on others. I am constantly deteriorating. I am always tired and in pain, and must constantly anticipate this. This means I have an energy-driven

schedule, because sometimes I have energy to do something and sometimes I do not. People around me cannot always cope well with this. When I have to cancel appointments, people often find it difficult.

Because I have had FSHD for so long (I am 51 now), the muscle weakness in my face is severe, which means that I have very little facial expression. This limited facial expression is one of the most difficult aspects for me. Recently I was at a party with many strangers. A young girl across the room smiled at me, but I could not smile back. Her father (who knows me) was standing next to her, saw it happening and explained to her that I cannot smile. You could see comprehension dawning on her face. On the one hand, this is nice, it removes the tension for both the other person and me. At the same time, it is also very confronting.

Your facial expression is literally the first contact with someone. That is especially difficult when you meet someone for the first time. I always have to look for a suitable moment to explain things in a first, often fleeting conversation. Without an explanation, people sometimes find me serious and difficult to fathom, and that makes me insecure. If you know me better, you can read a lot from my eyes. But for those who know me less well, I have to name every emotion."

Why do you participate in the FSHD registry?
"When the FSHD registration started, I immediately signed up. I found and still find it important to participate in research, particularly aimed at increasing knowledge about the disease and treatments, such as research into useful outcome measures for drug research. A lot of valuable information can be obtained from patients and their experiences.

In 2017, as an ambassador for the FSHD Foundation, I participated in a comedy campaign to raise awareness of FSHD. The campaign aimed at highlighting the challenges associated with facial muscle weakness. We sat in the audience of a comedian named Ronald Snijders, and no one laughed. Both people with FSHD, because they often cannot laugh, and other people involved were silent because they were in on the plan. Ronald did not know what was happening to him, it made him very insecure. I was the one who put him out of his misery by explaining what was happening. This incident was widely covered on TV and social media, which resulted in an interview with Jeroen Pauw, the host of a popular TV show in the Netherlands. I still use those videos to explain my situation to people I meet.

And this campaign also generated enough donations for the FSHD Foundation (that also funded the set-up of the FSHD registry) to conduct research into facial muscle weakness. Participants for this research were also found via the FSHD registry. This research has resulted in all kinds of advice, which the expertise centre in turn uses to inform people with FSHD about their facial expressions."

Read more of this conversation in Box 1 of the General discussion chapter.

DESCRIPTIVE EPIDEMIOLOGY

Epidemiology is the discipline that studies how often diseases occur in groups of people over time, and why [7]. The first part of the definition – how often diseases occur – is called descriptive epidemiology; the second part – about aetiological and prognostic questions – is called analytical epidemiology. This dissertation focuses on the first part: the frequency of neuromuscular diseases.

In everyday language, as well as in medical and epidemiological terms, the term 'occurrence' has several different meanings. According to the Longman Dictionary, two separate meanings are presented with a subtle yet very important difference: 1) the fact or frequency of something happening, and 2) the fact that something exists or is found in a place or under a certain set of circumstances. These two descriptions are reflected in the two different forms of disease occurrence used by the epidemiological discipline: incidence and prevalence. Box 2 summarises these prevailing concepts of language use.

To know how often diseases occur, either newly diagnosed in a specific time period (incidence) or the number of people with the specific disease at a specific point in time (prevalence), it all starts with simply counting people of interest. To make counts useful and interpretable, additional information is needed: 1) what exactly is counted, 2) where or in what area are they counted, 3) within what time frame are the counts done, and 4) in what population? It is the added information about what, where, and when things are counted that 'makes sense' of the count. The added time frame is the essential component of an incidence measure, and is described as the number of newly diagnosed patients with the disorder per time frame. Often, this time frame is one year, providing the annual incidence rate. The population from which these patients come and the size of the population must also be clear and may be expressed per 100,000 or 1,000,000 population.

Box 2 - The meaning of the term occurrence of disease and its associated measures in epidemiology

Longman Dictionary	**Descriptive epidemiology**
Occurrence of disease	Disease frequency
1. the fact or frequency of something *happening*	*incidence* – the number of times something happens, for example crime, disease
2. the fact of something *existing* or being found in a place or under a particular set of conditions	*prevalence* – common at a particular time, in a particular place, or among a particular group of people; cf., the prevalence of deafness in older age groups

To further describe a disease in epidemiological terms, the duration of the disease can be specified. This quantity is defined as the period from age at onset, often replaced by the more easily quantifiable measure of age at diagnosis, until individuals die of the disease, die of another cause, or recover. With the duration known, it becomes clear how the disease behaves in a given population over time. In a steady state – the situation in which incidence rates and disease duration are stable over time – prevalence, incidence, and disease duration are linearly related [8]. Then, the prevalence is a function of incidence and duration, and can be approximated by multiplying incidence by duration. For example, for facioscapulohumeral muscular dystrophy with an annual incidence rate of 0.3 per 100,000 population and an estimated disease duration of 39 years, the prevalence rate is estimated to be 12 per 100,000 population (0.3 per 100,000 population x 39 years) [9, 10].

REGISTRIES IN PRACTICE

One of the most important tools for determining disease frequencies is the initiation and maintenance of disease registries [11]. The first large registry worldwide was the Framingham Study, launched in the 1940s. This American initiative was driven by the then upcoming epidemic of cardiovascular disease in the western world [12]. This first-of-its-kind registry made a major contribution to the understanding of the underlying causes of the disease. It provided information

that is still used and elaborated upon, which in turn has led to improvements in health care, regulations and lifestyle advice. Many small and large registries have been initiated since then, prompted by emerging disease in a relatively short period of time, or out of curiosity. They have in common that they simply count events and personal characteristics.

The registries studied in this thesis were initiated with the aim of overcoming the research limitations inherent to the study of rare diseases. These typically include small numbers of patients, limited funding opportunities, and difficulties in conducting clinical trials [13]. More than eight hundred rare disease registries were listed in a December 2021 report from the Orphanet Network in Europe, including the Dutch CRAMP project, which is short for Computer Registry of All Myopathies and Polyneuropathies [14]. CRAMP was launched by collaborating neurologists and patient advocacy groups in the Netherlands. It collected data from seven university medical centres and one large regional medical centre on newly diagnosed persons with a NMD (Figure 1). A limited set of variables was collected, minimizing the workload for clinicians. These stand-alone databases were locally connected to the electronic health record systems, enabling the entry of patient contact information with little effort. This reuse of data 'straight from the source' was an important first step towards trial readiness by making patients discoverable and by collecting nationally relevant information on the occurrence of the individual as well as grouped diseases.

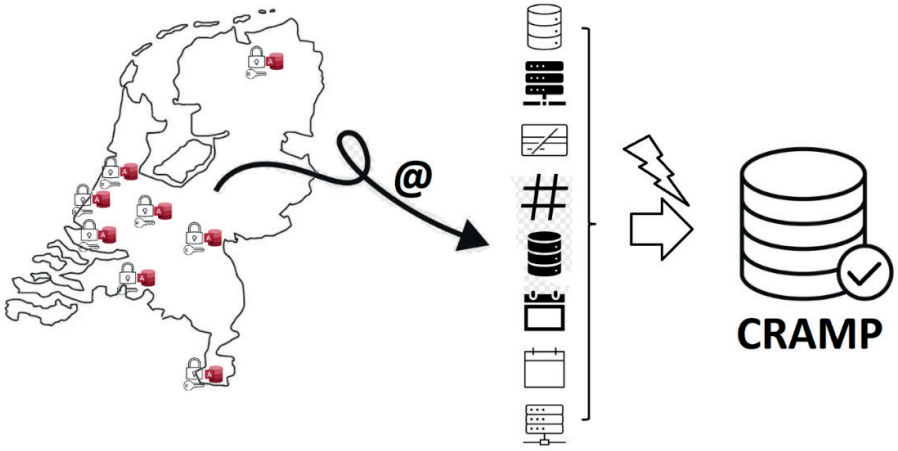


Figure 1. Schematic representation of the CRAMP registry.

CRAMP consists of a separate, stand-alone database in each of the eight participating centres, locally connected with the electronic health records for data extraction. After a few years of registering newly diagnosed patients with a NMD, each centre exported their pseudonymised data and mailed it to the Radboud university medical center. These exports should be similar in layout and content but appeared to differ in several ways. The data from these sets were standardised and combined into one CRAMP dataset.

Another example is the Dutch FSHD registry which was started in the Netherlands in 2015 (Figure 2). It is open to (Dutch and Belgian) patients with facioscapulohumeral muscular dystrophy; together with myotonic dystrophy, these are the two most common NMDs. In contrast to CRAMP, where patients are registered by clinicians, the FSHD registry patients have to register themselves by downloading informed consent forms from a website.

Completeness of registries

There are various ways to investigate completeness. Some of these methods make it possible to estimate the number of unregistered people if a registry turns out to be incomplete. These methods were first used a century ago to assess the number of wild animals in a certain area [15]. It was impossible to capture them all. Therefore, a number of animals were captured and marked (Figure 3). The researchers then returned the marked animals to the original population. After allowing them to disperse, they performed a "recapture" and counted the number of marked and unmarked animals, which gave them the ratio of these animals. Since the total number of marked animals is known, as well as the ratio of marked versus unmarked animals, the total population can be inferred, of course taking into account a number of methodological assumptions.

Applied to disease registries, these assumptions imply that an appropriate matching of the subjects captured by the registries is achieved; the patient population under study is closed and stable, i.e., no new people entering or leaving the population during the studied period; the probability of being included in each registry is equal; and the captures should be independent (Figure 4). In epidemiological settings, these assumptions are almost always at least partially unmet. However, the detrimental effects can be limited by applying a number of counter-measures, on which we will elaborate in the consecutive chapters.

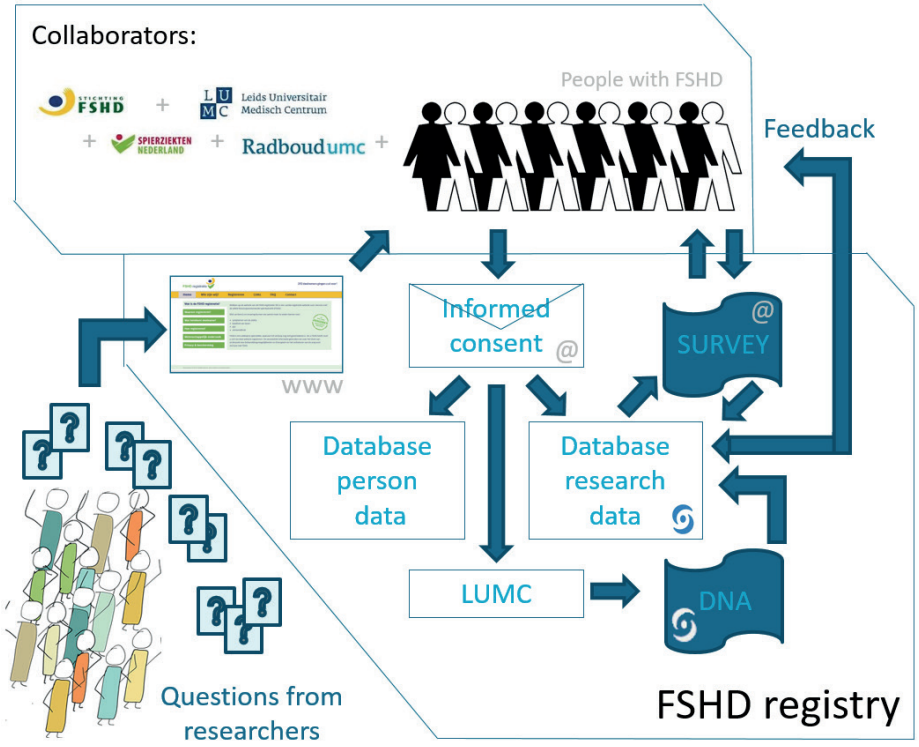


Figure 2. Schematic representation of the FSHD registry.

The registry was set up in collaboration with the four presented organisations and people with FSHD. To enter the registry, individuals download a suitable (mainly age-based) informed consent form and information letter from the website FSHDregistratie.nl, fill it in and return it to the Radboud university medical center. Here, the contact details are entered in one database. Research data are stored in a second database, using the Castor EDC system [16]. From this database, surveys with multiple questionnaires are regularly sent to the participants. The research database is filled with their answers, and with their genetic diagnosis data if available, provided by the Leiden University Medical Center. Participants were also asked what (research) questions were on their minds. These questions were combined in a questionnaire and sent out to all participants. After data analysis, the answers are returned to the participants. Researchers are encouraged to use the registry, either by requesting collected or new data, requesting participants for their own studies, or a combination. Information on how to submit a request can be found on the website.

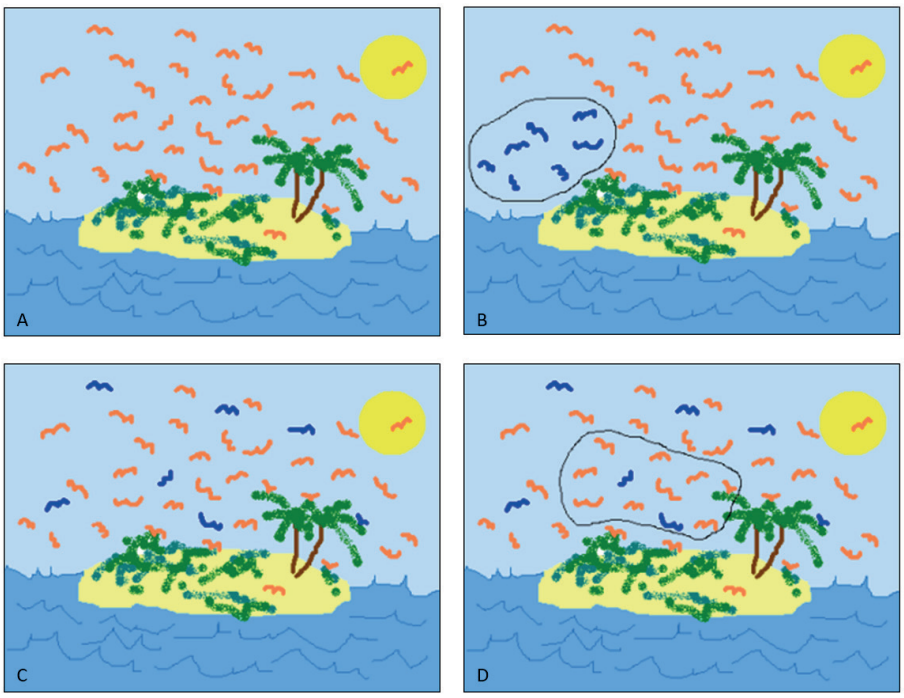


Figure 3. Illustration of steps taken in a two-source capture-recapture approach.

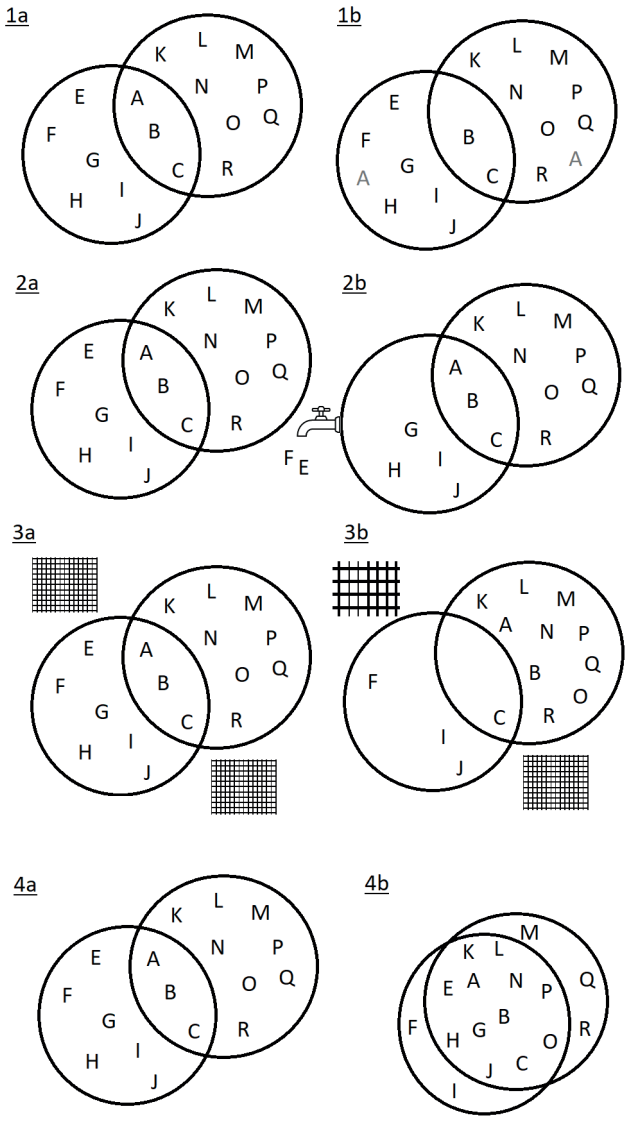
(A) The capture-recapture approach was derived from biology to estimate the number of individuals in a population in case not all individuals could be counted directly, for instance birds on an island. (B) A number of birds are captured, marked, and released again. (C) After waiting long enough for the marked birds to disperse into the population, (D) a second set of birds is captured. In this group we count the number of marked and unmarked birds, which gives a dilution factor of the known number of birds from the first capture. With this finding, the total number of individuals in the population can be estimated, including those that were never captured: seven birds in first capture, labelled blue. The second capture contained eleven birds in total, nine unlabelled and two of the previously labelled birds. Then the whole population N is estimated by (n1 * n2) / m3 = (7 * 11) / 2 ≈ 38 [17].

THESIS AIMS AND OUTLINE

Disease registries form the starting point for new studies and applied medical research on diagnosis, aetiology, prognosis and treatment of individuals, as well as preventive interventions in the general population. One of the first reasons for setting up a registry to document individuals with a certain (group of) disorder(s) is to learn more about the disease frequencies, which is a main goal of the epidemiological discipline. The simple numbers of patients ('the counts'), however, are meaningless in themselves and cannot be properly interpreted unless they are related to the time frame involved and the populations where patients were found and converted to population-based disease frequencies.

In order to adequately analyse data collected by registries, it is important to evaluate their completeness. In this thesis on descriptive epidemiology of NMDs, the degree of under-ascertainment of individuals in the datasets is assessed by applying the capture-recapture method, which uses a combination of registries. Further, we aim to update and extensively discuss the epidemiology of NMDs using data from the two available registries in the Netherlands. All objectives will be covered in four parts: the first one describes the available evidence from the literature, the second part provides new data arising from the CRAMP registry of multiple neuromuscular disorders, the third section covers the capture-recapture approach, and the fourth part will focus on patient-reported findings in FSHD, as collected by the Dutch FSHD registry. See graphical representation of the thesis below (Figure 5).

More specifically, the aims in **chapters 2 and 3** are to investigate current morbidity rates in the general population based on the literature. The CRAMP project was initiated as a starting point for research to further increase the trial readiness. In **chapters 4 and 5** we use data from the CRAMP database to provide age- and sex-specific numbers and a first NMD atlas of the Netherlands. In **chapters 6 and 7** the capture-recapture approach and its applications are explained and applied to the CRAMP database. Subsequently, in **chapters 8 and 9**, the Dutch FSHD registry, initiated in 2015 as a result of international collaboration to achieve trial readiness, is used to provide evidence in the collection of longitudinal patient-reported outcome measures. **Chapter 10** comprises a summary and discussion of all the above empirical research.



	Situation a	Situation b	Effect
1. Appropriate matching	$N_a = (9 * 11) / 3 \approx 33$	$N_b = (9 * 11) / 2 \approx 50$	Overestimate
2. Closed population	$N_a = (9 * 11) / 3 \approx 33$	$N_b = (7 * 11) / 3 \approx 26$	Underestimate
3. Equal probability of capture	$N_a = (9 * 11) / 3 \approx 33$	$N_b = (4 * 11) / 1 \approx 44$	Overestimate
4. Independence of captures	$N_a = (9 * 11) / 3 \approx 33$	$N_b = (9 * 11) / 2 \approx 18$	Underestimate

Figure 4. Schematic explanation of the four assumptions in a capture-recapture model.

The (general) effects in case one of the four assumptions is not met are outlined here. Situation a) depicts the situation where the assumption is not violated; Situation b) shows what happens if 1) matching is inappropriate, 2) the population is not closed, 3) the probability of being caught is inequal, or 4) the captures are not independent. The direction of the effect of these deviations are mentioned in the last column as over- or underestimation of the total population size.

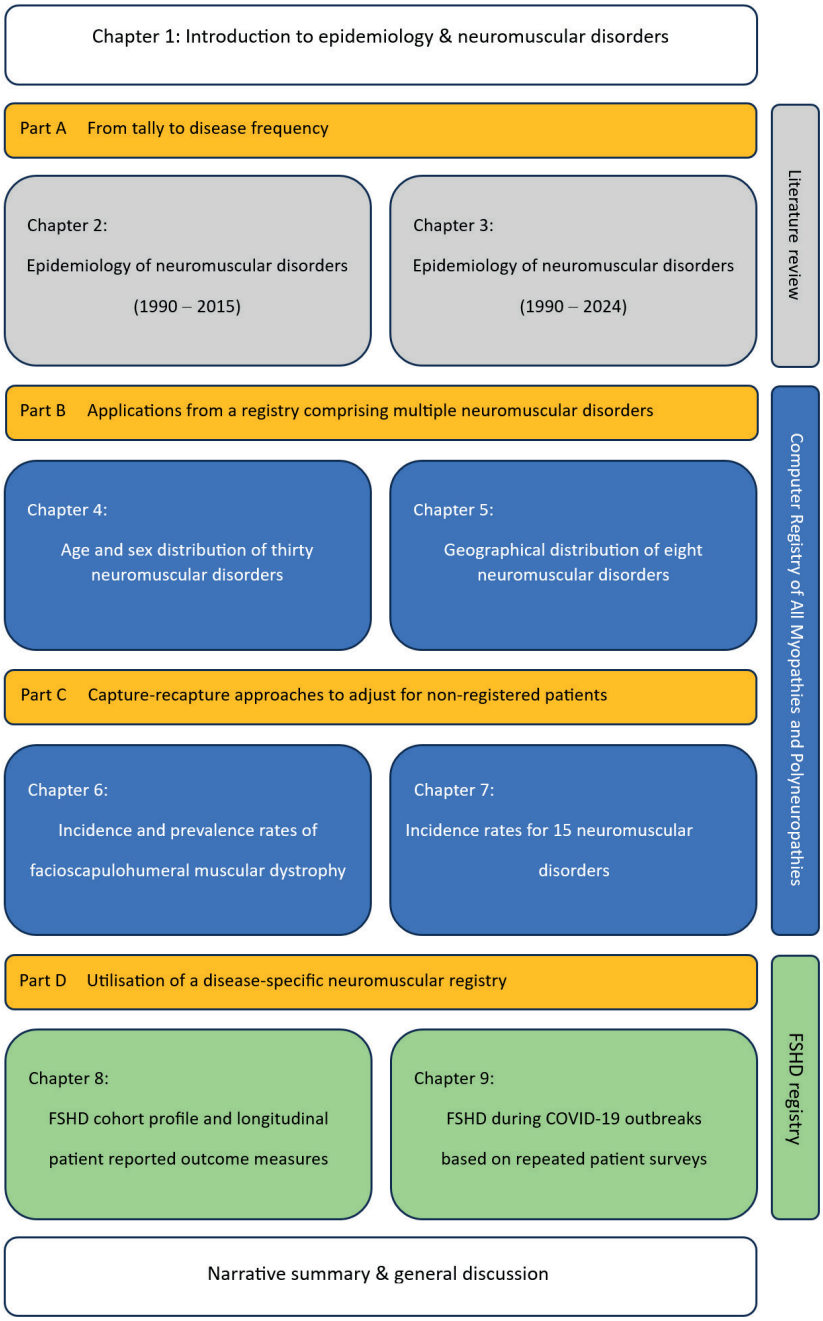


Figure 5. Graphical representation of the chapters in this thesis.

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Part I

From tally to disease frequency in literature

Chapter 2

The epidemiology of neuromuscular disorders: a comprehensive overview of the literature

Johanna CW Deenen, Corinne GC Horlings, Jan JGM Verschuuren, André LM Verbeek, Baziel GM van Engelen

Published in: Journal of Neuromuscular Diseases 2015; 2: 73-85

ABSTRACT

Background In 1991, the first world survey of neuromuscular disorders (NMDs) was published in the peer reviewed literature. Since then, diagnostics have been greatly improved through genetic confirmation and consensus on criteria. This prompted us to search the scientific literature since 1990 for the epidemiology of NMDs.

Objectives To study occurrence rates, sex distribution and age distribution.

Methods Pubmed was searched for 'epidemiology', 'incidence' and 'prevalence' regarding thirty NMDs for peer reviewed literature from 1990–2014.

Results We found incidence rates for ten disorders, ranging from 0.05 to 9 per 100,000/yr. Most NMDs showed prevalence rates between 1 and 10 per 100,000 population, except for multifocal motor neuropathy, Lambert-Eaton myasthenic syndrome, Emery-Dreifuss dystrophy, oculopharyngeal muscular dystrophy, and congenital muscular dystrophies, which were 10/100,000. Information regarding incidence, prevalence, age distribution and sex distribution was complete for eight disorders. No data were found for chronic inflammatory demyelinating polyneuropathy, neuralgic amyotrophy, progressive spinal muscular atrophy, McArdle and Pompe disease. For the 17 remaining disorders, information was partially available.

Conclusions Compared to 1991, prevalence rates of Becker muscular dystrophy, facioscapulohumeral dystrophy, myotonic dystrophy and Charcot-Marie-Tooth disease showed increase, yet with highly overlapping ranges with the exception of myotonic dystrophy. The sum of the available prevalence rates comprises only the tip of the iceberg, but is already in range with the prevalence of Parkinson's disease. Although individual NMDs are rare, as a group they are not.

Keywords
Neuromuscular diseases, epidemiology, incidence, prevalence

INTRODUCTION

Knowledge on disease mechanisms of neuromuscular disorders is growing fast, facilitating identification of potential therapeutic targets [1, 2]. As clinical studies on interventions can be expected in the near future, reliable information regarding disease epidemiology is needed for trial readiness and will help to identify gaps in the knowledge on the epidemiology of neuromuscular disorders.

In 1991, the first world survey of mostly inheritable neuromuscular disorders was published in the peer reviewed literature [3, 4]. In addition, Great Britain's patient association Muscular Dystrophy Campaign presented a report in 2010 that included thirteen groups of neuromuscular diseases [5]. Three years later, Orphanet reported on the prevalence of rare diseases, including neuromuscular disorders as those are almost invariably rare [6].

Since the 1991 survey, genetic confirmation of various neuromuscular disorders has become common practice. Also, consensus on diagnostic criteria was reached for a number of diseases [7]. Therefore, we expanded the scope of the first world survey by investigating the epidemiology of thirty disorders, that are either relatively frequent, or have a particular distinguishable phenotype. We searched published peer reviewed literature for available incidence and prevalence rates and for information regarding the distribution of age and sex distribution within the diseases. With this overview, we aim to give useful estimates of prevalence, incidence and age and sex distribution distribution based on the recent world literature.

MATERIALS AND METHODS

Search terms, period and inclusion criteria

We searched Pubmed for thirty neuromuscular disorders frequently seen or clearly distinguishable in the neuromuscular clinic, using the mentioned disease names as search term (Table 1). Symptomatic disorders such as neuropathies secondary to HIV or diabetes mellitus were excluded. We additionally searched for articles using the terms neuromuscular disorder, neuromuscular disease, neurological disorder, or muscle disease in the title. We combined all search terms with the keywords epidemiology, incidence, and prevalence in the title and as MeSH term. We studied the peer reviewed literature published between January 1990 up until July 2014. Inclusion criteria were: published in English, research concerning

humans, looking into one of the 30 scrutinised neuromuscular disorders, in case of multiple publications of the same or overlapping data: inclusion of the most recently reported data only, concerning the general population and not specific subgroup(s), findings for the overall disorder, no specific disease type(s), containing information regarding incidence or prevalence rates, original data therefore excluding reviews, and finally, methods of ascertainment and calculation of disease frequency needed to be mentioned in the article.

Frequency measures

Selected articles were scrutinised for incidence and prevalence rates. To facilitate comparison, estimates that used the number of live births as the denominator (birth prevalences) were excluded. In addition, all prevalence rates were standardised into units of 100,000 persons and all incidence rates into units of 100,000 persons per year. Next, the articles containing data regarding incidence or prevalence were searched for information about sex distribution and age distribution. We classified the age at diagnosis of each disorder as early, uniform or late, depending on the highest frequency of the occurrence rates and their range. For sex distribution, we reported the percentage of males within the total group of patients per disease.

Table 1. The considered thirty neuromuscular disorders, arranged by anatomical origin.

Disorder	Common abbreviation	Referenced articles
Anterior horn cells		
spinal muscular atrophy	SMA	[8-13]
progressive spinal muscular atrophy	PSMA	-
amyotrophic lateral sclerosis	ALS	[14-63]
post-polio syndrome	PPS	[9, 64]
Peripheral nerve		
Charcot-Marie-Tooth disease	CMT	[8, 10, 65-72]
chronic inflammatory demyelinating polyneuropathy	CIDP	[73-79]
Friedreich ataxia	FA	[80-84]
hereditary neuropathy with liability to pressure palsies	HNPP	[72, 85]
Guillain-Barré syndrome	GBS	[73, 86-113]
idiopathic neuralgic amyotrophy	INA	-
multifocal motor neuropathy	MMN	[79]
neuropathy with monoclonal gammopathy of unknown significance	MGUS	[75, 79]

Table 1. Continued

Disorder	Common abbreviation	Referenced articles
chronic idiopathic axonal polyneuropathy	CIAP	-
Neuromuscular junction		
myasthenia gravis	MG	[9, 114-144]
Lambert-Eaton myasthenic syndrome	LEMS	[9, 115, 145]
Muscle		
Duchenne muscular dystrophy	DMD	[8-10, 13, 146-149]
Becker muscular dystrophy	BMD	[8, 10, 13, 146, 148, 150-153]
facioscapulohumeral dystrophy	FSHD	[8, 10, 13, 146, 154, 155]
limb-girdle muscular dystrophies	LGMD	[10, 13, 146, 156, 157]
Emery-Dreifuss dystrophy	EDD	[10, 13]
oculopharyngeal muscular dystrophy	OPMD	[13]
myotonic dystrophy	MD	[8-10, 13, 146, 158-161]
congenital muscular dystrophies	CMD	[10, 13, 146, 162, 163]
non-dystrophic myotonia	-	[9, 10]
chronic progressive external ophthalmoplegia	CPEO	[164]
Pompe disease	-	-
McArdle disease	-	-
polymyositis	PM	[9, 165-170]
dermatomyositis	-	[9, 165, 167-171]
inclusion body myositis	IBM	[166, 170, 172-176]

Summarising the findings

We presented the range of the identified rates, the number of estimates and we calculated the mean and median of the findings. Means and medians were rounded to one significant digit, thus reporting on the general order of magnitude rather than seemingly exact numbers. We did not perform significance tests or determine confidence intervals for comparisons, as these would imply a level of precision that does not match the methods applied or our aim to present the general order of magnitude of the rates rather than exact numbers.

RESULTS

We identified 169 articles containing relevant information on one or more of the 30 specified disorders (Table 1). Incidence and prevalence rates and data about sex distribution and age were found for eight of the thirty neuromuscular disorders: amyotrophic lateral sclerosis, chronic inflammatory demyelinating polyneuropathy, Friedreich ataxia, myasthenia gravis, Lambert-Eaton myasthenic syndrome, polymyositis, dermatomyositis and inclusion body myositis (Table 2). We were able to identify incidence rates for 11 disorders. Rates ranged from 0.05/100,000 population per year for Lambert-Eaton myasthenic syndrome to 9/100,000 in spinal muscular atrophy.

We found prevalence data for 24 of the 30 disorders. The rates ranged from 0.1/100,000 population for oculopharyngeal muscular dystrophy to 60/100,000 population for post-polio syndrome. Twenty-three disorders had prevalences lower than 50/100,000 and thus are considered to be rare diseases [177]. when we added up the 24 obtained prevalence rates, we found a total of 160/100,000 population.

Age distribution was available for 17 disorders, the majority presenting a uniform age distribution. Friedreich ataxia, Duchenne muscular dystrophy and congenital muscular dystrophies occurred early in life, whereas amyotrophic lateral sclerosis, post-polio syndrome, Lambert-Eaton myasthenic syndrome and inclusion body myositis are revealed later in life. In five disorders, the age distribution was ambiguous.

Table 2A. Occurrence rates for 30 neuromuscular disorders arranged by anatomical origin.

***Anatomical* location**	**Incidence rate**				**Prevalence rate**			
Disorder	**mean (per 100,000 PY)**	**median (per 100,000 PY)**	**range (per 100,000 PY)**	**based on # studies**	**mean (per 100,000)**	**median (per 100,000)**	**range (per 100,000)**	**based on # studies**
Anterior horn cells								
SMA	9	9	5.1 – 13.7	2	2	2	1.3 – 3.2	4
PSMA	-	-	-	-	-	-	-	-
ALS	2	2	0.42 – 5.3	45	5	4	1.07 – 11.31	26
PPS	-	-	-	-	60	60	18 – 92	2
Peripheral nerves								
CMT	-	-	-	-	20	10	3.1 – 82.3	10
CIDP	0.9	0.8	0.35 – 1.6	4	4	3	0.67 – 8.9	6
Friedreich Ataxia	4	4	2.7 – 6.19	2	2	1	0.6 – 3.98	5
GBS	1	1	0.4 – 3.0	30	-	-	-	-
INA	-	-	-	-	-	-	-	-
HNPP	-	-	-	-	9	9	2.0 – 16	2
MMN	-	-	-	-	0.5	0.5	-	1
MGUS with neuropathy	-	-	-	-	3	3	1.04 – 5.1	2
CIAP	-	-	-	-	-	-	-	-
Neuromuscular junction								
MG	1	0.8	0.3 – 2.8	24	10	10	5.35 – 35	24
LEMS	0.05	0.05	-	1	0.3	0.3	0.23 – 0.40	3
Muscle								
DMD	-	-	-	-	3	3	0.70 – 4.7	8

Table 2A. Continued

Anatomical location	Incidence rate				Prevalence rate			
Disorder	**mean (per 100,000 PY)**	**median (per 100,000 PY)**	**range (per 100,000 PY)**	**based on # studies**	**mean (per 100,000)**	**median (per 100,000)**	**range (per 100,000)**	**based on # studies**
BMD	-	-	-	-	2	2	0.07 – 3.65	9
FSHD	-	-	-	-	4	4	2.03 – 6.8	6
LGMD	0.7	0.7	-	1	3	2	0.81 – 6.9	5
Emery Dreifuss dystrophy	-	-	-	-	0.3	0.3	0.13 – 0.4	2
OPMD	-	-	-	-	0.1	0.1	-	1
MD	-	-	-	-	10	10	7.1 – 26.5	9
CMD	-	-	-	-	1	0.8	0.6 – 3.90	5
Non-dystrophic myotonia	-	-	-	-	1	1	1.1 – 1.1	2
CPEO	-	-	-	-	3	3	-	1
Pompe disease	-	-	-	-	-	-	-	-
McArdle disease	-	-	-	-	-	-	-	-
Polymyositis	2	0.6	0.27 – 3.80	8	7	7	3.45 – 9.7	6
Dermatomyositis	0.9	0.8	0.08 – 1.78	8	8	5	1.97 – 21.42	6
IBM	0.4	0.3	0.09 – 0.79	3	2	1	0.07 – 7.06	6

Table 2B. Age distribution and sex distribution for 30 neuromuscular disorders arranged by anatomical origin.

Anatomical location	**Age distribution**		**Sex distribution, male**		
Disorder	**early, uniform, late (number of studies)**	**number of studies**	**mean %**	**range**	**number of studies**
Anterior horn cells					
SMA	-	-	53	40 – 67	2
PSMA	-	-	-	-	-
ALS	late	47	57	45 – 69	48
PPS	late	2	-	-	-
Peripheral nerves					
CMT	uniform	4	51	44 – 62	5
CIDP	uniform (3) late (1)	4	68	57 – 80	7
Friedreich Ataxia	early	3	55	46 – 68	3
GBS	uniform (19) late (6)	25	57	38 – 68	25
INA	-	-	-	-	-
HNPP	-	-	52	-	1
MMN	-	-	-	-	-
MGUS with neuropathy	-	-	-	-	-
CIAP	-	-	-	-	-
Neuromuscular junction					
MG	uniform (20) late (1) ♂late/♀uniform (5)	26	38	20 – 48	30
LEMS	late	3	59	58 – 60	2

Table 2B. Continued

Anatomical location	**Age distribution**		**Sex distribution, male**		
Disorder	**early, uniform, late (number of studies)**	**number of studies**	**mean %**	**range**	**number of studies**
Muscle					
DMD	early	3	97	91-100	6
BMD	early (2) uniform (1)	3	100	100-100	7
FSHD	uniform	1	63	-	1
LGMD	-	-	39	-	1
Emery Dreifuss dystrophy	-	-	-	-	-
OPMD	-	-	-	-	-
MD	uniform	3	54	43 – 61	3
CMD	early	1	45	-	1
Non-dystrophic myotonia	uniform	1	33	-	1
CPEO	-	-	-	-	-
Pompe disease	-	-	-	-	-
McArdle disease	-	-	-	-	-
Polymyositis	uniform	4	36	17 – 50	5
Dermatomyositis	uniform	3	35	27 – 42	5
IBM	late	4	51	33 – 66	4

Sex distribution data for 19 disorders could be retrieved. For the most part, disorders were equally distributed among men and women. Seven disorders showed male predominance, including amyotrophic lateral sclerosis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome, Duchenne and Becker muscular dystrophies and facioscapulohumeral dystrophy. Myasthenia gravis, non-dystrophic myotonia, polymyositis and dermatomyositis occurred up to twice as often in women.

We found no information on five disorders: progressive spinal muscular atrophy, idiopathic neuralgic amyotrophy, chronic idiopathic axonal polyneuropathy, Pompe disease and McArdle disease. We compared the collected data with two peer reviewed articles dating from 1991 and two reports (Table 3, Figure 1) [3-6].

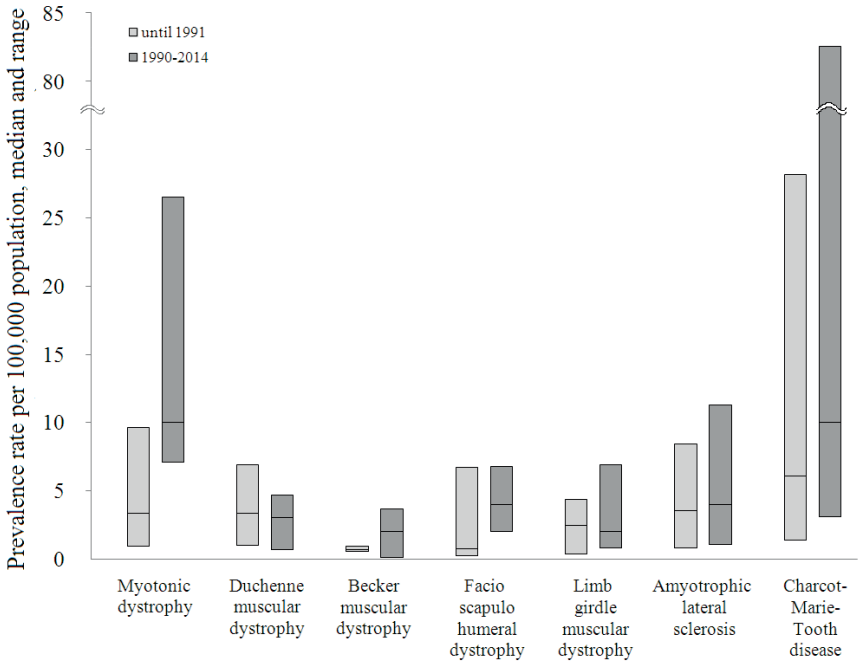

Figure 1. Median prevalence rates for seven neuromuscular disorders until 1991 and 1990 – 2014 [3, 4]. Note the interrupted prevalence scale.

DISCUSSION

This study presents epidemiologic data from the recent literature for thirty individual neuromuscular disorders, to serve as a reference for both clinicians, researchers and policymakers. The added value lies in the grouped epidemiology that is made available, enabling comparisons in the order of magnitude as well as the identification of lacunas in the body of knowledge.

When we compared our findings to the earlier peer reviewed survey, data on nine of thirty disorders were available in this survey and only seven were comparable (Table 3, Figure 1). Amyotrophic lateral sclerosis, Duchenne muscular dystrophy and limb-girdle muscular dystrophy showed stable prevalence estimates over time. Becker muscular dystrophy, facioscapulohumeral dystrophy, myotonic dystrophy and Charcot-Marie-Tooth disease prevalences seemed to have increased considerably. However, in most disorders also the overlap of the ranges of both observations overlapped considerable, except for myotonic dystrophy [3, 4].

The prevalence estimate of myotonic dystrophy, in contrast, appeared to be at least twice as high compared to the 1991 estimate and it displayed less overlapping ranges. The current estimate was based on nine separate observations with prevalence rates ranging from 7.1 to 26.5/100,000 and therefore can hardly be contributed to chance alone. Genetic testing may be one of the contributing factors, as the genetic origin of myotonic dystrophy was identified in 1993, in addition to reaching consensus on diagnostic criteria. The increased prevalence rate in myotonic dystrophy could also be due to improved levels of ascertainment in the included studies compared to the studies reported in the 1991 survey.

Table 3. Surveys regarding the prevalence of neuromuscular disorders per 100,000 population.

Anatomical origin Disorder	*Our median findings regarding thirty NMDs*	*Emeryinherited NMDs1991[3, 4]*	*Muscular Dystrophy Campaign NMDs 2010 [5]*	*Orphanet rare diseases 2013 [6]*
Methods	Pubmed search for available peer reviewed literature 1990-2014	No search methods described, likely all available estimates in 1991 including unpublished info; reported finding followed by calculated median in parentheses	Mix of a number of articles (British as well as European), unpublished data, expert opinions and fact sheets MDC	Systematic survey of literature incl websites, registries, Medline, medical books, grey literature and expert opinions; outcome = mean of lowest and highest finding
Peer reviewed?	yes	yes	no	no
Anterior horn cells				
SMA[1]	2	1.2 (1.2)	2.0	3.45[2]
PSMA	-			
ALS	4*	4.16 (3,5*)		5.2
PPS	60			
Peripheral nerve				
CMT	10*	10 (6.1*)	38.0	23.6[3]
CIDP	3			3.7
Friedreich ataxia	1			2
HNPP	9		10.6	
GBS	-			6.75[4]
CIAP	-			
INA	-			3.3
MMN	0.5			1.5
MGUS with neurop.[5]	3			
Neuromuscular junction				
MG	10	-[6]	-[7]	20
LEMS	0.3			1
Muscle				
DMD	3*	3.2 (3,4*)	14.9	5
BMD	2*	0.7 (0.7*)		
FSHD	4*	2 (0.8*)		4
LGMD	2*	4 (2,5*)		3.43[8]
CMD	0.8			5.46[9]

Table 3. Continued

Anatomical origin Disorder	*Our median findings regarding thirty NMDs*	*Emeryinherited NMDs1991[3, 4]*	*Muscular Dystrophy Campaign NMDs 2010 [5]*	*Orphanet rare diseases 2013 [6]*
Emery-Dreifuss dystr.	0.3			0.3
OPMD	0.1			1
MD	10*	5 (3.5*)	15.7	5.5[10]
Non-dystr myotonia	1[11]	1 (0.44)		5[12]
CPEO	3		5.8[13]	2[14]
Pompe disease	-		1.2[15]	
McArdle disease	-			
Polymyositis	7		9.1	6.5
Dermatomyositis	5			17
IBM	1			0.49

* depicted in Figure 1

1. each report includes different combination of disease types, thus outcomes are incomparable
2. includes childhood- and adult-onset autosomal dominant proximal spinal muscular atrophy, proximal spinal muscular atrophy type 1, 2, 3, 4 and Kennedy disease
3. includes Charcot-Marie-Tooth disease and X-linked Charcot-Marie-Tooth disease
4. includes acute inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome, acute motor axonal neuropathy, acute motor-sensory axonal neuropathy
5. neuropathy associated with paraproteinaemia/monoclonal gammopathy of unknown significance (MGUS)
6. estimate combined with 'familial motor neurone disease'
7. estimate combined with myasthenic syndrome
8. includes limb girdle muscular dystrophy, autosomal dominant limb girdle muscular dystrophy type 1B, autosomal recessive limb girdle muscular dystrophy type 2A, 2B, 2C, 2F, 2I
9. includes congenital muscular dystrophy, congenital muscular dystrophy type 1A, congenital muscular dystrophy with integrin deficiency and congenital muscular dystrophy, Ullrich type
10. includes Steinert myotonic dystrophy and proximal myotonic myopathy
11. not included in Figure 1 our survey rendered only one observation
12. includes Thomsen and Becker disease, hyperkalemic and hypokalemic periodic paralysis
13. referred to as mitochondrial myopathies
14. includes Kearns-Sayre syndrome
15. referred to as metabolic myopathies

We added up the 24 available prevalence estimates, to enable comparison with other diseases. As such, the prevalence of neuromuscular disorders as a group is at least similar to that of Parkinson's disease worldwide (100 - 300/100.000) and twice that of multiple sclerosis in Europe (80/100.000) [178, 179].

As our methods, although systematic, were not designed to capture all studies, the general order of magnitude rather than seemingly exact numbers were presented. For future research it would be interesting to present these data, as well as data on disease subgroups. In our experience however, specific information for subgroups was limited, and data on several subgroups were often combined in changing combinations.

In conclusion, prevalence rates of Becker muscular dystrophy, facioscapulohumeral dystrophy, Charcot-Marie-Tooth disease and in particular myotonic dystrophy showed increase, with highly overlapping ranges except for myotonic dystrophy. The summed estimate for neuromuscular disorders as a group represents only the tip of the iceberg. Although neuromuscular disorders are rare as individual disease entities, as a group they are not.

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Chapter 3

Prevalence and incidence rates of 17 neuromuscular disorders: an updated review of the literature

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ABSTRACT

Background Epidemiological frequency measures serve as reference point for patients, clinicians, researchers, and policymakers. Previously, we published a comprehensive review of the literature with prevalence and incidence rates for thirty neuromuscular disorders frequently encountered in the neuromuscular clinic. No meta-analyses were available at the time.

Objective We included various new studies and meta-analyses that have been published since 2014, we aim to update our previous review.

Methods Pubmed was searched for 'incidence' and 'prevalence' in combination with seventeen acquired and inherited neuromuscular disorders to identify peer-reviewed literature from 1990 to 2023. If multiple prevalence and incidence rates were found, these were summarized by providing the mean, the number of the estimates on which the mean was based and the range of these estimates. Additionally, we searched for meta-analyses to compare the found mean prevalence rates based on the summary of individual studies with the pooled prevalence rates based on the meta-analyses.

Results The mean prevalence estimates for 17 disorders ranged from 0.3/100,000 population for Lambert-Eaton myasthenic syndrome, glycogenosis type V and nemaline myopathy to 20/100,000 for Charcot-Marie-Tooth disease type I. We found annual incidence rates for eight disorders, ranging from 0.3/100,000 population for progressive (spinal) muscular atrophy and facioscapulohumeral muscular atrophy to 1/100,000 for Charcot-Marie-Tooth disease type 1 and myotonic dystrophy type 1. Plotting the mean prevalence estimates from the current study against the pooled prevalence estimates from eight meta-analyses showed reasonable agreement.

Conclusions Epidemiological frequencies about neuromuscular diseases- and in particular data on incidence are scarce. The mean prevalence estimates based on recently published studies on individual cohorts correspond well with the findings from the sparingly performed meta-analyses.

Keywords

Neuromuscular disease, muscular diseases, epidemiology, incidence, prevalence

INTRODUCTION

The group of neuromuscular disorders (NMDs) comprises many different, individually rare diseases, but includes a large number of patients. As disease mechanisms are elucidated at a fast pace, clinical trials are being initiated for a growing number of disorders. Here, descriptive epidemiology serves as reference point for researchers as well as patients and clinicians. Epidemiological frequencies are not always readily available. This is especially the case for the rarer types of neuromuscular disorders.

In 1991, Emery published the first survey of the world literature with population frequencies of various neuromuscular disorders [1, 2]. We published in 2015 a literature review in order to update the epidemiological disease frequencies for several neuromuscular disorders covering the period from 1990 to June 2014 [3].

No systematic reviews or meta-analyses regarding the estimates of disease frequencies, including incidence and prevalence, were available at that time. The current study was performed to enable comparison with and consider completeness of a nationwide registry of newly diagnosed neuromuscular disorders in the Netherlands. It provided grouped epidemiological information and was also meant to serve as a reference point for patients, clinicians, researchers, and policymakers. We searched Pubmed using a simple search strategy and used a number of in- and exclusion criteria to serve as quality assessment. The choice for this search strategy was motivated by the sheer number of rare diseases we aimed to research: thirty neuromuscular disorders on multiple epidemiological aspects such as prevalence, incidence, age at onset and sex distribution.

Since July 2014, various new studies with disease frequencies of the neuromuscular disorder diagnoses of interest were published (see Figure 1). Additionally, systematic reviews and meta-analyses have emerged in the literature for the more common neuromuscular disorders, providing estimate ranges (in systemic reviews) and pooled disease frequency estimates (in meta-analyses). However, these meta-analyses focused on prevalence estimates, whereas pooled incidence estimates were still scarce [4].

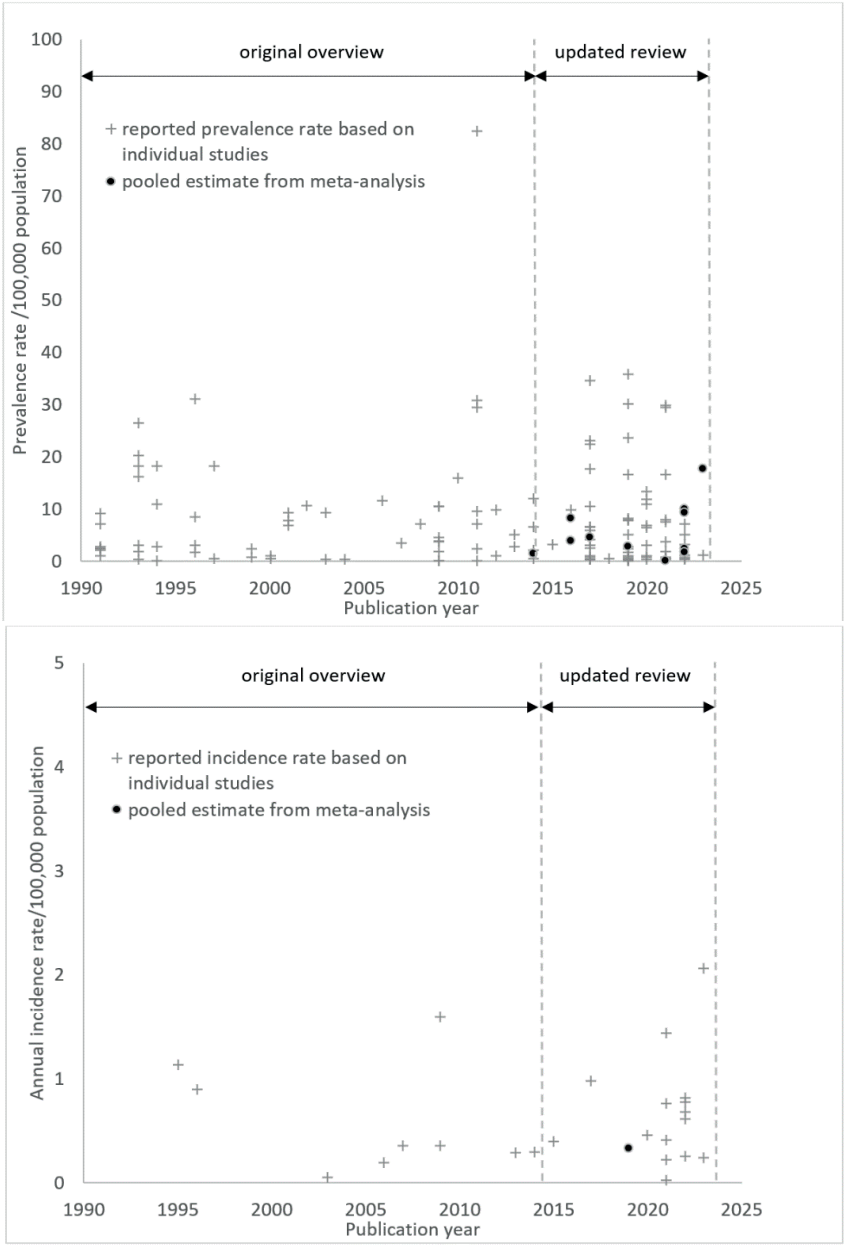

Figure 1. All identified studies presenting one or more disease frequency estimates.

An incidence or prevalence rate for the researched 17 neuromuscular disorders is depicted as a plus. All identified pooled incidence or prevalence rate estimates are shown as dots. Note the lack of meta-analyses up until 2015, the (rare) occurrence of meta-analyses since 2015, the scarcity of research-based incidence estimates and an even greater lack of pooled incidence rates based on meta-analyses.

The interest in accurate information on epidemiological disease frequency has increased considerably, not only for patients and researchers, but also in clinical care and public health. The aim of this study is to update our previous literature overview on the incidence and prevalence of neuromuscular disorders with a summary of the existing knowledge from 1990 until 2024. This will be helpful to identify the gaps in the current knowledge of disease occurrence. Furthermore, it will also enable comparison of the recent findings to the current body of knowledge.

METHODS

Researched neuromuscular disorders

This study, albeit an extension of our previous paper, focused solely on incidence and prevalence rates for a number of specific neuromuscular disorders, and contrary to the previous work it did not report age- and sex distributions [3]. The researched disorders were based on previous yet still unpublished results. We limited the number of studied disorders to those passing a set of five criteria enhancing validity. These five criteria arose from either capture-recapture specifics or characteristics of the used databases, and comprised the following items: 1) the disorder is also diagnosed in adulthood, 2) the disorder is chronic, 3) the diagnosis is sufficiently specific, 4) the Spierziekten Nederland patients association is findable by patients with the specific disorder, and 5) the diagnosis is predominantly made or confirmed in university medical centres. Applying these criteria deemed incidence rates to be estimated based on two nationwide datasets sufficiently accurate for the reporting (unpublished results). This resulted in a list of 17 neuromuscular disorders presented in Table 1.

Table 1. The 17 neuromuscular disorders included in this study arranged by anatomical location and in alphabetical order, accompanied by their common abbreviations.

Origin **Disorders (and search term)**	**Common abbreviation**
Anterior horn cells	
progressive (spinal) muscular atrophy	P(S)MA
Peripheral nerve	
Charcot-Marie-Tooth disease/ hereditary motor and sensory neuropathy	CMT / HMSN
Charcot-Marie-Tooth disease type 1 / hereditary motor and sensory neuropathy type 1*	CMT1 / HMSN1
Charcot-Marie-Tooth disease type 2/ hereditary motor and sensory neuropathy type 2*	CMT2 / HMSN2
chronic inflammatory demyelinating poly(radiculo)neuropathy	CIDP
multifocal motor neuropathy	MMN
Neuromuscular junction	
Lambert-Eaton myasthenic syndrome	LEMS
Muscle	
Becker muscular dystrophy	BMD
facioscapulohumeral muscular dystrophy	FSHD
glycogen storage disease type 2 / Pompe disease	GSD-II
glycogen storage disease type 5 / McArdle disease	GSD-V
inclusion body myositis	IBM
myotonic dystrophy	MD
myotonic dystrophy type 1 / Steinert disease*	MD1
myotonic dystrophy type 2 / Proximal myotonic myopathy*	MD2/ PROMM
nemaline myopathy*	-
oculopharyngeal muscular dystrophy	OPMD

* not researched in previous review [3]

Search strategy

Pubmed was searched for articles from July 2014 to October 2023 for the neuromuscular disorders mentioned. For the newly added (subtypes of) disorders nemaline myopathy, myotonic dystrophy types 1 and 2, and Charcot-Marie-Tooth disease/hereditary motor and sensory polyneuropathy types 1 and 2, we searched the period from January 1990 to October 2023 (spanning the time frame of our first review and the current extension).

The literature search was similar to our Pubmed search in 2014, here we included the disorders mentioned in Table 1 instead of 30 disorders previously researched. We left out the MeSH-terms as we expected these would increase the number of found papers enormously without delivering additional relevant information. We combined all search terms with the keywords 'incidence' and 'prevalence' in title and abstract. Full search details are provided in the Supplementary materials Table S1. To enable comparison with systematic reviews and meta-analyses, we searched Pubmed for the words "systematic", "review", "meta" and "analys*" in the titles. These were combined with the search terms for the specific disorders (Supplementary Table 1).

Inclusion criteria

Articles were considered eligible for data extraction if they met the following inclusion criteria: 1) published in English, 2) concerning the general population, not (a) specific ethnic group(s), 3) containing original data on incidence or prevalence, 4) methods of ascertainment and calculation of disease frequency mentioned, and 5) in case of multiple publications of the same or overlapping data: inclusion of the most recently reported data only.

Rating of quality of evidence

Inclusion criterion 4 (mentioned methods of ascertainment and calculation of disease frequency) also served as the only quality rating we performed. If research outcomes are abundantly available, there is room for turning down findings based on quality assessment. We were in a situation where findings were still limited or even non-existent, and did not aim to include a meta-analysis where this information was needed. Furthermore, bias was to be expected in all articles due to the observational character of the studies and known heterogeneity of findings within multiple countries. Therefore, we did not apply a risk of bias assessment tool.

Synthesis

After application of the inclusion criteria, the remaining articles were scrutinised for incidence and prevalence rates, and these were extracted. Prevalence rates were standardised to units of 100,000 population and incidence rates to units of 100,000 population per year. To facilitate comparison, estimates that used the number of live births as denominator (birth prevalence or live-birth incidence) were excluded.

Based on the findings from the identified studies we presented the range of the rates and the number of estimates, and calculated the mean of the available rates. Means were rounded to one significant digit, thus reporting on the general order of magnitude rather than seemingly exact numbers.

The data supporting the findings of this study are available within the article and/or its Supplementary materials.

RESULTS

The searched period from 1990 to 2023 yielded 69 eligible publications, including 26 new publications not included in our previous review (Table 2) [3]. The various incidence and prevalence rates for the 17 disorders are presented in Table 3 and Figure 1. The seven mean incidence estimates previously unavailable in the earlier review paper were on progressive (spinal) muscular atrophy, Charcot-Marie-Tooth disease types 1 and 2, multifocal motor neuropathy, Becker muscular dystrophy, facioscapulohumeral muscular dystrophy and myotonic dystrophy type 1. The incidence rate estimates varied from 0.3/100,000 population per year for progressive (spinal) muscular atrophy and facioscapulohumeral muscular atrophy to 1/100,000 for Charcot-Marie-Tooth disease type 1 and myotonic dystrophy type 1.

We found prevalence rate estimates for all 17 disorders under investigation, ranging from 0.3/100,000 population for Lambert-Eaton myasthenic syndrome, glycogenosis type V and nemaline myopathy to 20/100,000 for Charcot-Marie-Tooth disease type 1. When these prevalence rates were summed, the 17 disorders comprised of a prevalence rate of 48/100,000, which is approximately 1 in 2100 of the population.

In addition, we identified eight publications providing one or more pooled prevalence estimates, see Table 4 and Figure 1, and one with a pooled incidence estimate. The lowest pooled prevalence estimate was calculated for nemaline myopathy: 0.20 per 100,000 population (95% CI, 0.10 – 0.35). The highest estimate was for CMT/HMSN: 17.69 (95% CI, 12.32 – 24.33). The seven mean prevalence estimates from the current study were plotted against the pooled prevalence estimates from the meta-analyses, see Figure 2. A slightly oscillating pattern around the diagonal was noticed.

Table 2. The 17 neuromuscular disorders included in this study arranged by anatomical location and in alphabetical order, accompanied by their common abbreviations and the papers we identified reporting on their incidence and prevalence.

Origin **Disorders (and search term)**	**Referenced publications**
Anterior horn cells	
progressive (spinal) muscular atrophy	[5]
Peripheral nerve	
Charcot-Marie-Tooth disease/ hereditary motor and sensory neuropathy	[6-20]
Charcot-Marie-Tooth disease type 1 / hereditary motor and sensory neuropathy type 1*	[6, 7, 11-15, 17, 18, 20]
Charcot-Marie-Tooth disease type 2/ hereditary motor and sensory neuropathy type 2*	[6, 7, 11-13, 15, 18, 20]
chronic inflammatory demyelinating poly(radiculo)neuropathy	[14, 21-31]
multifocal motor neuropathy	[14, 27, 30, 32]
Neuromuscular junction	
Lambert-Eaton myasthenic syndrome	[14, 19, 33-35]
Muscle	
Becker muscular dystrophy	[8, 14, 20, 36-46]
facioscapulohumeral muscular dystrophy	[8, 20, 37, 38, 43-51]
glycogen storate disease type 2 / Pompe disease	[44, 45]
glycogen storage disease type 5 / McArdle disease	[14, 44-46]
inclusion body myositis	[52-61]
myotonic dystrophy	[8, 33, 37, 38, 43, 45, 46, 62-65]
myotonic dystrophy type 1 / Steinert disease*	[14, 20, 43-46, 50, 66-68]
myotonic dystrophy type 2 / Proximal myotonic myopathy*	[20, 43, 45, 46]
nemaline myopathy*	[14, 20, 45]
oculopharyngeal muscular dystrophy	[14, 20, 43-45]

Table 3. Mean incidence and prevalence rates per 100,000 population of 17 researched neuromuscular disorders and the number of studies they are based on, arranged by anatomical location and in alphabetical order. We found prevalence rate estimates for all researched disorders, whereas incidence rate estimates were only encountered for eight of them.

Disorder	Incidence rate			Prevalence rate		
	mean /100,000	range /100,000	based on # studies	mean /100,000	range /100,000	based on # studies
Anterior horn cells						
progressive (spinal) muscular atrophy	0.3	0.222 –0.415	1*	0.5	0.480 – 0.602	1*
Peripheral nerve						
Charcot-Marie-Tooth disease / hereditary motor and sensory neuropathy	1	0.98 – 1.44	2	20	9.7 – 82.3	15
Charcot-Marie-Tooth disease type 1/ hereditary motor and sensory neuropathy type 1	-	-	-	10	4.19 – 30.9	10
Charcot-Marie-Tooth disease type 2/ hereditary motor and sensory neuropathy type 2	-	-	-	9	2,1 – 29,5	9
chronic inflammatory demyelinating polyneuropathy	0.7	0.24 – 1.6	8	4	0.67 – 8.1	11
multifocal motor neuropathy	0.6	-	1	0.8	0.53 – 1.33	4
Neuromuscular junction						
Lambert-Eaton myasthenic syndrome	0.04	0.03 –0.048	2	0.3	0.25 – 0.40	5
Muscle						
Becker muscular dystrophy	-	-	-	1	0. 065 – 3.645	14
facioscapulohumeral muscular dystrophy	0.3	-	1	5	0.79 – 12	14
glycogen storage disease type 2 (Pompe disease)	-	-	-	0.3	0.24 – 0.31	2
glycogenosis type 5	-	-	-	0.7	0.35 – 0.94	5
inclusion body myositis	0.4	0.09-0.76	5	3	0.0679 – 7.06	8

Table 3. Continued

Disorder	Incidence rate			Prevalence rate		
	mean /100,000	range /100,000	based on # studies	mean /100,000	range /100,000	based on # studies
myotonic dystrophy	-		-	10	7.1 – 26.5	11
myotonic dystrophy type 1	1	0.2 – 2.061	3	10	0.47 – 35.9	10
myotonic dystrophy type 2/ proximal myotonic dystrophy	-	-	-	2	0.17 – 6.8	4
nemaline myopathy	-	-	-	0.3	0.14 – 0.4	3
oculopharyngeal muscular dystrophy	-	-	-	0.6	0.05 – 1.9	5

- no findings; * two findings in one publication.

DISCUSSION

This review aimed to provide an update of valid grouped epidemiological information to both serve as a basis for comparison and as a reference point for patients, clinicians, researchers, and healthcare policymakers using studies of the last ten years. From the combined number of 68 articles published in 1990–2023, we calculated mean incidence rates for eight disorders ranging from 0.3 to 1.0 patients per 100,000 population per year. Eight meta-analyses have appeared in literature since our previous review.

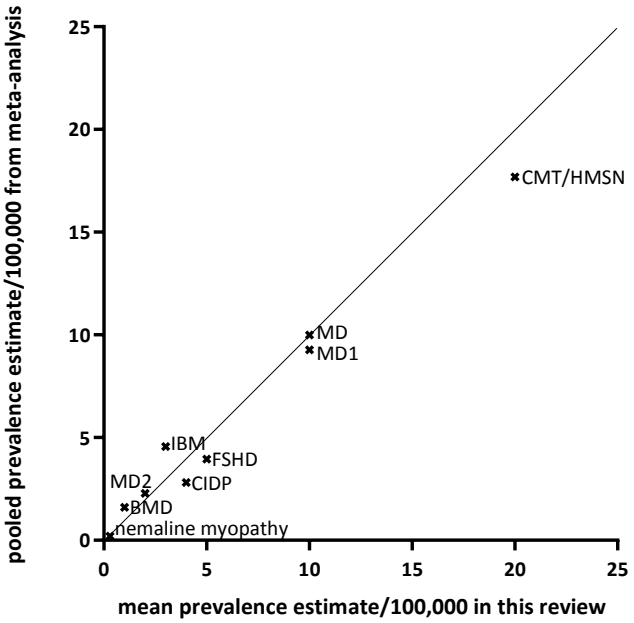

Figure 2. Comparison between meta-analysis-based pooled prevalence estimates per 100,000 population and the mean prevalence rates calculated from the individual studies found in this review for the neuromuscular disorders where a meta-analysis was available.

BMD – Becker muscular dystrophy; CIDP – chronic inflammatory demyelinating polyneuropathy; CMT/HMSN – Charcot-Marie-Tooth disease / hereditary motor and sensory neuropathy; FSHD – facioscapulohumeral muscular dystrophy; IBM – inclusion body myositis; MD – myotonic dystrophy, types 1 and 2.

Newly diagnosed patients are easier to register than all patients who were ever diagnosed. Depending on (disease-)specific needs, people often become lost to follow-up, especially in chronic disorders and in the absence of treatment options. Furthermore, these patients might only have received a diagnosis based on clinical

and / or histopathology features, without revision with currently available diagnostic methods (genetic testing, antibody screening). Moreover, incidence rates are more useful in the diagnostic process of rare diseases, because for prevalence, disease diagnostic process of rare diseases, because for prevalence, disease duration and therefore treatment effects need to be taken into account when using prevalence estimates [76, 77]. This is illustrated by the recent treatment developments in SMA, which will likely show an increase of disease duration in the near future due to the treatment success and an associated elevation of the prevalence [19, 78].

Table 4. Available pooled prevalence estimates per 100,000 population for 17 (groups of) neuromuscular disorders included in this study based on review and meta-analyses. Arranged from highest to lowest mean prevalence estimate, with grouped subtypes. We found meta analyses or reviews for only half of the researched disorders. The available estimates were matched to the findings from this study to see how they relate.

	Current review		Meta-analyses		
Disorder	**Mean estimate**	**Range**	**Pooled estimate**	**95% CI pooled estimate**	**Reference**
MD	10	7.1 – 26.5	9.99*	5.62 – 15.53	[69]
			8.26	4.99 – 13.68	[70]
MD1	10	0.47 – 35.9	9.27	4.73 – 15.21	[69]
MD2	2	0.17 – 6.8	2.29	0.17 – 6.53	[69]
CMT/HMSN	20	9.7 – 82.3	17.69	12.32 – 24.33	[71]
CIDP	4	1.16 – 8.1	2.81	1.58 – 4.39	[4]**
IBM	3	0.0679 – 7.06	4.56	3.59 – 5.52	[72]
BMD	1 (/pop)	0.4 – 1.67 (/pop)	1.6 (/pop)	1.1 – 2.4 (/pop)	[73]
			1.53 (/male)	0.26 – 8.94 (/male)	[74]
FSHD	5	0.79 – 12	3.95	2.89 – 5.40	[70]
nemaline myopathy	0.3	0.14 – 0.4	0.20	0.10 – 0.35	[75]

* The most recent finding was used for comparison; ** One pooled incidence estimate was found for CIDP: 0.33/100,000/yr (95% CI, 0.21 – 0.53)

Although the screening of titles and abstracts and the assessment of full text was performed using a straightforward protocol, the current method has some disadvantages. Firstly, our search method was limited to Pubmed only and did not comprise other scientific sources such as Embase and CINAHL. This choice was driven by the need to research a large number of diseases. Therefore, we only used the database that encompasses the largest set of manuscripts and is most commonly used. Secondly, the screening of titles and abstract and of the full text

was performed by a trained epidemiologist, and the methods were discussed extensively with a team of experienced epidemiologists and neurologists. Thirdly, references in identified manuscripts were not checked, to prevent overlapping identified manuscripts. Finally, we neither took the number of cases nor the size of the population into account in the calculation of the summarizing means, as we were in search of the general order of magnitude of the estimates of interest.

For validity reasons, we compared the mean prevalence estimates from our current research with the sparsely available pooled prevalence outcomes of meta-analyses to assess the usefulness of these mean estimates in the absence of higher-level evidence. Despite the above-mentioned shortcomings, Table 4 and Figure 2 with the quantifications show considerable agreement between the findings of our simplified review exercise compared to the findings of the meta-analyses.

Patients, clinicians, researchers, and policymakers who are involved in neuromuscular disorders are interested in disease frequencies. However, due to the rarity of most neuromuscular disorders, accurate and representative epidemiological data are lacking. This review has shown that the number of publications on incidence and prevalence is rising, and even meta-analyses on disease frequency emerge amid the clinical literature. To monitor this trend and identify new and updated epidemiological information our PubMed searches appeared to be productive and our findings approached the available outcomes from meta-analyses remarkably well. Nonetheless, we prefer registry-based preferably nationwide data to fill the gaps in numerical disease data. Patient registries serve to overcome the research limitations inherent in the study of rare diseases, where patient numbers are typically small. Despite the value of real-world data collected through registries, adequate design and maintenance are integral to data quality [79].

Conclusion

The updated information on the incidence and prevalence of 17 neuromuscular disorders is specifically meant to enable comparisons in the absence of level-1 evidence from meta-analyses. High-quality studies based on nationwide (or wider) neuromuscular registries with clear standardized diagnostic criteria to estimate incidence and prevalence are expected to provide the required valid data.

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SUPPLEMENTARY MATERIALS

Table S1. Search strategy for literature on descriptive epidemiological frequencies of the 17 neuromuscular disorders.

For each neuromuscular disorder listed below, the provided search term was combined with:
1. AND prevalence [tiab]
2. AND incidence [tiab]
3. AND ((systematic[ti] AND review[ti]) OR (meta[ti] AND analys*[ti]))
4. AND ("1990/01/01"[Date - Publication]: "2023/10/01"[Date - Publication]) for newly researched disorders
5. AND ("2014/07/01"[Date - Publication]: "2023/10/01"[Date - Publication]) for previously researched disorders

MD
(myotonic dystrophy [tiab])
MD1
(myotonic dystrophy [tiab] OR Steinert [tiab])
MD2
(myotonic dystrophy [tiab] OR PROMM [tiab])
CMT/HMSN
(hereditary motor sensory neuropathy [tiab] OR charcot marie tooth [tiab])
P(S)MA

(progressive spinal muscular atrophy [tiab]) OR (progressive muscular atrophy [tiab])
Pompe
(glycogenosis type 2 [tiab]) OR (glycogenosis type II [tiab]) OR (glycogen storage disease type 2 [tiab]) OR (glycogen storage disease type II [tiab]) OR (pompe [tiab])
MMN
(multifocal motor neuropathy [tiab])
OPMD
(oculopharyngeal muscular dystrophy [tiab])
BMD
(becker muscular dystrophy [tiab])
Lambert-Eaton myasthenic syndrome
(lambert eaton [tiab] OR eaton lambert [tiab])
chronic inflammatory demyelinating polyneuropathy
(chronic inflammatory demyelinating polyneuropathy) [tiab] OR
(chronic inflammatory demyelinating polyradiculoneuropathy [tiab])
facioscapulohumeral muscular dystrophy
(facioscapulohumeral muscular dystrophy [tiab])
nemaline myopathy
(nemaline myopathy [tiab])
glycogenosis V
((glycogenosis type 5 [tiab]) OR (glycogenosis type V [tiab]) OR
(glycogen storage disease type 5 [tiab]) OR (McArdle [tiab]))
IBM
(Inclusion body myositis [tiab])
General
(neuromuscular [ti] AND disorder* [ti]) OR (neuromuscular [ti] AND disease* [ti]) OR
(neurological [ti] AND disorder* [ti]) OR (muscle [ti] AND disease* [ti])

Part II

Applications from a registry comprising multiple neuromuscular disorders

Chapter 4

The epidemiology of neuromuscular disorders: age at onset and sex distribution in the Netherlands

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ABSTRACT

Based on approximately eight years of data collection with the nationwide Computer Registry of All Myopathies and Polyneuropathies (CRAMP) in the Netherlands, recent epidemiologic information for thirty neuromuscular disorders is presented. This overview includes age and sex distribution data for a number of neuromuscular disorders that are either relatively frequently seen in the neuromuscular clinic, or have a particular phenotype. Since 2004, over 20,000 individuals with a neuromuscular disorder were registered in CRAMP; 56% men and 44% women. The number per diagnosis varied from nine persons with Emery–Dreifuss muscular dystrophy to 2057 persons with amyotrophic lateral sclerosis. Proportions of men ranged from 38% with post-polio syndrome to 68% with progressive spinal muscular atrophy, excluding X-chromosome linked disorders. Inclusion body myositis showed the highest median age at diagnosis of 70 years. These data may be helpful in the diagnostic process in clinical practice and trial readiness.

Keywords

Neuromuscular disorders, neuromuscular diseases, epidemiology, age, sex distribution

INTRODUCTION

Since the early nineties, consensus on the diagnostic criteria of a number of neuromuscular disorders was reached and published previously [1]. In addition, genetic diagnosis has become available for several inherited neuromuscular disorders [2, 3]. Clinical practice benefits from up-to-date information on age and sex distribution distribution regarding neuromuscular disorders, as this information forms the basis for the diagnostic process in every-day clinical practice.

In 2004, the Dutch nationwide database CRAMP (Computer Registry of All Myopathies and Polyneuropathies) for newly diagnosed individuals with a neuromuscular disorder was initiated [4]. CRAMP was the first nationwide registry that did not focus on a specific (group of) disorder(s) in contrast to various registries across the world. It allows registration of a vast number of neuromuscular disorders, including certain neuromuscular features (such as myalgia, cramps, dys- or atrophy of the muscle) in case a classified neuromuscular diagnosis is lacking [5]. One of the incentives was to gather up-to-date nationwide epidemiological data regarding neuromuscular disorders. It was implemented in seven university medical centres with specific knowledge on neuromuscular disorders and one large regional medical centre.

Based on the nationwide CRAMP registry, clinical epidemiologic information is presented regarding the age and sex distribution distribution of 30 neuromuscular disorders that are either relatively frequent, or have a particularly distinguishable phenotype. We assessed the completeness of CRAMP data collected in 2010 by comparing it to data regarding persons with a neuromuscular disorder cared for across all hospitals (specified in regional and university medical centres) in the Netherlands in 2010, made available by the Dutch reimbursement information system. We aim to give useful age and sex distribution estimates to expand the epidemiologic knowledge regarding neuromuscular disorders, to present it in a ready-to-use way for (starting) neuromuscular neurologists and to compare our findings to the world literature.

PATIENTS AND METHODS

The CRAMP registry was used as the basis for this report [4]. CRAMP is a stand-alone system that is locally connected to the participating hospitals' information system. Individual patient data are stored at the local hospital and only coded

data with diagnosis, approximate location and date of entry in the registry is relayed anonymously to the central CRAMP database. Usually, the date of entering the registry corresponds to date of diagnosis. However, there are exceptions, for instance persons diagnosed in childhood.

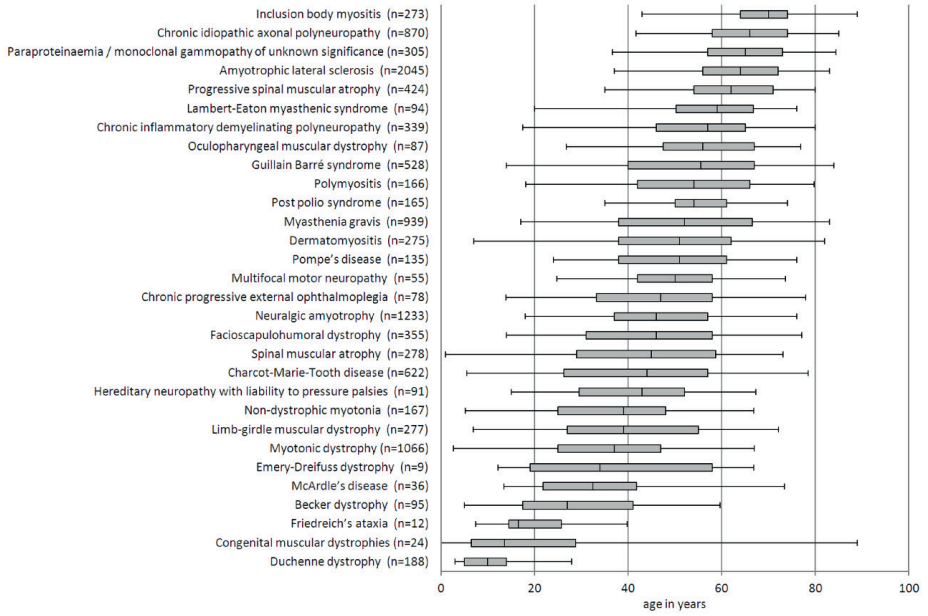

Figure 1. Age at diagnosis of registered persons for thirty neuromuscular disorders; (interquartile) range and median.

We extracted sex distribution and age at diagnosis data from CRAMP for all registered individuals with a diagnosis belonging to 30 selected neuromuscular disorders (Figure 1). These disorders were selected based on relative frequency or distinguishable phenotype. The CRAMP database gathered information provided by eight (university) medical centres with specific expertise on neuromuscular disorders. Diagnoses of all entered patients were made by Dutch neuromuscular neurologists in one of seven university medical centres and one large regional medical centre, where particular knowledge on neuromuscular disorders was available. Diagnoses were made according to current guidelines [1, 6]. After application, we were informed by the regional review board that approval was not needed due to the use of anonymous data (medical ethical committee of the Radboud University Nijmegen Medical Centre, file 2011-397).

Age at diagnosis is presented in box plots, showing the median value, range (2.5–97.5 percentile to eliminate outliers) and interquartile range plus the number of individuals on which the observations were based (Figure 1). To allow comparison with an overview of the world literature, the data on age at diagnosis were classified as developing 'early' in life, 'uniform' across the continuum of age or 'late' in life [7]. For information on sex distribution, the proportion of men and women, including the total count that comprised the denominator of the presented proportions is shown (Figure 2). In addition, the 95% confidence interval was calculated based on the binomial distribution, where the standard error of the proportion is estimated by $SE = \sqrt{(p\,(1-p))/n)}$ (Table 1). The differences between the findings from CRAMP and the findings from an overview of the world literature were provided along with 95% confidence intervals as well, using $SE(p_1 - p_2) = \sqrt{(p(1-p)((1/n_1) + (1/n_2))}$ (Table 1).

To assess the completeness of the CRAMP data, we obtained the number of persons in care due to neuromuscular disorders in all Dutch hospitals in 2010 from the Dutch reimbursement information system (DBC), Dutch abbreviation for Diagnosis & Treatment Combination [8]. Dutch hospitals need to register these DBC codes to enable payment for provided care and therefore data derived from this system are considered to approach completeness. We used data collected in 2010 because it was the first year these (anonymous) data were fully available.

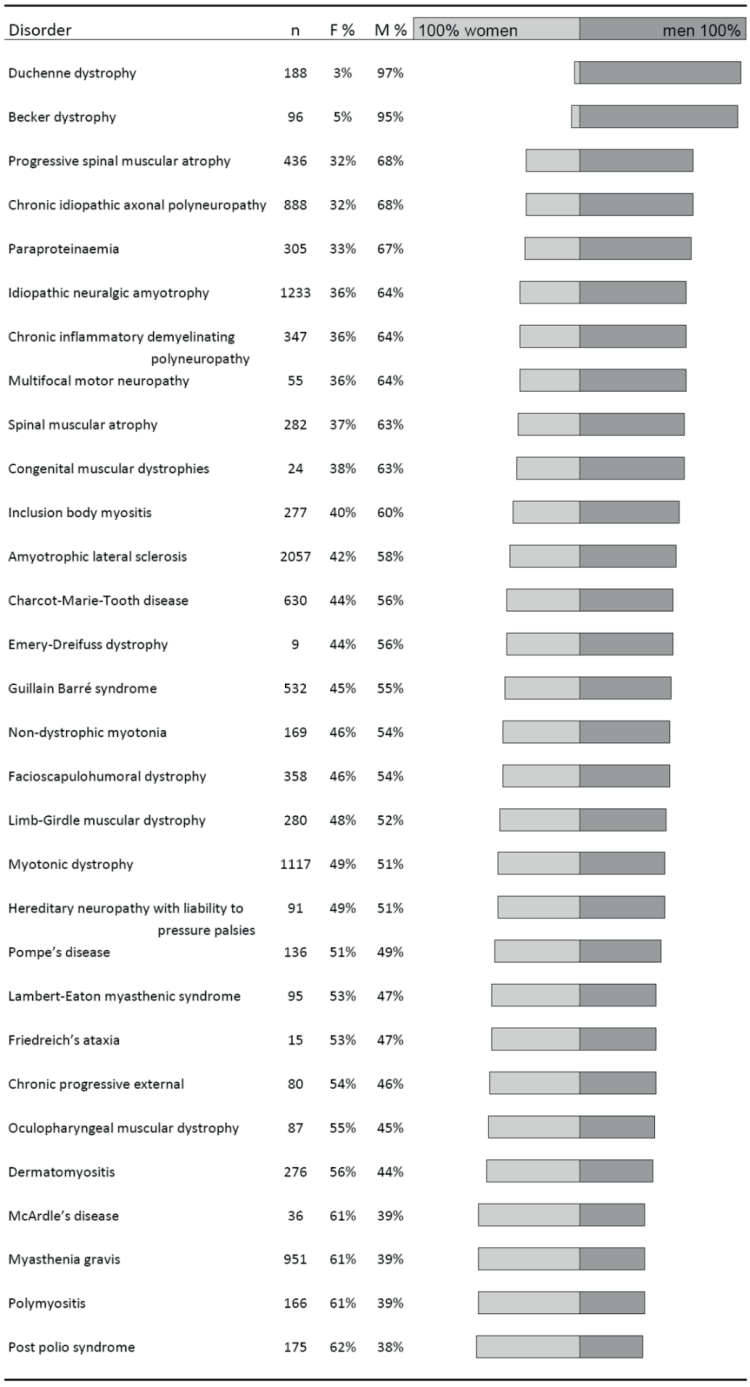

Figure 2. Numbers and proportions of men and women diagnosed with one of thirty neuromuscular disorders.

Table 1. Comparison of sex distribution distribution with findings from the literature.

Anatomical location	Current findings		Findings recent overview of the world literature			Comparison	
Disorder	**male % [95% CI]**	**total number**	**mean %**	**range**	**number of studies**	**Diff. % [95% CI]**	**Equal**
Anterior horn cells							
SMA	63 [60,66]	282	53	40 – 67	2	10 [-16,36]	yes
PSMA	68 [66,70]	436	-	-	-	-	-
ALS	58 [57,58]	2057	57	45 – 69	48	1 [-1,3]	yes
PPS	38 [34,42]	175	-	-	-	-	-
Peripheral nerves							
CMT	56 [54,58]	630	51	44 – 62	5	5 [-1,11]	yes
CIDP	64 [61,67]	347	68	57 – 80	7	4 [-11,3]	yes
Friedreich Ataxia	47 [42,52]	95	55	46 – 68	3	8 [-21,5]	yes
GBS	55 [53,57]	532	57	38 – 68	25	2 [-6,2]	yes
INA	64 [63,65]	1233	-	-	-	-	-
HNPP	51 [46,56]	91	52	-	1	1 [-18,16]	yes
MMN	64 [58,70]	55	-	-	-	-	-
MGUS with neuropathy	67 [64,70]	305	-	-	-	-	-
CIAP	68 [66,70]	888	-	-	-	-	-
Neuromuscular junction							
MG	39 [37,41]	951	38	20 – 48	30	1 [-2,4]	yes
LEMS	47 [42,52]	95	59	58 – 60	2	12 [-28,4]	yes
Muscle							
DMD	97 [96,98]	188	97	91-100	6	0 [-3,3]	yes
BMD	95 [93,97]	96	100	100-100	7	5 [-8,-2]	no

Table 1. Continued

Anatomical location	Current findings		Findings recent overview of the world literature			Comparison	
Disorder	**male % [95% CI]**	**total number**	**mean %**	**range**	**number of studies**	**Diff. % [95% CI]**	**Equal**
FSHD	54 [51,57]	358	63	-	1	9 [-25,7]	yes
LGMD	52 [49,55]	380	39	-	1	13 [2,24]	no
Emery Dreifuss dystrophy	56 [39,73]	9	-	-	-	-	-
OPMD	45 [40,50]	87	-	-	-	-	-
MD	51 [50,52]	1117	54	43 – 61	3	3 [-10,4]	yes
CMD	63 [53,73]	24	45	-	1	18 [-12,48]	yes
Non-dystrophic myotonia	54 [50,58]	169	33	-	1	21 [-36,78]	yes
CPEO	46 [40,52]	80	-	-	-	-	-
Pompe's disease	49 [45,53]	136	-	-	-	-	-
McArdle's disease	39 [31,47]	36	-	-	-	-	-
Polymyositis	39 [35,43]	166	36	17 – 50	5	3 [-6,12]	yes
Dermatomyositis	44 [41,47]	276	35	27 – 42	5	9 [-1,19]	yes
IBM	60 [57,63]	277	51	33 – 66	4	9 [0,18]	yes

Based on the DBC codes (DBC codes 0521, 0522, 0811, 0812, 0901, 0911, 0999, 3504 and 3515), the datasets were ordered by their anatomical origin (respectively disorders of the motor neuron, the peripheral nerve, the neuromuscular junction and the muscle). By only including initial care codes, this approximates the registration of incident individuals. We compared the number of individuals in the CRAMP database, diagnosed during 2010 by university hospitals only (excluding data from the only general hospital that registered in CRAMP), with the number of individuals registered in the reimbursement system of the same university hospitals, and with the number registered in the reimbursement system by all hospitals (Table 2).

Table 2. Number of persons registered in 2010 with a neuromuscular disorder respectively in CRAMP and in the Dutch nationwide reimbursement system.

Anatomical origin of disorder	**Registry source**		
	Data CRAMP (university hospitals only)	**Data reimbursement system**	
		University hospitals	**All hospitals**
Motor neuron	246	275	388
Peripheral nerve	1012	996	3770
Neuromuscular junction	160	146	307
Muscle	719	966	1892
Total	2137	2383	6357

In addition, we combined available information on sex distribution and age. Lists were generated for men and women separately and included 30 disorders frequently seen or clearly distinguishable by neuromuscular neurologists and an extra category 'other' (Table S1). The lists were based on the total CRAMP dataset in available in 2012. The first list provides the total number of persons for each of the 30 neuromuscular disorders and category 'other' and their relative proportions. Next, for each 20-year category of age at diagnosis (0–19, 20–39, 40–59, 60–79 and >79), a separate list of the number of persons with these 30 disorders and category 'other' is provided with their proportion and ordered within the age category. This essentially gives a top-30 of disorders to be expected, based on age and sex distribution, providing an indication on disorders to be considered first in the differential diagnosis.

RESULTS

From 2004, 25,392 individuals with a neuromuscular disorder were registered in CRAMP, 14,159 (56%) men and 11,233 (44%) women. The number of individuals per diagnosis varied from nine persons with Emery–Dreifuss muscular dystrophy to 2057 persons with amyotrophic lateral sclerosis (Figure 2).

Proportions of men ranged from 38% in post-polio syndrome to 68% in progressive spinal muscular atrophy (PSMA), excluding Duchenne and Becker muscular dystrophies with respectively 97% and 95% male involvement (Figure 2). The lowest median age at diagnosis within the 30 scrutinized disorders was seen in Duchenne muscular dystrophy at ten years of age. The patients with the highest median age at diagnosis (70 years) were those with inclusion body myositis (Figure 1).

The dataset from the Dutch reimbursement system in 2010 comprised 6357 individuals with a neuromuscular disorder, of which 37% was registered in university hospitals (Table 2). The number of individuals registered by university hospitals in CRAMP comprised 2137 individuals. Comparing the numbers of registered individuals in CRAMP to those registered in the reimbursement system per anatomical origin, disorders of the motor neuron, the peripheral nerve and the neuromuscular junction corresponded quite well. Although disorders of the muscle were not complete in CRAMP, 75% of all persons with a muscle disease registered in the reimbursement system by university hospitals in 2010 showed up in CRAMP. Overall, 90% of all individuals cared for in the university hospitals and registered in the reimbursement system ended turned up in CRAMP.

DISCUSSION

We present age and sex distribution information for 30 neuromuscular disorders based on approximately eight years of data collection with the nationwide CRAMP registry in the Netherlands. Data collection started after major changes in diagnostic testing and after diagnostic criteria were agreed on. Furthermore, we converted the findings into pocket-sized lists combining sex distribution and age at onset to aid in selecting a first differential diagnosis based on the age and sex distribution of a person in the neuromuscular clinical practice.

Table 3. Comparison of the age distribution with findings from the literature.

Anatomical location	**Current findings**	**Findings recent overview of the world literature**		**Comparable?**
Disorder	**range: early, uniform, late**	**early, uniform, late (number of studies)**	**number of studies**	
Anterior horn cells				
SMA	uniform	-	-	-
PSMA	late	-	-	-
ALS	late	late	47	yes
PPS	late	late	2	yes
Peripheral nerves				
CMT	uniform	uniform	4	yes
CIDP	uniform	uniform (3) late (1)	4	yes
Friedreich Ataxia	early	early	3	yes
GBS	uniform	uniform (19) late (6)	25	yes
INA	uniform	-	-	-
HNPP	uniform	-	-	-
MMN	uniform	-	-	-
MGUS with neuropathy	late	-	-	-
CIAP	late	-	-	-
Neuromuscular junction				
MG	uniform	uniform (20) late (1) ♂late/♀uniform (5)	26	yes
LEMS	uniform	late	3	no
Muscle				
DMD	early	early	3	yes
BMD	uniform	early (2) uniform (1)	3	yes
FSHD	uniform	uniform	1	yes
LGMD	uniform	-	-	-
Emery Dreifuss dystrophy	uniform	-	-	-
OPMD	uniform	-	-	-
MD	uniform	uniform	3	yes
CMD	uniform	early	1	no
Non-dystrophic myotonia	uniform	uniform	1	yes
CPEO	uniform	-	-	-
Pompe's disease	uniform	-	-	-
McArdle's disease	uniform	-	-	-

Table 3. Continued

Anatomical location	**Current findings**	**Findings recent overview of the world literature**		**Comparable?**
Disorder	**range: early, uniform, late**	**early, uniform, late (number of studies)**	**number of studies**	
Polymyositis	uniform	uniform	4	yes
Dermatomyositis	uniform	uniform	3	yes
IBM	late	late	4	yes

The data we presented originated from two sources: CRAMP and the Dutch reimbursement system [4, 8]. CRAMP contained 90% of all reimbursed diagnoses in university medical centres in 2010. For the separate groups of neuromuscular disorders CRAMP was approximately complete, except for muscle disorders where three-quarters of all persons diagnosed in university hospitals were present in CRAMP. This might be due to the fact that a considerable number of persons with neuromuscular disorders are diagnosed during (early) childhood by paediatricians and paediatric neurologists, and up until now they have no or only partially access to the CRAMP registry. Therefore, our information on minors is incomplete and the median age presented for several diseases with an early onset may be overestimated.

This is reflected in the median age found in for example Duchenne patients and other disorders that may arise early in life or even at birth. The presented overall numbers also included all reimbursed diagnoses made in general hospitals. These showed that roughly half of the neuromuscular diagnoses are made in the general hospitals and half in university medical centres, except for disorders of the peripheral nerve where the majority of diagnoses were made in general hospitals. A future registration would benefit tremendously from linkage to the reimbursement system, especially if this system would be fitted with a sufficiently specific recording system for diagnoses.

Overall, the CRAMP database is a good representation of Dutch adult individuals with neuromuscular disorders diagnosed at university hospitals. As we do not have any indication that age and sex distribution are different in the general hospitals, sex distribution and adult age distribution of these 30 disorders are expected to be representative for the Dutch adult population.

Based on a recent overview regarding the epidemiology of neuromuscular disorders, we compared our findings to the literature (Tables 1 and 3) [7]. The

findings regarding age as well as sex distribution (if available) were statistically almost similar, with the exception of LEMS and CMD for age, and BMD and LGMD for sex distribution. However, even if the findings could be considered statistically the same, some of the found results were unexpected. For example, the fact that SMA was diagnosed in males more often than females, 63%.

To conclude, we presented several population-based age and sex distribution estimates previously unavailable and compared these findings to the literature, if available. These data may be helpful in the daily practice both in the diagnostic process of individuals, as well as in other health care issues like the assessment of trial feasibility and planning of care, providing the necessary information for this large – in part invisible – group of persons.

Acknowledgments

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SUPPLEMENTARY MATERIALS

TABLE S1. Sex-specific lists for 30 disorders frequently seen or clearly distinguishable by neuromuscular neurologists and an extra category 'other', including the total number of persons and their relative proportions, overall and ordered within the age category ategory of age at diagnosis (0–19, 20–39, 40–59, 60–79 and >79).

male			male	age 0-19		male	age 20-39		male	age 40-59		male	age 60-79		male	age >79	
	total	%		#	%		#	%		#	%		#	%		#	%
amyotrophic lateral sclerosis (ALS)	1199	8.5%	DMD	169	14.6%	MD	219	10.3%	NA	405	7.8%	ALS	686	13.7%	ALS	56	10.6%
Becker muscular dystrophy (BMD)	90	0.6%	MMN	85	7.3%	NA	202	9.5%	ALS	401	7.7%	CIAP	359	7.2%	CIAP	47	8.9%
Charcot-Marie-Tooth disease (CMT)	353	2.5%	CPEO	51	4.4%	CMT	90	4.2%	MD	190	3.7%	PSMA	167	3.3%	MG	22	4.2%
chronic idiopathic axonal polyneuropathy (CIAP)	588	4.2%	LGMD	31	2.7%	FSHD	60	2.8%	CIAP	172	3.3%	NA	156	3.1%	MGUS	15	2.8%
Chronic inflammatory demyelinating polyneuropathy (CIDP)	218	1.6%	SMA	29	2.5%	MG	58	2.7%	MG	144	2.8%	MG	133	2.7%	GBS	13	2.5%
chronic progressive external ophthalmoplegia (CPEO)	36	0.3%	BMD	27	2.3%	ALS	56	2.6%	CMT	137	2.6%	IBM	129	2.6%	PSMA	11	2.1%
congenital muscular dystrophies (CMD)	15	0.1%	IBM	21	1.8%	GBS	52	2.4%	GBS	105	2.0%	MGUS	118	2.4%	CIDP	8	1.5%
dermatomyositis	122	0.9%	GBS	15	1.3%	LGMD	39	1.8%	PSMA	100	1.9%	GBS	108	2.2%	IBM	8	1.5%
Duchenne dystrophy (DMD)	182	1.3%	non-dystr. myot.	15	1.3%	BMD	38	1.8%	CIDP	88	1.7%	CIDP	88	1.8%	NA	7	1.3%
Emery-Dreifuss dystrophy (EDD)	5	0.04%	FA	13	1.1%	SMA	33	1.6%	FSHD	75	1.4%	CMT	69	1.4%	CMT	6	1.1%
facioscapulohumoral dystrophy (FSHD)	189	1.3%	CIDP	11	0.9%	CIDP	30	1.4%	SMA	70	1.3%	MD	46	0.9%	FSHD	4	0.8%
Friedreich ataxia (FA)	7	0.05%	dermato myositis	9	0.8%	non-dystr. myot.	30	1.4%	MGUS	62	1.2%	SMA	42	0.8%	dermato myositis	2	0.4%
Guillain Barré syndrome (GBS)	293	2.1%	MG	6	0.5%	dermato myositis	22	1.0%	dermato myositis	58	1.1%	FSHD	37	0.7%	SMA	2	0.4%
hereditary neuropathy with liability to pressure palsies (HNPP)	46	0.3%	CIAP	4	0.3%	Pompe	17	0.8%	LGMD	54	1.0%	dermato myositis	31	0.6%	LEMS	1	0.2%
neuralgic amyotrophy (NA)	791	5.6%	CMD	4	0.3%	HNPP	15	0.7%	PPS	43	0.8%	LEMS	25	0.5%	LGMD	1	0.2%
inclusion body myositis (IBM)	166	1.2%	HNPP	4	0.3%	DMD	12	0.6%	non-dystr. myot.	35	0.7%	poly myositis	23	0.5%	MD	1	0.2%
Lambert-Eaton myasthenic syndrome (LEMS)	45	0.3%	FSHD	3	0.3%	PSMA	12	0.6%	IBM	29	0.6%	LGMD	19	0.4%	poly myositis	1	0.2%
limb-girdle muscular dystrophy (LGMD)	144	1.0%	CMT	2	0.2%	poly myositis	11	0.5%	Pompe	28	0.5%	Pompe	19	0.4%	BMD	0	0%
McArdle's disease (McArdle)	14	0.1%	EDD	2	0.2%	CPEO	9	0.4%	poly myositis	27	0.5%	PPS	19	0.4%	CPEO	0	0%
multifocal motor neuropathy (MMN)	35	0.2%	McArdle	2	0.2%	CIAP	8	0.4%	BMD	23	0.4%	OPMD	17	0.3%	CMD	0	0%
myasthenia gravis (MG)	363	2.6%	MGUS	2	0.2%	McArdle	7	0.3%	MMN	23	0.4%	non-dystr. myot.	9	0.2%	DMD	0	0%
myotonic dystrophy type 1&2 (MD)	541	3.9%	poly myositis	2	0.2%	MGUS	6	0.3%	HNPP	21	0.4%	CPEO	7	0.1%	EDD	0	0%
non-dystrophic myotonia (non-dystr. myot.)	89	0.6%	Pompe	2	0.2%	MMN	5	0.2%	OPMD	21	0.4%	HNPP	6	0.1%	FA	0	0%
oculopharyngeal muscular dystrophy (OPMD)	39	0.3%	LEMS	1	0.1%	FA	4	0.2%	CPEO	16	0.3%	MMN	6	0.1%	HNPP	0	0%
monoclonal gammopathy of unknown significance (MGUS)	203	1.4%	MD	1	0.1%	LEMS	4	0.2%	LEMS	14	0.3%	McArdle	4	0.1%	McArdle	0	0%
polymyositis	64	0.5%	ALS	0	0%	CMD	3	0.1%	EDD	1	0.02%	BMD	2	0.0%	MMN	0	0%
Pompe disease (Pompe)	66	0.5%	NA	0	0%	PPS	2	0.1%	McArdle	1	0.02%	CMD	1	0.0%	non-dystr. myot.	0	0%
post polio syndrome (PPS)	64	0.5%	OPMD	0	0%	EDD	1	0.05%	CMD	0	0%	DMD	1	0.02%	OPMD	0	0%
progressive spinal muscular atrophy (PSMA)	290	2%	PPS	0	0%	OPMD	1	0.05%	DMD	0	0%	EDD	1	0.02%	Pompe	0	0%
spinal muscular atrophy (SMA)	176	1%	PSMA	0	0%	IBM	0	0%	FA	0	0%	FA	0	0%	PPS	0	0%
other	7593	54.1%	other	648	55.9%	other	1082	50.8%	other	2852	54.9%	other	2687	53.6%	other	324	61.2%
total	14026		total	1159		total	2128		total	5195		total	5015		total	529	

female			female	age 0-19		female	age 20-39		female	age 40-59		female	age 60-79		female	age >79	
	total	%		#	%		#	%		#	%		#	%		#	%
amyotrophic lateral sclerosis (ALS)	850	7.6%	MD	69	9.1%	MD	225	10.4%	ALS	238	6.0%	ALS	517	14.2%	ALS	74	12.5%
Becker muscular dystrophy (BMD)	5	0.04%	CMT	54	7.1%	MG	167	7.7%	MG	212	5.3%	CIAP	166	4.6%	CIAP	38	6.4%
Charcot-Marie-Tooth disease (CMT)	272	2.4%	MG	30	3.9%	NA	151	7.0%	NA	194	4.9%	MG	138	3.8%	MG	29	4.9%
chronic idiopathic axonal polyneuropathy (CIAP)	283	2.5%	SMA	21	2.8%	CMT	73	3.4%	MD	180	4.5%	GBS	82	2.3%	GBS	18	3.0%
Chronic inflammatory demyelinating polyneuropathy (CIDP)	124	1.1%	dermatomyositis	17	2.2%	LGMD	58	2.7%	CMT	91	2.3%	IBM	82	2.3%	IBM	14	2.4%
chronic progressive external ophthalmoplegia (CPEO)	42	0.4%	FSHD	17	2.2%	GBS	51	2.4%	CIAP	71	1.8%	NA	77	2.1%	dermatomyositis	9	1.5%
congenital muscular dystrophies (CMD)	9	0.1%	NA	14	1.8%	FSHD	48	2.2%	GBS	71	1.8%	PSMA	69	1.9%	MGUs	7	1.2%
dermatomyositis	153	1.4%	non-dystr. myot.	14	1.8%	non-dystr. myot.	32	1.5%	PPS	71	1.8%	MGUS	64	1.8%	CMT	6	1.0%
Duchenne dystrophy (DMD)	6	0.1%	GBS	13	1.7%	dermatomyositis	29	1.3%	FSHD	66	1.7%	MD	51	1.4%	NA	6	1.0%
Emery-Dreifuss dystrophy (EDD)	4	0.04%	LGMD	12	1.6%	SMA	29	1.3%	dermatomyositis	65	1.6%	CMT	48	1.3%	PSMA	5	0.8%
facioscapulohumoral dystrophy (FSHD)	166	1.5%	CIDP	8	1.1%	CIDP	21	1.0%	PSMA	56	1.4%	CIDP	46	1.3%	CIDP	4	0.7%
Friedreich ataxia (FA)	8	0.07%	CMD	5	0.7%	ALS	20	0.9%	CIDP	45	1.1%	poly myositis	34	0.9%	polymyositis	4	0.7%
Guillain Barré syndrome (GBS)	235	2.1%	FA	5	0.7%	HNPP	18	0.8%	LGMD	45	1.1%	dermato myositis	33	0.9%	PPS	3	0.5%
Hereditary neuropathy with liability to pressure palsies (HNPP)	45	0.4%	DMD	4	0.5%	poly myositis	18	0.8%	poly myositis	42	1.1%	FSHD	33	0.9%	FSHD	2	0.3%
neuralgic amyotrophy (NA)	442	4.0%	McArdle	4	0.5%	Pompe	15	0.7%	SMA	33	0.8%	PPS	25	0.7%	Pompe	2	0.3%
inclusion body myositis (IBM)	107	1.0%	poly myositis	4	0.5%	CPEO	13	0.6%	Pompe	30	0.8%	SMA	22	0.6%	CMD	1	0.2%
Lambert-Eaton myasthenic syndrome (LEMS)	49	0.4%	HNPP	3	0.4%	McArdle	13	0.6%	MGUS	27	0.7%	Pompe	21	0.6%	OPMD	1	0.2%
limb-girdle muscular dystrophy (LGMD)	133	1.2%	PSMA	3	0.4%	CIAP	8	0.4%	LEMS	26	0.7%	LEMS	18	0.5%	BMD	0	0%
McArdle's disease (McArdle)	22	0.2%	OPMD	2	0.3%	PPS	5	0.2%	non-dystr. myot.	26	0.7%	LGMD	18	0.5%	CPEO	0	0%
multifocal motor neuropathy (MMN)	20	0.2%	ALS	1	0.1%	LEMS	4	0.2%	OPMD	25	0.6%	OPMD	17	0.5%	DMD	0	0%
myasthenia gravis (MG)	576	5.2%	CPEO	1	0.1%	MMN	4	0.2%	HNPP	19	0.5%	CPEO	10	0.3%	EDD	0	0%
myotonic dystrophy type 1&2 (MD)	525	4.7%	EDD	1	0.1%	MGUS	4	0.2%	CPEO	18	0.5%	MMN	6	0.2%	FA	0	0%
non-dystrophic myotonia (non-dystr. myot.)	78	0.7%	LEMS	1	0.1%	PSMA	4	0.2%	IBM	11	0.3%	non-dystr. myot.	6	0.2%	HNPP	0	0%
oculopharyngeal muscular dystrophy (OPMD)	48	0.4%	Pompe	1	0.1%	BMD	3	0.1%	MMN	10	0.3%	HNPP	5	0.1%	LEMS	0	0%
monoclonal gammopathy of unknown significance (MGUS)	102	0.9%	BMD	0	0%	CMD	3	0.1%	McArdle	4	0.1%	BMD	1	0.03%	LGMD	0	0%
polymyositis (PM)	102	0.9%	CIAP	0	0%	OPMD	3	0.1%	FA	2	0.1%	EDD	1	0.03%	McArdle	0	0%
Pompe disease (Pompe)	69	0.6%	IBM	0	0%	DMD	2	0.1%	BMD	1	0.03%	McArdle	1	0.03%	MMN	0	0%
post polio syndrome (PPS)	104	0.9%	MMN	0	0%	EDD	2	0.1%	CMD	0	0%	CMD	0	0%	MD	0	0%
progressive spinal muscular atrophy (PSMA)	137	1%	MGUS	0	0%	FA	1	0.05%	DMD	0	0%	DMD	0	0%	non-dystr. myot.	0	0%
spinal muscular atrophy (SMA)	105	1%	PPS	0	0%	IBM	0	0%	EDD	0	0%	FA	0	0%	SMA	0	0%
other	6296	56.6%	other	456	60.0%	other	1138	52.6%	other	2292	57.7%	other	2040	56.2%	other	370	62.4%
total	11117		total	760		total	2162		total	3971		total	3631		total	593	

Chapter 5

Geographical distribution of eight neuromuscular disorders in the Netherlands based on a nationwide registry

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ABSTRACT

Neuromuscular disorders are a very heterogeneous group of diseases and comprise a large number of patients. Epidemiological key figures on incidence, prevalence and mortality serve as basic information for individualised and public health care and researchers. Geographical mapping of the specific disorders is expected to provide valuable insights into clustering of the conditions, which points to possible environmental and genetical determinants. So far, mostly geographical maps of motor neuron diseases have been reported. By using record information from the Dutch nationwide Computer Registry of All Myopathies and Polyneuropathies (CRAMP) we aimed to generate geographical maps for eight disorders predominantly diagnosed in adults.

We investigated the geographical distribution of newly diagnosed patients in the Netherlands from 2004-2011. The variables used were diagnosis, date of diagnosis, and the first two digits of the postal code for geographical location from CRAMP. The number of incident cases was divided by the total number of people populating the postal code area.

Nationwide incidence maps were constructed for myotonic dystrophy, progressive (spinal) muscular atrophy, chronic inflammatory demyelinating polyneuropathy, facioscapulohumeral muscular dystrophy, inclusion body myositis, hereditary motor and sensory neuropathy, Pompe disease and oculopharyngeal muscular dystrophy. Considerable regional variation between disorders was observed, particularly for myotonic dystrophy and facioscapulohumeral muscular dystrophy.

We provided the first neuromuscular atlas of the Netherlands with maps for eight disorders commonly seen in the neuromuscular practice. To address possible outliers due to low population numbers, Bayesian smoothing techniques should be considered in future research.

Highlights

- Nationwide maps for eight neuromuscular disorders for the Netherlands are provided.
- Geographical distributions may provide new insights into the etiology of these disorders.
- Considerable regional variation was observed for MD and FSHD.

Keywords
Neuromuscular disorder, muscular disease, epidemiology, incidence, geographical distribution

INTRODUCTION

Neuromuscular disorders are a very heterogeneous group comprising a considerable number of patients [1]. They account for a major burden of neurological diseases, also due to the high costs per diseased person [2-4]. Epidemiological key figures on incidence, prevalence and mortality serve as basic information for individualised and public health care and researchers. Until now, spatial distribution or geographical mapping of a neuromuscular disorder has mostly been limited to motor neuron diseases [5-8]. In the Netherlands, the nationwide Computer Registry for All Myopathies and Polyneuropathies (CRAMP) recorded over 18,000 newly diagnosed patients with neuromuscular disorder in the period 2004–2011[9, 10]. By using record information from CRAMP we aim to generate geographical distribution images for eight disorders predominantly diagnosed in adults.

METHODS

Dataset

CRAMP was the first nationwide registry covering a vast number of neuromuscular disorders and using the same method of data collection, which facilitates comparison between disorders[9]. It was initiated in 2004 to enable epidemiological studies and advance trial readiness [9]. All seven university medical centres in the Netherlands with specific expertise on neuromuscular disorders and one large regional medical centre in the Netherlands participated (Figure 1A).

All diagnoses in CRAMP were based on the observations and examinations by neuromuscular neurologists from the participating centres according to the contemporary guidelines [11-15]. By the end of 2011, CRAMP contained records of over 18,000 patients diagnosed with a neuromuscular disorder. After removing duplicate and incomplete records we analysed the data from the period 2004 – 2011.

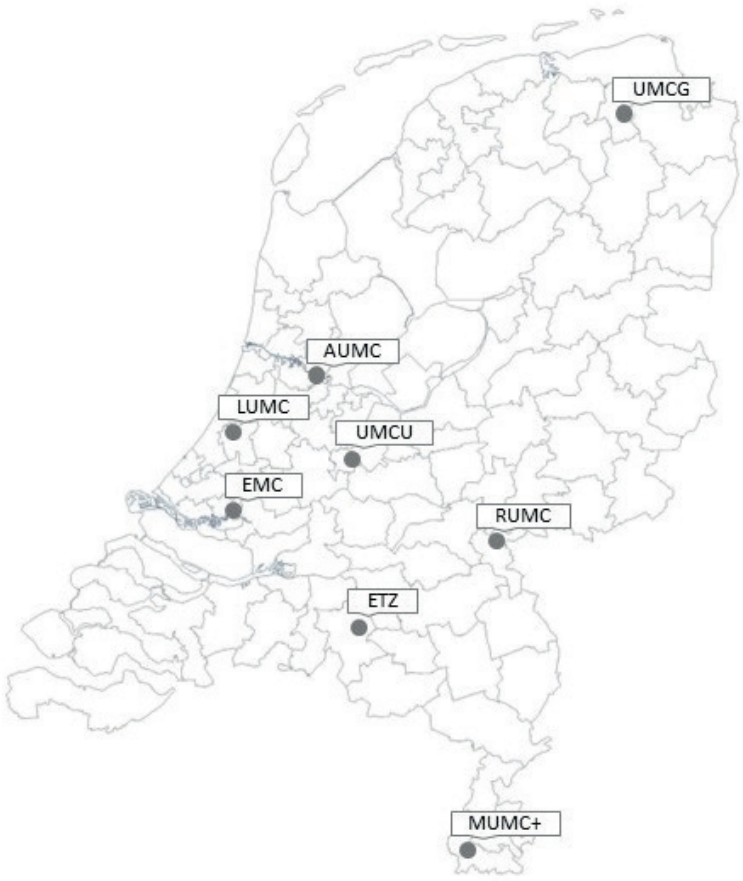

Figure 1A. Map of the Netherlands with the participating centres in CRAMP. AUMC - Amsterdam University Medical Center; EMC - Erasmus University Medical Centre, Rotterdam; ETZ - Elisabeth Tweesteden Ziekenhuis, Tilburg; LUMC - Leiden University Medical Center; MUMC+ - Maastricht University Medical Center; RUMC - Radboud university medical center, Nijmegen; UMCG - University Medical Center Groningen; UMCU - University Medical Center Utrecht.

Selection of disorders

CRAMP used a classification system of 1,400 diagnoses to register newly diagnosed patients [16]. It employed a system that comprised many subtypes and very rare (combinations of) disorders. These were lumped and partially discarded in a previous study into 82 more or less common (groups of) neuromuscular diagnoses encountered in neurological practice (unpublished results). This list of diagnoses served as starting point for the selection of disorders to be depicted here. The ICD-10 classification could not be used because it did not contain enough sufficiently specific diagnoses for neuromuscular disorders.

To enhance the validity of the displayed geographical distributions, three previously formulated criteria were applied in this study: 1) the disorder is (also) diagnosed in adulthood, 2) the diagnosis refers to a specific disorder, and 3) the diagnosis is predominantly made or confirmed in a university medical center. A fourth (additional) criterion was added to limit the number of one-person-per-area instances: 4) at least 50 cases were available in the dataset. Only disorders that passed these four criteria were analysed in this manuscript.

Determining geographical distribution and incidence rates

To employ the mapping of the geographical distributions of the disorders, three items were used: 1) the diagnosis, 2) the date of diagnosis to include diagnoses from the period 2004-2011, and 3) the first two positions of the postal code of residence at the time of diagnosis. Due to the rarity of the presented disorders and to guarantee anonymity we restricted the resolution of the postal code maps to the first two numerical positions of the codes which consist of six positions, the first four comprise numerical data and the latter two alphabetical letters. This created maps with which the Netherlands were divided into a maximum of ninety areas.

To enable comparison of disease frequency between postal code areas, incidence rates were calculated by dividing the incident number of patients by the number of people living in the postal code area (range 35620 - 685940), based on the population numbers available from Statistics Netherlands [17]. To create maps we used SAS version 9.4 and the PROC GMAP procedure. To facilitate visual comparison of the disorders, we applied one scaling range of the incidence rates per area ranging from 0 to 139 per 1,000,000 population in steps of 10/1,000,000 population. For the map with the summed incidence of the eight neuromuscular disorders, the applied scale ranged from 0 to 275/1,000,000 with steps of 25/1,000,000.

Standard protocol approval for registration and patient consent

The CRAMP study was discussed by the Medical Ethics Review Committee of the Radboud University Nijmegen Medical Centre (file No. 2011-397). The committee deemed participant consent was not required in case of use of anonymized data for quality purposes and epidemiological analysis.

RESULTS

We started with a list of 82 neuromuscular disorders. The application of the three selection criteria (diagnosis in childhood or in adulthood; sufficiently specific

diagnosis; diagnosis in a university medical centre) resulted in 48 disorders fit for mapping (Table 1). Adding the fourth criterion (at least 50 cases in the dataset) narrowed the selection down to eight disorders: myotonic dystrophy (types 1 and 2), progressive (spinal) muscular atrophy, chronic inflammatory demyelinating polyneuropathy, facioscapulohumeral muscular dystrophy, inclusion body myositis, hereditary motor and sensory neuropathy (types 1 and 2), glycogenosis type 2 (Pompe disease), and oculopharyngeal muscular dystrophy (Tables 2 and 3). The incidence rates were displayed for the Netherlands based on 90 areas (Figures 1b and 2).

Table 1. Three inclusion criteria and the numbers registered in CRAMP for the period 2004 – 2011 for the included neuromuscular disorders listed in alphabetical order.

Disorder with observations in CRAMP	Diagnosis (also) in adults[1]	Specific disorder[2]	UMC based[3]	Fulfilling three criteria	Number of observations in CRAMP
Amyotrophic lateral sclerosis	+	+	-		
Autoimmune myositis not specified	+	+	-		
Becker muscular dystrophy	+	+	+	+	40
Becker myotonia	+	+	+	+	32
Bethlem disease	+	+	+	+	13
Carnitine deficiency	+	+	+	+	17
Central core disease	+	+	+	+	16
Chronic idiopathic axonal polyneuropathy	+	+	-		
Chronic inflammatory demyelinating polyneuropathy	+	+	+	+	232
Congenital fibre type disproportion	+	+	+	+	4
Congenital muscular dystrophy	-	-	+		
Congenital myasthenia gravis	+	+	+	+	16
Congenital myopathies not specified	+	-	+		
Dermatomyositis	+	+	-		
Distal spinal muscular atrophy	+	+	+	+	39
Duchenne muscular dystrophy	-	+	+		
Emery-Dreifuss muscular dystrophy	+	+	+	+	7
Eulenberg myotonia	+	+	+	+	24

Table 1. Continued

Disorder with observations in CRAMP	Diagnosis (also) in adults[1]	Specific disorder[2]	UMC based[3]	Fulfilling three criteria	Number of observations in CRAMP
Facioscapulohumeral muscular dystrophy	+	+	+	+	230
Focal spinal muscular dystrophy	+	+	+	+	16
Fukuyama congenital muscular dystrophy	+	+	+	+	3
Guillain Barré syndrome	+	+	-		
Glycogen storage disease type 2 (Pompe)	+	+	+	+	98
Glycogen storage disease type 5 (McArdle)	+	+	+	+	14
Glycogen storage disease type VII	+	+	+	+	29
Hereditary motor and sensory neuropathy not specified	+	-	-		
Hereditary motor and sensory neuropathy type 1	+	+	+	+	95
Hereditary motor and sensory neuropathy type 2	+	+	+	+	69
Hereditary motor and sensory neuropathy type 3	+	+	+	+	8
Hereditary motor and sensory neuropathy type 4	+	+	+	+	14
Hereditary motor and sensory neuropathy type 5	+	+	+	+	1
Hereditary motor and sensory neuropathy X-linked	+	+	+	+	7
Hereditary sensory and autonomic neuropathy	+	+	+	+	4
Hereditary neuropathy with liability to pressure palsies	+	+	-		
Hereditary sensory and autonomic neuropathy	+	+	+	+	4
Hereditary periodic paralysis disorders	+	+	+	+	44
Inclusion body myositis	+	+	+	+	171
Kearns-Sayre syndrome	+	+	+	+	34
Kennedy's disease	+	+	+	+	14
Laing distal myopathy	+	+	+	+	1

Table 1. Continued

Disorder with observations in CRAMP	Diagnosis (also) in adults[1]	Specific disorder[2]	UMC based[3]	Fulfilling three criteria	Number of observations in CRAMP
Lambert-Eaton myasthenic syndrome	+	+	+	+	41
Limb girdle muscular dystrophy	+	-	+		
Markesbery-Griggs distal myopathy	+	+	+	+	2
Miller-Fisher syndrome	+	+	+	+	49
Minicore or multicore myopathy	+	+	+	+	12
Mioshi distal myopathy	+	+	+	+	2
Mitochondrial myopathies	+	+	+	+	44
Myotonic dystrophy type 1	+	+	+	+	472
Myotonic dystrophy type 2	+	+	+	+	26
Metabolic myopathies	+	-	+		
Myasthenia gravis	+	+	-		
Monoclonal gammopathy of unknown significance with neuropathy	+	-	+		
Nonaka distal myopathy	+	+	+	+	2
Other mitochondrial myopathies	+	-	+		
Multifocal motor neuropathy	+	+	+	+	37
Other myasthenic syndrome	+	-	+		
Other myopathies	+	-	+		
Myositis not specified	+	-	+		
Myotonia not specified	+	-	+		
Myotubular and centrotubular myopathies	+	+	+	+	4
Neuralgic amyotrophy	+	+	-		
Nemaline myopathy	+	+	+	+	23
Oculopharyngeal muscular dystrophy	+	+	+	+	53
Polymyositis	+	+	-		
Post-polio syndrome	+	+	-		
Progressive spinal muscular atrophy	+	+	+	+	265
Rigid spine syndrome	-	+	+	+	3

Table 1. Continued

Disorder with observations in CRAMP	Diagnosis (also) in adults[1]	Specific disorder[2]	UMC based[3]	Fulfilling three criteria	Number of observations in CRAMP
Scapuloperoneal syndrome	+	-	+		
Spinal muscular atrophy not specified	+	-	+		
Spinal muscular atrophy type 1	-	+	+		
Spinal muscular atrophy type 2	-	+	+		
Spinal muscular atrophy type 3	+	+	+	+	18
Thomsen myotonia	+	+	+	+	12
Welander distal myopathy	+	+	+	+	4

[1] the disorder is (also) diagnosed in adulthood; [2] the diagnosis refers to a specific disorder; [3] diagnosis usually made in university medical centre.

The dataset included diagnoses registered by seven of eight participating centres. The participating Elisabeth TweeSteden Ziekenhuis (ETZ), not a university medical center, has registered patients although none ended up in the applied timeframe, and from University Medical Center Groningen only a very limited number of registered patients were present in this dataset (Table 2). Figure 2 showed considerable variation between the disorders. For myotonic dystrophy, facioscapulohumeral muscular dystrophy and also hereditary motor and sensory neuropathy, the cases were evenly spread across the country, with the latter two showing some areas in the east of seemingly higher incidence. Pompe disease and oculopharyngeal muscular dystrophy, the two disorders with the lowest incidence, displayed some spots of higher (but still very low) incidence rates in the north and middle of the country, and in the province of Zeeland compared to the more north-eastern (slightly) regions.

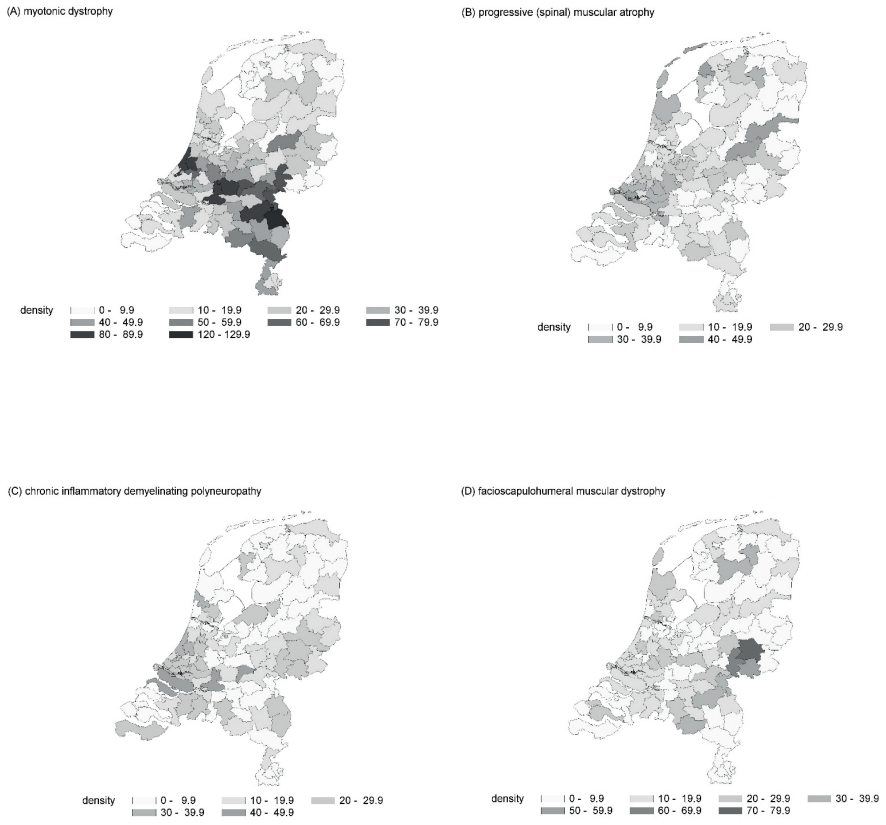

Figure 1B. Geographical incidence rate per 1,000,000 population for the eight neuromuscular disorders combined in the Netherlands in 2004-2011.

Figure 1. Continued

DISCUSSION

Based on the nationwide comprehensive CRAMP registry, this study provided the first neuromuscular atlas of the Netherlands with incidence rates for the eight neuromuscular disorders predominantly diagnosed in adult life. The disorders showed considerable variation in geographical distribution. Myotonic dystrophy and facioscapulohumeral muscular dystrophy had an uneven geographical distribution over the country.

The only two studies available for comparison from literature were actually based on CRAMP, or looked at a different neuromuscular condition: motor neuron disease [5] [9]. In 2007, Van Engelen, et al., showed that data collection was concentrated around the university cities of Leiden, Amsterdam and Nijmegen. These centres started data collection much earlier and in a more comprehensive way than the other centres. The current study showed a much more evenly distributed geographical distribution, although myotonic dystrophy still seemed to display more cases around the west-east axis, which can indicate the presence of selection bias. Despite this, the current study illustrates the progress of data collection made by the registry during the first decades [9].

Table 2. Participating centres, their location and summed numbers of newly diagnosed patients registered in the period 2004 - 2011.

Participating centre	City	Number of newly diagnosed neuromuscular disorders*	Percentage
Radboud university medical center	Nijmegen	587	34%
University Medical Center Utrecht	Utrecht	372	21%
Erasmus University Medical Center	Rotterdam	367	21%
Amsterdam University Medical Center	Amsterdam	164	9%
Leiden University Medical Center	Leiden	140	8%
Maastricht University Medical Center	Maastricht	112	6%
University Medical Center Groningen	Groningen	3	0%
Elisabeth Tweesteden Ziekenhuis	Tilburg	0	0%
	Combined:	*1745*	*100 %*

*) Myotonic dystrophy, progressive (spinal) muscular atrophy, chronic inflammatory demyelinating polyneuropathy, facioscapulohumeral muscular dystrophy, hereditary motor and sensory neuropathy (incl. type 1 - 5, x-type and hereditary sensory and autonomic neuropathy), inclusion body myositis, glycogen storage disease type 2 (Pompe) and oculopharyngeal muscular dystrophy.

The situation for patients with rare neuromuscular disorders in the Netherlands is considered unique. It has an adequately operating and accessible healthcare system. In addition, the expertise centres for neuromuscular disorders are closely collaborating. Furthermore, the distance from any point in the country to one of the highly specialised university medical hospitals is 200 kilometres at a maximum. For geographical comparisons, the country's limited size is beneficial but can be disadvantageous to identify possible latitudinal or longitudinal gradients. Still, the region appears large enough to be informative about disease distributions, although challenging for the rare diseases under scrutiny [18, 19].

The CRAMP registry is incomplete, and some participating centres contributed more than others (Table 3). The medical centres in Groningen and Tilburg provided limited or no data in the period 2004 to 2011. This is likely due to the low degree of registration in combination with the distribution of expertise for these disorders. Nevertheless, we expect that the different patterns in the mapping of the individual disorders (Figure 2) give a good approximation of the real underlying distributions. If the patterns had heavily been influenced by asymmetrical data collection, they would most likely be less diverse.

Table 3. Incidence numbers of newly diagnosed patients registered in CRAMP in 2004-2011 per 1,000,000 population for eight disorders that passed the four eligibility criteria.

Disorder	Type of disorder	Total number of persons in CRAMP	Depictedincidence rate range per 1,000,000 population
Myotonic dystrophy	autosomal dominant	498	0 – 129.9
Progressive (spinal) muscular atrophy	mostly acquired, sometimes autosomal dominant	265	0 – 49.9
Chronic inflammatory demyelinating polyneuropathy	acquired	232	0 – 79,9
Facioscapulohumeral muscular dystrophy	autosomal dominant	230	0 – 49.9
Hereditary motor and sensory neuropathy	autosomal dominant	198	0 – 59.9
Inclusion body myositis	acquired	171	0 – 49.9
Glycogen storage disease type 2 (Pompe)	autosomal recessive	98	0 – 49.9
Oculopharyngeal muscular dystrophy	autosomal dominant	53	0 – 39.9

The usefulness of cluster analysis as a starting point for hypothesis generation is under debate [20, 21]. Cluster analysis is often initiated after the initial observation of high numbers of (new) cases with a specific disease. Subsequently, the area of interest around this group of seemingly unexpectedly high (or low) disease occurrence needs to be strictly defined. In contrast, we chose a geographically extensive area where we looked at incident cases and used administrative units (postal codes) as starting point. This was a predetermined choice and not guided by the results on the defined areas. In this way, the method applied bypasses the raised issues to a considerable extent.

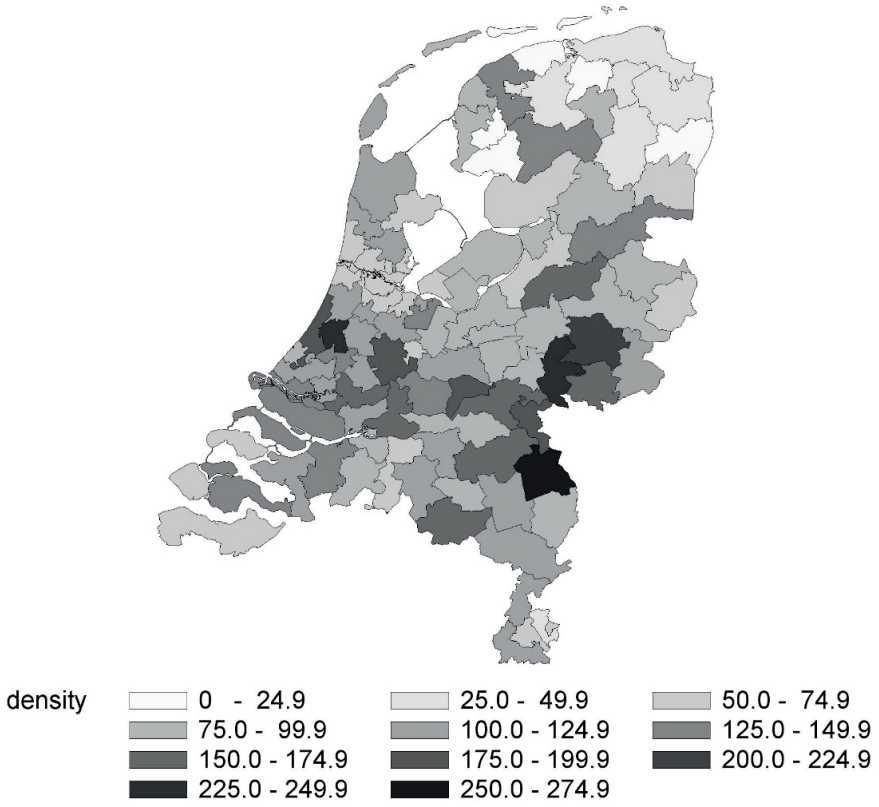

Figure 2. Geographical incidence rates per 1,000,000 population of eight neuromuscular disorders based on data from CRAMP 2004-2011.

To facilitate comparisons between disorders we chose to display the individual diseases in the same way using the same legend distribution. However, for diseases with low incidence this resulted in relatively wide legend intervals, limiting the number levels for the depicted data.

Table 4. Incidence numbers of newly diagnosed patients registered in CRAMP in 2004-2011 per 1,000,000 population for eight disorders that passed the four eligibility criteria.

Disorder	Type of disorder	Total number of persons in CRAMP	Depicted incidence rate range per 1,000,000 population
Myotonic dystrophy	autosomal dominant	498	0 – 129.9
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Glycogen storage disease type 2 (Pompe)	autosomal recessive	98	0 – 49.9
Oculopharyngeal muscular dystrophy	autosomal dominant	53	0 – 39.9

This study has several limitations. First, the depicted diagnoses date from before the era of whole-exome-sequencing (WES) as a diagnostic test. Current use of WES has changed the diagnostic process enormously. However, four of the five genetic diagnoses included in this study were detected by targeted genetic testing (myotonic dystrophy types 1 and 2, facioscapulohumeral muscular dystrophy and oculopharyngeal muscular dystrophy). We therefore expect that our data still provide valuable information. Moreover, there is no reason to suspect that the nationwide distribution-pattern will show major changes for WES-based diagnoses.

A second issue is the varying registration rate, possibly due to either low registered numbers and/or the distribution of neuromuscular expertise within the centres. When we look at the geographical distributions (Figures 1B and 2), the rural areas close to the country's frontier, especially the more northern and southern regions seem to be less densely populated with (newly) diagnosed persons. This may be due to differences in the level of registration for the participating centres or travel-options for these persons. Also, some patients may receive care from centres in neighbouring countries Germany and Belgium. Still, the differences in mapping patterns for the specific disorders are intriguing, especially for myotonic dystrophy (types 1 and 2) and facioscapulohumeral muscular dystrophy as these were based

on considerable numbers of persons. These genetically determined disorders show possible incidence elevations, whereas the acquired disorders seem to be more evenly distributed.

The third limitation concerns our approach of depicting incident cases by dividing them by the total population number of that area. Although straightforward and clear, this may easily result in enlarged incidences per population. A low number of inhabitants in smaller or more rural geographical areas combined with just a few extra cases may already result in a possible visual outlier. We have reduced this risk by including eight years of observation. A more comprehensive way will be to apply a Bayesian approach of calculation with the incidence of the surrounding areas taken into consideration. This smoothing technique is methodologically complex: the incidence in a particular area is corrected by the average incidence of the neighbouring areas. For example, in two areas with an unchanged risk of neuromuscular disorders in periods of similar duration and having an identical population structure, one will not observe equal numbers of patients due to random fluctuation. However, our interest was not in the observed (potentially biased) incidence but the true underlying incidence. Here, the incidences of the neighbouring areas provide a good impression of the underlying incidence.

We expect that in the future fully automated data collection systems will become available. This will result in true underlying incidence rates based on mandatory data collection of quality assessment or insurance data.

Conclusions

We provided the first neuromuscular atlas of the Netherlands with maps for eight disorders commonly seen in the neuromuscular practice. Data were collected by CRAMP, a successful nationwide multi-disorder registry. The derived geographically based incidence rates may serve as starting point for health care planning as well as research into etiological questions. To address possible outliers due to low population numbers Bayesian smoothing techniques should be considered for future research. If these maps can be generated for larger areas and regions within Europe, this may provide additional insights into for instance north-south gradients of disorders.

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Part III

Capture-recapture approaches to adjust for non-registered patients

Chapter 6

Population-based incidence and prevalence of facioscapulohumeral dystrophy

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ABSTRACT

Objective To determine the incidence and prevalence of facioscapulohumeral muscular dystrophy (FSHD) in the Netherlands.

Methods Using 3-source capture-recapture methodology, we estimated the total yearly number of newly found symptomatic individuals with FSHD, including those not registered in any of the 3 sources. To this end, symptomatic individuals with FSHD were available from 3 large population-based registries in the Netherlands if diagnosed within a 10-year period (January 1, 2001 to December 31, 2010). Multiplication of the incidence and disease duration delivered the prevalence estimate.

Results On average, 52 people are newly diagnosed with FSHD every year. This results in an incidence rate of 0.3/100,000 person-years in the Netherlands. The prevalence rate was 12/100,000, equivalent to 2,000 affected individuals.

Conclusions We present population-based incidence and prevalence estimates regarding symptomatic individuals with FSHD, including an estimation of the number of symptomatic individuals not present in any of the 3 used registries. This study shows that the total number of symptomatic persons with FSHD in the population may well be underestimated and a considerable number of affected individuals remain undiagnosed. This suggests that FSHD is one of the most prevalent neuromuscular disorders.

Glossary

CI = confidence interval; CRAMP = Computer Registry of all Myopathies and Polyneuropathies; FSHD = facioscapulohumeral muscular dystrophy; LGD = Leiden Genetic Database.

INTRODUCTION

Recently, a unifying genetic model of facioscapulohumeral muscular dystrophy (FSHD) was described, thereby facilitating identification of potential therapeutic targets [1]. As clinical studies on FSHD interventions can be expected in the near future, accurate data on FSHD epidemiology are needed for trial readiness.

Several studies reported on FSHD epidemiology (Figure 1, Table E-1); four were performed after genetic testing became available but did not report on population-based incidence estimates [2]. In the Netherlands, people newly diagnosed with a neuromuscular disorder are registered nationwide by seven neuromuscular centers in CRAMP (Computer Registry of all Myopathies and Polyneuropathies) [3]. This registry provides an opportunity to study frequencies of FSHD among the Dutch population.

FSHD frequencies are prone to underestimation because this disease is characterized by a high degree of clinical variability with a large proportion of individuals with mild symptoms. Moreover, relatives of persons diagnosed with FSHD may not seek medical attention [4]. We used capture-recapture methodology to estimate the total number of symptomatic individuals with FSHD by combining CRAMP data with two other large population-based registries. This includes those not present in any of the three available registries. We aim to provide an accurate estimate of FSHD incidence and prevalence in the Netherlands for a ten-year period (2001–2010).

METHODS

To estimate the total FSHD population, we applied a 3-source capture-recapture method [5]. Data regarding symptomatic persons with FSHD (with complaints and signs) were obtained from three sources: CRAMP; Spierziekten Nederland, the Dutch Association of Neuromuscular Diseases; and the Leiden Genetics Database (LGD) of the Department of Clinical Genetics, Leiden University Medical Center, where all genetic tests for FSHD in the Netherlands are carried out (Table E-2). Date of birth, sex, and date of diagnosis were made available. CRAMP and LGD also provided the first two characters of the person's surname. No regional review board approval was needed due to the use of anonymous data.

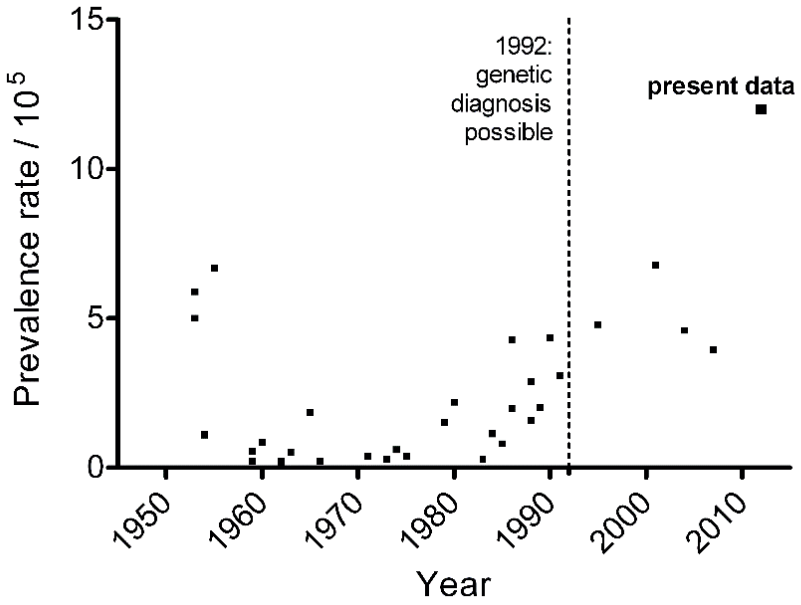

Figure 1. Reported FSHD prevalence from the literature. See Table E-1 for data and references.

In order to apply capture-recapture, symptomatic individuals from the three different registry sources were matched based on date of birth, sex, and, if available, the first two letters of the surname. When we identified multiple persons with the same date of birth and sex and the first characters of the surname were missing, date of diagnosis was used to distinguish between individuals in the matching process. Next, we sorted all persons by date of diagnosis and included those diagnosed from January 1, 2001 through December 31, 2010 (Figure 2). If the dates of diagnosis were not the same for matched individuals, we used the earliest available date.

We derived a separate estimate for each year, based on date of diagnosis. Because the overlap of persons within 1 year was frequently low, we used combined numbers from the previous, current, and next year as input for the regression analyses. For this purpose, we extended the inclusion to people diagnosed in 2000 and 2011 and they were matched. Other advantages of combining data from three years are better convergence of the regression models and enhanced opportunities for identification of possible interaction terms.

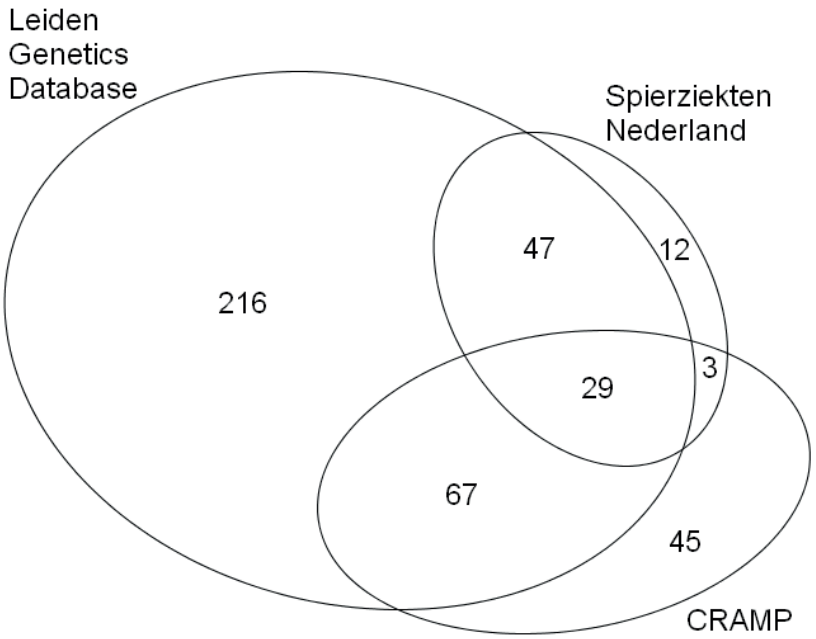

Figure 2. The number of symptomatic individuals with FSHD in the three source registries. Area-proportional Euler diagram depicts the absolute number of symptomatic individuals with FSHD for each of three registries and their overlap, created with EulerAPE [10].

For data analysis we applied Poisson regression, a technique for modeling occurrence of rare events in a population, using Statistical Analysis System software 9.2 (supplemental data include input and SAS syntax) [5]. The modeling process started with the most saturated model possible (three two-way interaction terms). Subsequently, non-significant interaction terms ($p > 0.05$) were removed to obtain the most parsimonious model. Decisions about removing interaction terms were based on the Wald χ^2 test for significance and the log likelihood goodness of fit criterion for the total model. We based associated 95% confidence intervals (CIs) on a simple variance formula for population size estimators [6].

We derived the total numbers of affected individuals and the associated CI with the regression analyses. To obtain yearly estimates, we divided the numbers of individuals and CIs by three. Finally, we divided the outcomes by the total number of person-years in the Dutch population in that specific year, made available by Statistics Netherlands (Table E-3) [7]. To estimate the prevalence in the Netherlands, the incidence rate was multiplied by the disease duration [8]. As FSHD does not decrease life expectancy, we estimated disease duration by taking the residual life

expectancy based on mean age at diagnosis. Residual life expectancy data were available from Statistics Netherlands [9].

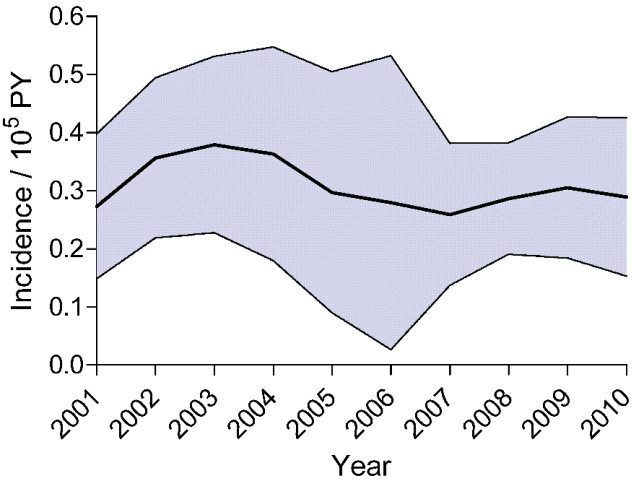

Figure 3. Annual incidence of FSHD in the Netherlands with 95% confidence interval for the period 2001-2010.

RESULTS

The results of person matching and the overlap within the registries are provided in Table E-3. These formed the input for the regression models. In all but two years (2005 and 2007) all interaction terms were deemed non-significant and thus were removed from the final regression models. Also, maintaining interaction terms in 2005 and 2007 led to very high standard errors and only slightly increased the estimated numbers of affected individuals. Therefore we applied regression models without interaction terms for 2005 and 2007.

The annual incidence rates derived with the regression models varied moderately (Figure 3, Table E-3). On average, this was 0.3/100,000 person-years (95% CI 0.2–0.5/100,000 person-years) or 52 individuals yearly for the period 2001–2010. The mean age at diagnosis in all registered symptomatic individuals was 42 years and the average life expectancy left was estimated to be 39 years. Therefore, we estimated the prevalence rate at 12/100,000 or 2,000 individuals with FSHD in the Netherlands.

DISCUSSION

By applying capture-recapture methodology using three large registries, we corrected for the number of symptomatic individuals with FSHD not present in any of these registries and we found a rather stable yearly incidence. The literature (Table E-1) revealed five estimates of FSHD incidence: three studies reported incidence per live births and were therefore incomparable with our finding. The other available incidence estimates were 0.7 and 0.38/100,000 person-years [11, 12]. The latter is remarkably close to our estimate.

Several studies reported prevalence estimations between 0.21 and 6.8/100,000. Prevalences found since the introduction of genetic confirmation were on average 5/100,000 (Table E-1). Our calculated prevalence estimate is more than twice as high. This reflects a large number of unidentified symptomatic individuals, possibly because they do not feel the need to seek medical attention. In the literature, availability of disease duration estimates was limited. We found an average duration of 27.9 years in Denmark, where more than 80% of the studied persons were still alive when the study closed, probably highly underestimating the duration [13]. Our estimated duration is therefore considered to be in line with this finding.

Capture-recapture is based on several assumptions: a steady state in the observed population, equal probability of ascertainment for affected individuals, appropriate person matching, and registry independence [14]. Because we used 3-source capture-recapture, the last assumption does not need to be met; the interaction terms enable identification and correction of estimates. Nevertheless, the interaction terms mainly turned out to be nonsignificant, implying non-dependence of the registries. The steady state assumption is never met in nationwide studies. The threat lies in nonmatching due to immigration, emigration, births, and deaths, causing overestimation of the population. By taking one-year intervals, changes within the population were kept to a minimum, limiting any effects this non-conformation may have. Furthermore, we have no indication that the assumption about equal probability of ascertainment in the registries was violated. Finally, although the matching process of persons was based on relatively few variables, we do not expect that significant numbers of individuals were mismatched or unmatched, as FSHD is a rarely occurring disease.

Our findings show that considerable numbers of affected individuals remain undiagnosed. As the recorded mean age at diagnosis is high compared to other reports, this prevalence is possibly a lower limit [15, 16] This suggests that FSHD is among the most prevalent neuromuscular disorders.

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SUPPLEMENTARY MATERIALS

Table E-1. FSHD prevalence and incidence estimates from the literature.

Location	Year or period	Prevalence ($x10^{-5}$)	Incidence ($x10^{-5}$)	Comments
South-Baden, Germany[17]	1953	5.9*/5.0*		Prevalence: including sporadic cases/ excluding sporadic cases
Northumberland & Durham, Great Britain[18]	1954	1.1*		
Minnesota, USA[11]	1955	6.7*	0.7	
Wisconsin, USA[12]	1959	0.23*/ 0.56*	0.38	Prevalence based on: own data/pooled data
Niigata, Japan[19]	1960	0.85*		In Japanese, info from Nakagawa et al[20]
Alberta, Canada[21]	1962	0.21*		
Iceland[22]	1963	0.53*		
Kanton Bern, Switzerland[23]	1966	0.22*		
Warsaw region, Poland[24]	1971	0.40*		Presumably mix up of terms in discussion. Applied incidence estimate not correct
Israel[25]	1973	0.29*		
Italy (north-east)[26]	1974	0.61*		
Shimane, Japan[27]	1975	0.39*		Info from Tangsrud & Halvorsen[28]
Alberta, Canada[29]	1979	1.52*	1.44**	
Province of Noord-Holland, the Netherlands[15]	1980	2.2*		
Kumamoto district, Japan[30]	1983	0.3*		
Northwest Tuscany, Italy[31]	1984	1.14*		
Benghazi, libya[32]	1985	0.8*		
Denmark[13]	1985	1.86*	2.6**/ 4.6**	estimated by two different methods
Wales, United Kingdom[33]	1986	2.0*/4.3*	2.27**	Prevalence: Wales/Cardiff only Incidence: Wales
South Wales, Great Britain[34]	1988	2.9*		
Kagoshima, Japan[35]	1988	1.59*		In Japanese, info from Nakagawa et al[20]
Okinawa, Japan[20]	1989	2.03*		

Table E-1. Continued

Location	Year or period	Prevalence ($x10^{-5}$)	Incidence ($x10^{-5}$)	Comments
Ljubljana, Slovenia[36]	1990	4.36*		In Croatian, info from Emery
Northern Ireland[37]	1991	3.1*		
The Netherlands[4]	1995	4.8*		
Utah & Idaho, USA[38]	2001	6.8*		
Northern England[39]	2007	3.95*		
Northeast Italy	2004	4.6*		
Southern Norway[28]	1983	0.69		Children (<19)
Western Sweden[40]	1995	0.8		Children (<16)
Hong Kong, China	2001	0.7		Children (<19)
Northwest Tuscany, Italy[41]	2004	4.6		FSHD type 1A

* Depicted in Figure 1; ** Incidence rate based on live births rather than total population.

Table E-2. Characteristics of the three registries used for capture-recapture.

	CRAMP	Leiden Genetics Database	Spierziekten Nederland Database
Origin of data	Registry all universities with expertise in neuromuscular disorders	National centre for FSHD genetics	Membership file Dutch patients association for neuromuscular diseases
Available information	Date of birth Sex distribution Date of diagnosis* Diagnosis First two characters of patient's (maiden) surname	Date of birth Sex distribution Date of diagnosis* First three characters of patient's (maiden) surname	Date of birth Sex distribution Date of diagnosis*
Is the information within the registry of a dynamic nature?	No, once registered patients stay in the registry	No, once registered patients stay in the registry	Yes, if a person quits their membership, information is removed
Can non-patients be registered?	No	No	Relatives or friends can become a member, but are asked for the person's involvement and the key person is registered as a patient, to prevent duplicates. We reveived a patient's list, not members. However if the needed info is not provided, duplicates can occur, although this is rare.
Symptomatic patients or unsymptomatic screened family?	Symptomatic patients only	Symptomatic patients only	Symptomatic patients only
Distinction between FSHD1 and FSHD2?	No	Yes	No
Info concerning Coats syndrome?	Limited	No	No
How are possible duplicates handled?	Removed based on date of birth, sex distribution and two first characters of patient's (maiden) surname	Not present, due to unique identifier in original registration (unique social security number)	Where possible removed
What is used as date of diagnosis?	The date of diagnosis entered by the registering (and usually treating) physician	The date of genetic confirmation of the disease	The date of diagnosis as reported by the patient; especially with older patients this date is based on clinical examination will in some cases be approximate
How are diagnoses in multiple centres handled?	Duplicates due to that and other issues have been removed before capture-recapture was applied	Not applicable, Leiden University Medical Centre is the only centre in the Netherlands to do genetic diagnoses of FSHD	Not applicable, only one association, one registry

* Age of diagnosis was derived by deducting the date of diagnosis from the date of birth. We are aware that the age of diagnosis is a much higher age than age of symptom onset (which is reported to be on average 17 years). [4]

Table E-3. Registered numbers of patients from three source registries and calculated numbers by the capture-recapture approach.

Year	Number of patients in registry							Observed number of patients	Calculated number of patients (incl. un- observed patients)	Person-years Population	Incidence rate	95% Confidence interval
	S	C	L	SC	S L	CL	SCL					
2000	1	5	1	3	1	5	1	17				
2001	1	1	19	0	2	9	5	37	44	160	0.27	(0.15 – 0.40)
2002	2	8	27	0	8	7	1	53	57	161	0.36	(0.22 – 0.49)
2003	5	3	26	0	8	9	5	56	61	162	0.38	(0.23 – 0.53)
2004	1	3	20	1	8	9	4	46	59	163	0.36	(0.18 – 0.55)
2005	1	9	27	0	1	3	1	42	48	163	0.30	(0.09 – 0.50)
2006	0	5	12	1	1	2	2	23	46	163	0.28	(0.03 – 0.53)
2007	0	2	19	1	1	8	3	34	42	164	0.26	(0.14 – 0.38)
2008	0	6	28	0	5	5	4	48	47	164	0.29	(0.19 – 0.38)
2009	2	3	17	0	7	9	2	40	50	165	0.30	(0.18 – 0.43)
2010	0	5	21	0	6	6	2	40	48	166	0.29	(0.15 – 0.43)
2011	0	4	27	0	4	5	0	40				

S patients only registered in Spierziekten Nederland Database
C patients only registered in in CRAMP
L patients only registered in Leiden Genetics Database
SC patients registered in Spierziekten Nederland Database as well as in CRAMP
SL patients registered in Spierziekten Nederland Database as well as in Leiden Genetics Database
CL patients registered in CRAMP as well as in Leiden Genetics Database
SCL patients registered in Spierziekten Nederland Database, in CRAMP and in Leiden Genetics Database

SAS - Syntax capture-recapture method

```
data CaptureRecaptureFSHD3sources;        *Data 2001;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0    .
1 0 0    4
0 1 0    14
0 0 1    47
1 1 0    3
1 0 1    11
0 1 1    21
1 1 1    7
;
data CaptureRecaptureFSHD3sources;        *Data 2002;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0    .
1 0 0    8
0 1 0    12
0 0 1    72
1 1 0    0
1 0 1    18
0 1 1    25
1 1 1    11
;
data CaptureRecaptureFSHD3sources;        *Data 2003;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0    .
1 0 0    8
0 1 0    14
0 0 1    73
1 1 0    1
1 0 1    24
0 1 1    25
1 1 1    10
;
data CaptureRecaptureFSHD3sources;        *Data 2004;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0    .
1 0 0    7
0 1 0    15
0 0 1    73
1 1 0    1
1 0 1    17
0 1 1    21
1 1 1    10
;
```

```
data CaptureRecaptureFSHD3sources;      *Data 2005;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0   .
1 0 0   2
0 1 0   17
0 0 1   59
1 1 0   2
1 0 1   10
0 1 1   14
1 1 1   7
;
data CaptureRecaptureFSHD3sources;      *Data 2006;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0   .
1 0 0   1
0 1 0   16
0 0 1   58
1 1 0   2
1 0 1   3
0 1 1   13
1 1 1   6
;
data CaptureRecaptureFSHD3sources;      *Data 2007;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0   .
1 0 0   0
0 1 0   13
0 0 1   59
1 1 0   2
1 0 1   7
0 1 1   15
1 1 1   9
;
data CaptureRecaptureFSHD3sources;      *Data 2008;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0   .
1 0 0   2
0 1 0   11
0 0 1   64
1 1 0   1
1 0 1   13
0 1 1   22
1 1 1   9
;
data CaptureRecaptureFSHD3sources;      *Data 2009;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0   .
1 0 0   2
0 1 0   14
0 0 1   66
```

```
1 1 0    0
1 0 1    18
0 1 1    20
1 1 1    8
;
data CaptureRecaptureFSHD3sources;        *Data 2010;
input SN CRAMP LeidenGen count @@;
cards;
0 0 0    .
1 0 0    2
0 1 0    12
0 0 1    65
1 1 0    0
1 0 1    17
0 1 1    20
1 1 1    4
;
* Most saturated model possible;
proc genmod data= CaptureRecaptureFSHD3sources;
model count=SN CRAMP LeidenGen LeidenGen*CRAMP LeidenGen*SN
CRAMP*SN/dist=poisson link=log obstats;
run;
* Three models with two interaction terms each;
proc genmod data= CaptureRecaptureFSHD3sources;
model count=SN CRAMP LeidenGen SN*CRAMP SN*LeidenGen/dist=poisson link=log obstats;
run;
proc genmod data= CaptureRecaptureFSHD3sources;
model count=SN CRAMP LeidenGen CRAMP*LeidenGen CRAMP*SN /dist=poisson link=log obstats;
run;
proc genmod data= CaptureRecaptureFSHD3sources;
model count=SN CRAMP LeidenGen LeidenGen*CRAMP LeidenGen*SN /dist=poisson link=log obstats;
run;
* Three models with one interaction term each;
proc genmod data= CaptureRecaptureFSHD3sources;
model count=SN CRAMP LeidenGen SN*CRAMP /dist=poisson link=log obstats;
run;
proc genmod data= CaptureRecaptureFSHD3sources;
model count=SN CRAMP LeidenGen SN*LeidenGen /dist=poisson link=log obstats;
run;
proc genmod data= CaptureRecaptureFSHD3sources;
model count=SN CRAMP LeidenGen CRAMP*LeidenGen /dist=poisson link=log obstats;
run;
* Most parsimonious model, without interaction terms;
proc genmod data=CaptureRecaptureFSHD3sources;
model count=SN CRAMP LeidenGen/dist=poisson link=log obstats;
run;
```

Notes accompanying SAS syntax to estimate yearly outcomes based on capture-recapture (perform steps for each year separately)

1. For the year of interest, execute the specific SAS syntax datastep for that year and next, run the eight PROC GENMOD procedures in the SAS syntax.
2. The modeling process starts with the most saturated model possible (three two-way interaction terms). This first model is followed by models with less interaction terms and the final model is the model without interaction terms. Start with the most saturated model, then look in the output of subsequent models, removing interaction terms step by step based on Wald chi-square test for significance of the interaction terms and the log likelihood goodness of fit criterion for the total model observed ($p>0.05$). When all non-significant interaction terms are removed, this provides the most parsimonious model.
3. Next, take the predicted value of observation 1 in the observation statistics of the most parsimonious model. This is the estimated number of patients not registered in any of the three registries, for three years combined (if you look at year 2001, this is combined with outcomes of 2000 and 2002). Add this estimate to the total observed patients in the three-year window (for years 2001 and accompanying years 2000 and 2002, this is the sum of 17, 37 and 53, see Table E-2) and next and divide by three for a one-year estimate. This yields the total number of patients in the year under scrutiny (2001 in this example).

Chapter 7

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

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ABSTRACT

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.

Highlights

- Epidemiological data about individual neuromuscular disorders, especially incidence, is scarce.
- Incidence is underrated whilst just as important as prevalence to describe a disease.
- This study researched neuromuscular disorders predominantly diagnosed in adult life.
- We provide 15 capture-recapture incidence rates, including 9 previously unavailable.

Keywords

Neuromuscular disorder, muscular disease, myopathy, epidemiology, incidence

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.

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 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 centres work in close collaboration and distances to the

nearest centre is 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].

PATIENTS AND METHODS

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.

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 centres 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 centres according to the (then) current guidelines [14-17].

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 • Sex • Date of diagnosis • Two characters from the patients' name • 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	• Date of birth (sometimes only year and month) • Sex • Date of diagnosis • Diagnosis (96-item list)
Details on date of diagnosis	• Not prone to recall bias • Sometimes returning patients were registered with incorrect, belated date of diagnosis	• Possibly prone to recall bias
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

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 analysed data from the period 2004–2011. The CRAMP dataset was not fully complete since paediatricians 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.

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 (Figure 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. Figure 1 was made using MS Powerpoint, figure 2 was plotted with Graphpad Prism 9.5.0.

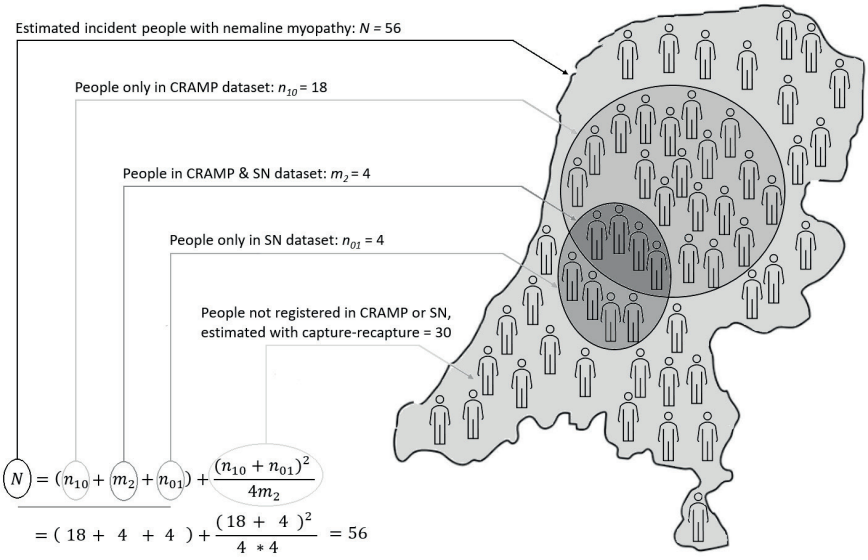

Figure 1. Graphical presentation of capture-recapture method using Chao's lower bound number estimate with our incidence findings for nemaline myopathy Chao [19].

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.

Calculations

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

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

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

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

$$95\%\ \mathrm{CI\ for}\ N = N \pm 1.96\sqrt{\mathrm{Var}(N)}$$

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 Figure 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.

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 centres. 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.

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].

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.

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	+	+	+	-	+	
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	+	+	+	+	+	+

Table 2. Continued

Disorder	Diagnosis (also) in adults[1]	Chronic nature[2]	Specific disorder[3]	SN Findable[4]	UMC based[5]	Fulfilling all criteria
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	+	+	+	+	+	+

Table 2. Continued

Disorder	Diagnosis (also) in adults[1]	Chronic nature[2]	Specific disorder[3]	SN Findable[4]	UMC based[5]	Fulfilling all criteria
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.

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) [35].

Table 3. Capture-recapture based numbers of neuromuscular disorders and sex-specific incidence with related information from literature, ordered by incidence rate from high to low rate.

Neuromuscular disorder	**Capture-recapture information from period 2004-2011**			
	Persons only in CRAMP	**Persons only in SN**	**Overlap CRAMP and SN**	**Estimated total number**
Myotonic dystrophy type 1	315	98	64	1143
Chronic inflammatory demyelinating polyneuropathy	188	44	28	741
Hereditary motor and sensory neuropathy type 1	72	49	7	651
Progressive spinal muscular atrophy	212	40	42	672
Facioscapulohumeral muscular dystrophy	149	33	26	527
Hereditary motor and sensory neuropathy type 2	57	47	11	361
Inclusion body myositis	122	39	35	381
Glycogenosis type 2	59	28	15	228
Multifocal motor neuropathy	28	19	6	145
Becker muscular dystrophy	17	17	9	75
Myotonic dystrophy type 2	21	3	1	169
Oculopharyngeal muscular dystrophy	32	8	8	98
Lambert-Eaton myasthenic syndrome	29	4	6	84
Nemaline myopathy	18	4	4	56
Glycogenosis type 5	12	1	2	36

* 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 [34].

Annual incidence rate per 100,000 population (95% CI)			Updated version of overview per 100,000 population	
Total population*	**Men**	**Women**	**Mean incidence rate**	**Range**
0.9 (0.7-1.0)	1.0 (0.7-1.3)	0.8 (0.6-1.0)	1	0.20-2.061 [23-25
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]
0.5 (0.2-0.8)	0.3 (0.1-0.6)	0.7 (0.0-1.4)	-	-
0.5 (0.4-0.6)	0.6 (0.5-0.8)	0.4 (0.2-0.6)	0.3	- [26]
0.4 (0.3-0.5)	0.5 (0.3-0.8)	0.3 (0.2-0.4)	- ***	-
0.3 (0.1-0.4)	0.6 (0.1-1.1)	0.1 (0.1-0.2)	-	-
0.3 (0.2-0.4)	0.4 (0.2-0.5)	0.2 (0.1-0.3)	0.4	0.09 – 0.76 [27-31]
0.2 (0.1-0.2)	0.2 (0.1-0.4)	0.1 (0.1-0.2)	-	-
0.1 (0-0.2)	0.2 (0-0.3)	0.1 (0-0.1)	0.2	- [32]
-	0.1 (0-0.2)	-	-	-
0.1 (0.0-0.4)	-	-	-	-
0.07 (0.04-0.1)	0.06 (0.03-0.09)	0.1 (0-0.2)	-	-
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, 33]
0.04 (0.01-0.07)	0.04 (0-0.08)	0.05 (0-0.1)	-	-
0.03 (0-0.06)	-	-	-	-

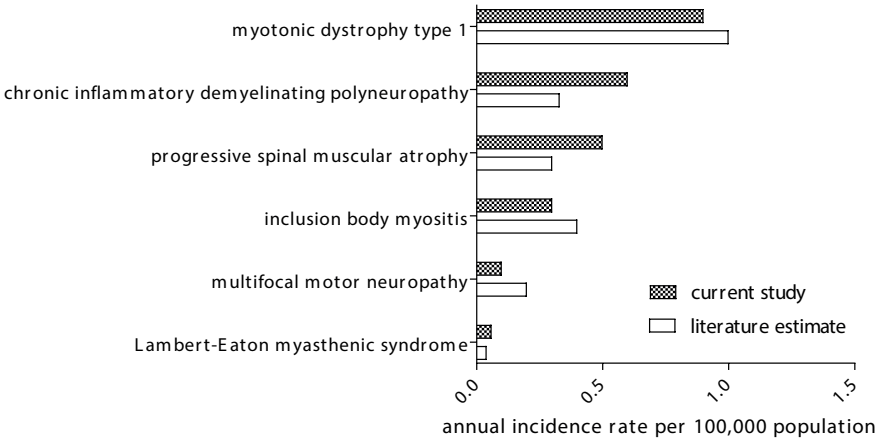

Figure 2. Comparison of capture-recapture results with findings from literature.

Of the fifteen calculated rates, only six could be compared with information from the literature (Figure 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 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 [34]. 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% [36-48].

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 [49, 50]. 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 [51]. Other disorders

such as myotonic dystrophy may exhibit a founder effect in specific countries [52, 53]. 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.

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.

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Part IV

Utilisation of a disease-specific neuromuscular registry

Chapter 8

The dutch registry for facioscapulohumeral muscular dystrophy: cohort profile and longitudinal patient reported outcomes

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ABSTRACT

Background Facioscapulohumeral dystrophy (FSHD) is the second most prevalent inherited muscular disorder and currently lacks a pharmaceutical treatment. The Dutch FSHD Registry was initiated in 2015 as a result of an international collaboration on trial readiness.

Objectives This paper presents the cohort profile and six years of follow-up data of the registered FSHD patients.

Methods At the time of self-registration and every six months thereafter, participants were invited to complete a digital survey of patient and disease characteristics and the Dutch versions of the Checklist Individual Strength (CIS20R), the Individualised Neuromuscular Quality of Life Questionnaire (INQoL), the Beck Depression Index – Primary Care and the McGill Pain Questionnaire.

Results From March 2015 to March 2021, 373 participants completed at least one survey. At baseline, fatigue and muscle weakness were the most frequently reported symptoms (median CIS20R sumscore 77 [IQR 60-92], median INQoL Fatigue score 58 [IQR 42-68] and median INQoL weakness score 58 [IQR 42-68]). Pain was experienced most often in the head and shoulder region (193, 52%). Nineteen of the 23 (sub)sections of questionnaires showed no significant changes over time.

Conclusions We conclude that the Dutch FSHD Registry was successfully set up, enabling collection of longitudinal data and facilitating recruitment in several studies.

INTRODUCTION

Facioscapulohumeral dystrophy (FSHD) is a muscular disorder with a wide variability in clinical symptoms, disease progression and functional impairments. Usually, the first symptoms develop in the second decade of life. Approximately 10% of patients present with an infantile onset, where the disease manifests before age 10 [1]. In general, patients experience weakness of facial, shoulder and upper extremity muscles and gradually weakness of the trunk and leg muscles will develop. In late adulthood, approximately 20% of the FSHD patients use a wheelchair in daily life (this is 40% in infantile-onset patients) [1, 2]. Although FSHD is one of the most common inherited myopathies in western countries, it is still classified as a rare disease with a prevalence of < 1/5,000 and an estimated incidence of 0.3/100,000 person-years [3-5].

Currently, no curative treatment for FSHD is available. Management of the disease consists of symptomatic therapy such as cognitive behavioural therapy, physical, occupational and speech therapy, aerobic training and adequate pain medication [6, 7]. The increase in pathophysiological knowledge of the disease enables the development of novel therapies for FSHD. A surge of new potential medications has arrived of which the first one reached a phase III trial. It is expected that the number of clinical trials will increase quickly in the near future [8-10]. FSHD registries were set-up across various countries to support these upcoming clinical trials [11, 12].

Fast and selective recruitment of patients with FSHD is crucial in order to run successful and well-powered trials in this small patient population. Registries are of great value in this process as they provide access to a large number of FSHD patients. Furthermore, the prospective, longitudinal data collected within these registries are valuable to gain insight in the natural history of FSHD, clinical subtypes and genotype-phenotype associations, and may be helpful in selecting outcome measures that are sensitive to change [13].

This study describes the cohort profile of the Dutch FSHD Registry participants registered between March 2015 and March 2021. Furthermore, longitudinal patient reported outcome measures on fatigue, quality of life, mental status and pain were analysed. Lastly, the studies that made use of the Dutch FSHD registry were reported.

METHODS

Registration and recruitment

The Dutch FSHD Registry started in the spring of 2015 by launching the website www.FSHDregistratie.nl. Registration of patients has continued ever since. Patients with FSHD can register themselves or their child by following the guidelines on the website. All forms and questionnaires are in the Dutch language. Foreign/non-Dutch-speaking patients are encouraged to find a registry in their country of residence and/or in a language they master. Genetic confirmation is not obligatory.

Treating physicians and/or the genetic lab are requested to provide the genetic test result of registered patients if permission is provided. Gathering data on genetic information is an ongoing process. Physicians, researchers, nurses and other health care professionals involved, repeatedly encourage FSHD patients to take part in the FSHD Registry. In addition, starting from 2019 onwards, information about the FSHD Registry is provided as standard practice when patients receive genetical confirmation of the disease. Patient advocacy group representatives also play an important role by informing FSHD patients about the FSHD Registry and its significance.

Governance and data access

The FSHD Registry is a collaboration of four parties: The Dutch Association of Neuromuscular Diseases (a nationwide patients association), the Dutch FSHD Foundation (fundraising organisation), Leiden University Medical Center, and Radboud University Medical Center (Radboudumc). The latter two are academic referral centres for FSHD and form the FSHD Expertise Center in the Netherlands. The ownership of the registry is delegated by these parties to Radboudumc. Its daily management and maintenance is carried out by a registry curator (JCWD).

A steering committee for the FSHD Registry was installed by the four collaborating parties and consists of delegates from the parties and a fifth independent rehabilitation physician. The committee decides on requests for data access and study recruitment. Requests can be made by filling in a form available on the website. Contact information and pseudonyms of registered patients are stored in a separate secured location accessible only by the registry manager and a backup manager. Research data are stored in Castor, a secured electronic data capture system operated by Radboud university medical center.

Ethical approval

The Registry, and the analysis of longitudinal patient reported outcome measures, involve medical research that do not fall within the scope of the Medical Research Involving Human Subjects Act, as declared by the local Medical Ethics Review Committee of the Radboud university medical center (amendment of file 2015-1812 on April 15th 2020). All participants of the FSHD registry provided their written informed consent before they entered the registry. The registry and its databases are in concordance with the General Data Protection Regulation and all other acting laws.

Study design

This study was a prospective cohort study. At the time of registration and every subsequent six months, participants received a digital survey invitation. Data collection ran from March 2015 to March 2021. Participants <16 years old could be registered, either by or with consent of their parents. However, the number of registered minors was limited, and they completed a different set of questionnaires. Therefore, these data were not included in this study. All registered Dutch FSHD patients aged ≥ 16 years old who completed at least one survey were included in this study.

Questionnaires

The surveys consisted of five Dutch questionnaires: a questionnaire on FSHD disease characteristics in accordance with the global FSHD registry framework, the Checklist Individual Strength (CIS20R), the Individualised Neuromuscular Quality of Life Questionnaire version 1 (INQoL), the Beck Depression Inventory for Primary Care (BDI-PC), and the McGill Pain Questionnaire – Dutch Language Version (MPQ-DLV). [14-18].

The global FSHD registry framework items included questions about demographics, diagnosis, muscle weakness and its time of onset, best motor function, presence of specific comorbidities like retinal vascular disease, hearing loss, retardation and epilepsy, use of (non-)invasive ventilation and FSHD family history.

The CIS20R measures four dimensions of fatigue and consists of 20 questions with a seven-point Likert scale answer option (1-7). The total CIS20R score ranges from 20-140 points with 20 meaning no symptoms and 140 meaning severe symptoms. The CIS20R can be divided into four subsections: 'Fatigue' containing eight items (score range 8-56), 'Concentration' with five items (score range 5- 35), 'Motivation' with four items (score range 4-28) and 'Activity' with three items (score range 3-21).

The INQoL measures quality of life and consists of ten subsections with questions on a seven-point Likert scale (0-6 or 1-7). The answers of the subsections are combined and converted to a 0-100% score, with 0% meaning no symptoms and 100% severe symptoms. In total, the INQoL consists of twelve different subscores.

The BDI-PC measures the severity of depression symptoms, consisting of seven questions with four answer options ranging from zero to three points for a possible total of 21 points. A value of ≥ 4 on the BDI-PC has a sensitivity and specificity of 82% for identifying patients with a major depressive disorder [16].

The MPQ-DLV measures pain symptoms and is divided in three subsections. In the first part, participants are asked to indicate where they experience pain and characterize the pain in more detail. In the second part, participants are asked to enter their current, minimum and maximum pain on a visual analogue scale (VAS), which is converted to a 0-10 score. The third part consists of a list of words that describe pain in increasing severity divided in 20 categories. Participants need to indicate which words describe their pain experience best. The third part results in the number of words chosen (NWC-T) ranging from 0-20, and the severity of the pain expressed as the Pain Rating Index (PRI-T), ranging from 0-36. Generally, a high NWC-T or PRI-T means a high burden of pain.

Data availability and statistical analysis

Incomplete surveys were excluded from analysis. The first completed survey was considered the baseline survey. Baseline data were reported as the median [IQR] value because some questionnaires did not show normally distributed data. Normality of data was determined via visual evaluation of the data. Means (SD) were presented in the tables to make comparisons with other studies more convenient and underpin the mixed models. For the INQoL and MPQ-DLV subsections, the median [IQR] and mean (SD) were calculated using the scores of patients who experienced the concerned symptoms (i.e. subsections with a score of zero were not used for these calculations). The reported percentages of experienced pain and analgesic use were based on the total number of included participants.

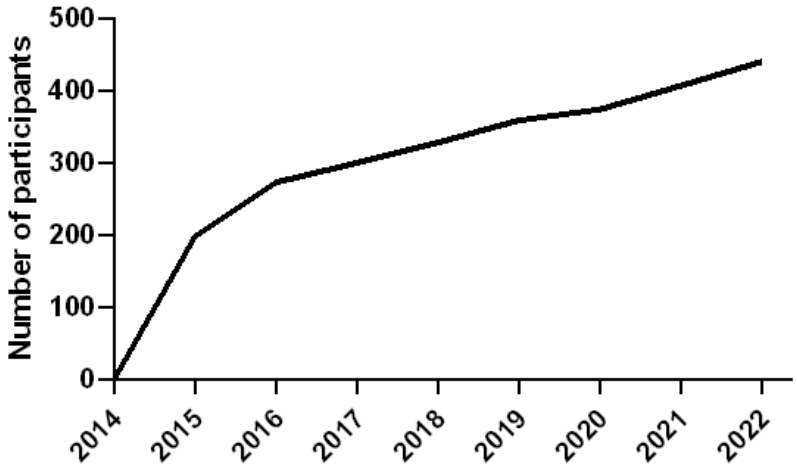

Figure 1. Number of participants in the registry.

Longitudinal changes were analysed using linear mixed effect models with compound symmetry matrices and the restricted maximum likelihood as estimation method. The sum scores were the dependent variables. Survey round was a repeated variable and fixed factor. A p-value <0.05 was considered statistically significant.

Current and upcoming trials usually select moderately affected patients (e.g. Ricci-score between 4-8 on a scale from 0-10), as these patients supposedly have the highest chance of rapid disease progression [8-10, 19, 20]. To simulate this while lacking actual clinical data, a sub-analysis was performed based on the responders' baseline mobility: ambulant, ambulant with assistive device(s) (e.g. brace, walker, or cane) and wheelchair dependent. For this subgroup analysis correction for multiple testing by the Bonferroni method was applied (statistical significance at p<0.017).

Data were collected in CastorEDC [21]. Analysis of the data was done in R (R Foundation for Statistical Computing, Vienna, Austria) and SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Graphs were created using GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, California USA). The data are not publicly available due to privacy or ethical restrictions, but can be requested using the registry's website.

RESULTS

Demographics

From March 2015 until March 2021, a total of 373 participants joined the Dutch FSHD Registry and completed at least one survey. During the first two years the annual number of new registered patients was high: 198 patients in 2015, 75 patients in 2016 and from 2017 onwards an average of 25 (Figure 1). During the six years of follow-up, thirteen participants were reported to be deceased, nine left the registry, and eighteen reported they did not want to receive the questionnaires anymore but remained in the registry. The response rate of the survey was 97% at baseline and gradually diminished to 65% at survey round twelve, with a mean response rate of 80%.

Baseline survey data

At baseline, the median age was 51 [39-63] years and 212 participants (57%) were female (Table 1). A genetically confirmed diagnosis was available for 111 participants (30%). Regarding mobility, 224 participants (60%) were ambulant, 109 (29%) were ambulant with assistive device and 40 (11%) were non-ambulant. The country of residence was the Netherlands for 344 participants (92%), 21 (6%) participants were living in Belgium and the remaining seven (2%) in other countries.

The baseline median total score of the CIS20R was 76 [59-92], mainly caused by a high score on the fatigue scale (38 [29-46]), indicating severe fatigue symptoms (Table 2). According to the INQoL scores, muscle weakness and fatigue were the most pronounced symptoms (median scores 63 [47-74] and 58 [42-68] respectively), yet social relations were barely affected (12 [0-33]).

Table 1. Characteristics of the FSHD patients in the registry at baseline.

	n (%*)
n	373 (100%)
Age (Median [IQR])	51 [39-62]
Female	212 (57%)
Age of onset (Median [IQR])	18 [10-30]
Family history with FSHD	91 (25%)
Country of residence	
The Netherlands	344 (92%)
Belgium	22 (6%)
Other	7 (2%)
Self-reported FSHD diagnosis	363 (97%)[a]
Type 1	113 (30%)
Type 2	16 (4%)
Unknown	233 (62%)
Mosaicism	1 (<1%)
Mobility	
Ambulant	224 (60%)
Ambulant with assistance	109 (29%)
Non-ambulant	40 (11%)
Wheelchair / scooter use	
None	225 (60%)
Part-time use	106 (28%)
Full-time	42 (11%)
Weakness	
Face	227 (61%)
Neck	129 (35%)
Shoulder girdle	344 (92%)
Trunk	267 (72%)
Lower arm	191 (51%)
Hand	129 (35%)
Hip girdle	268 (72%)
Foot extensor	225 (60%)
Ventilation status	
No assistance	360 (96%)
Non-invasive part-time	11 (3%)
Invasive part-time	0 (0%)
Invasive fulltime	2 (1%)
Comorbidities	
Hearing loss	246 (66%)
Coats (retinal vascular disease)	0 (0%)

* unless stated otherwise

[a] remaining responders reported to be undiagnosed at baseline

The BDI-PC median score was 1 [0-3] with 117 (23.6%) participants scoring ≥4. According to the MPQ-DLV, pain was most often experienced in the head-shoulder area (52% of the participants) (Figure 2). Furthermore, a large difference between the minimum and maximum pain was reported on the VAS (1.8 [1.0-3.0] vs. 7.3 [5.6-8.5]). Analgesics were used by 149 participants (40%), of which paracetamol (N=91, 24%) and nonsteroidal anti-inflammatory drugs (NSAIDs) (N=65, 17.5%) were the most common (Figure 3).

Follow-up survey data

Including all participants, nineteen out of the 23 (sub)scores showed no significant changes over time as presented in Figure 4 and Appendix A (CIS20R Sumsore, Fatigue, Concentration and Motivation; INQoL Weakness, Muscle Locking, Pain, Fatigue, Activities, Emotions, Quality of Life, Perceived Effect of Treatment and Expected Effect of Treatment; BDI-PC; MPQ-DLV VAS Current, VAS Minimum, VAS Maximum, NWC-T and PRI-T).

The mean CIS Activity score at baseline was 10.6 (SD=5.0, N=373) slowly increasing to 11.6 (SD=3.9, N=46) at survey round 12, indicating slightly more difficulty doing activities. The mean INQoL Independence score increased from 38.2 (SD=25.9, N=373) to 47.3 (SD=24.5, N=46), reflecting loss of independency over time. Unexpectedly, the mean INQoL Social Relations improved from 18.65 (SD=20.7, N=373) to 15.22 (SD=15.9, N=46). Lastly, the mean INQoL Body Image remained mostly stable from the mean baseline score of 43.2 (SD=26.8, N=373), but increased to 45.0 at survey round 11 (SD=23.5, N=121) and 12 (SD=22.6, N=46).

Table 2. Median scores of the CIS20R, INQoL, BDI-PC and MPQ-DLV at baseline.

Questionnaire subscore	Symptoms experienced by n (%)[a]	Possible scoring range[b]	Baseline Median [IQR] score[c]	Baseline Mean (SD) score[d]
CIS20R				
Sumscore	373 (100%)	20-140	76 [59-92]	76 (24)[N]
Fatigue	373 (100%)	8-56	38 [29-46]	37 (12)[S]
Concentration	373 (100%)	5-35	13 [8-20]	15 (8)[S]
Motivation	373 (100%)	4-28	13 [9-17]	14 (6)[S]
Activity	373 (100%)	3-21	10 [6-14.5]	11 (5)[N]
INQoL				
Weakness	351 (94%)	0-100	63 [47-74]	61 (19)[N]
Muscle Locking	138 (37%)	0-100	47 [32-63]	49 (20)[N]
Pain	262 (70%)	0-100	47 [37-63]	50 (20)[N]
Fatigue	314 (84%)	0-100	58 [42-68]	56 (19)[S]
Activities	373 (100%)	0-100	50 [30-64]	46 (23)[S]
Independence	373 (100%)	0-100	39 [19-56]	38 (26)[S]
Social Relations	316 (85%)	0-100	12 [0-33]	19 (21)[S]
Emotions	373 (100%)	0-100	25 [11-43]	29 (22)[S]
Body Image	373 (100%)	0-100	44 [19-64]	43 (27)[S]
Quality of Life	373 (100%)	0-100	42 [24-56]	40 (20)[N]
Perceived Effect of Treatment	190 (51%)	0-100	33 [17-44]	30 (25)[N]
Expected Effect of Treatment	190 (51%)	0-100	25 [8-42]	26 (25)[N]
BDI-PC	373 (100%)	0-21	1 [0-3]	2 (3)[S]
MPQ-DLV				
VAS current pain	149 (40%)	0-10	4.0 [2.0-5.5]	4 (2)[N]
VAS Minimal pain	149 (40%)	0-10	1.8 [1.0-3.0]	2 (2)[S]
VAS Maximal pain	149 (40%)	0-10	7.3 [5.6-8.5]	7 (2)[S]
NWC-T	259 (69%)	0-20	12 [9-15]	12 (4)[N]
PRI-T	259 (69%)	0-36	62 [43-83]	63 (26)[N]

[a] Number of participants (percentage of total responders) who experienced the symptoms of the concerned subsections of the questionnaires. [b] Possible scoring range for each subscore, a low score correlating to mild symptoms and a high score indicating severe symptoms in all scores. [c] The median and interquartile range [IQR] and [d]mean and standard deviation (SD) were calculated based on the scores of the number of participants in ([a]). [N] Data were normally distributed. [S] Data were skewed.
CIS20R = The Checklist Individual Strength, INQoL = Individualized Neuromuscular Quality of Life Questionnaire, BDI-PC = Beck Depression Inventory - Primary Care, MPQ-DLV = McGill Pain Questionnaire – Dutch Language Version, VAS = Visual Analogue Scale, NWC-T = Number of Words Chosen – Total, PRI-T = Pain Rating Index – Total.

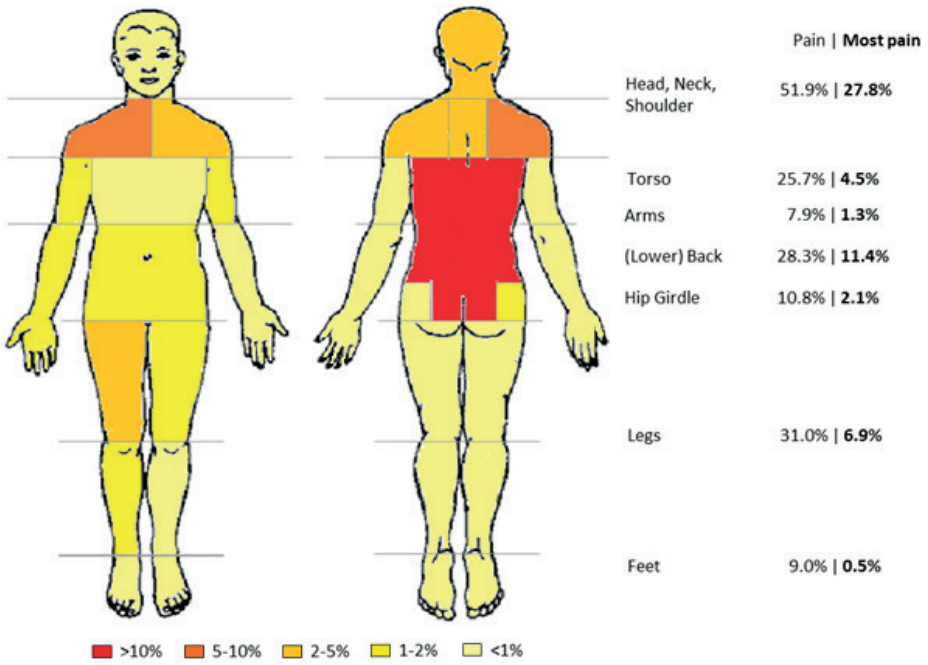

Figure 2. Pain experienced by FSHD participants at baseline.

The body areas are colored based on where participants experienced the most pain. Smaller body areas were combined into larger body areas, corresponding participant numbers are given in the right column. The left column shows the percentage of the total number of participants (N=373) that reported to experience pain in that body area. The right column shows where the most pain was experienced as a percentage of the total number of participants.

Sub-analysis mobility

At baseline, the mobility subgroup-analysis showed between-group differences in scores on the CIS Fatigue (p=0.044), CIS Activity (p=0.044), CIS Activity (p<0.001), INQoL Weakness, Muscle Locking, Activity, Independence, Social Relations, Body Image, and QoL (p<0.001 for all INQoL sub scores) (Figure 4). The wheelchair-dependent group showed the highest variability, most likely caused by a small number of participants (N=40 at visit 1, N=5 at visit 12) (Supplementary Table S2).

Within the ambulant participants group, 21 out of 23 (sub)scores showed no significant changes over time. The INQoL Social Relations improved from 15.5 (SD=18.4, N=173) at baseline to 11.6 (SD=14.6, N=19) at round 12. However, the INQoL Quality of Life worsened from 35.3 (SD=19.9, N=173) to 39.0 (SD=19.6, N=58) at round 11. It seemed to improve again at round 12 to 36.5 (SD=19.1, N=19), but this might have been caused by the relatively big drop in the number of participants.

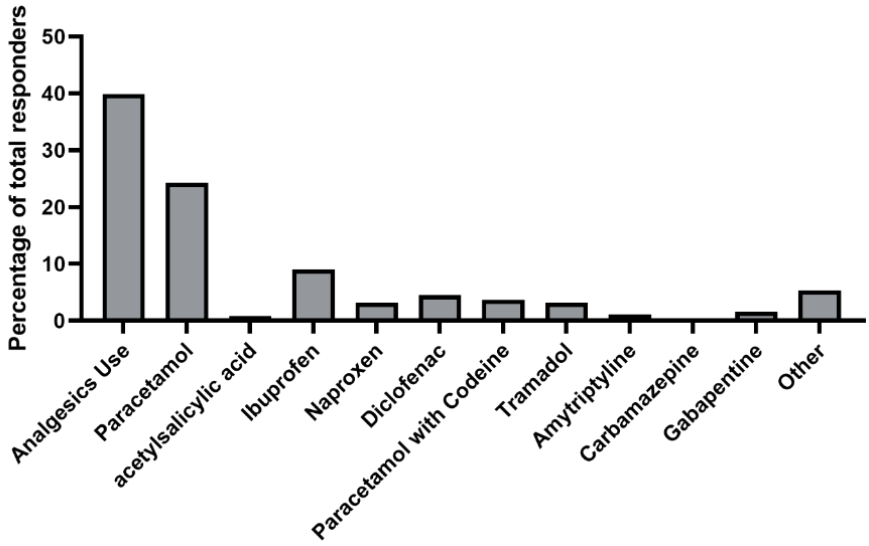

Figure 3. Analgesic usage in the Dutch FSHD registry participants at baseline.Percentages are calculated based on the number of participants reporting usage of analgesics and the total number of participants (n=373). Paracetamol is also known as acetaminophen.

In the subgroup of participants ambulant with assistive device, 22 out of 23 (sub) sections showed no changes over time. Only the INQoL Body Image improved from 54.4 (SD=23.6, N=92) to 44.2 (SD=23.8, N=22). In the wheelchair-dependent group, none of the (sub)scores showed a significant change over time, possibly caused by the small number of participants.

Studies facilitated

From 2015 until 2023, the registry received fourteen requests so far for either data (3), facilitating recruitment of participants (8) or a combination of both (3). These requests were all reviewed and approved by the steering board. Studies included patient-reported FSHD symptoms and their impact in daily life, a study on the socioeconomic burden of FSHD, and clinical drug trials and a questionnaire study regarding FSHD symptoms and received care during the COVID-19 pandemic was conducted using the registry [10, 20, 22-24]. In addition, the registry was used to inform all participants about early access to the first COVID-19-vaccination round in the Netherlands in 2021. A (Dutch) layman summary of all approved requests is posted on the website, accompanied by a results summary and link to the paper as soon as this becomes available (www.fshdregistratie.nl/gehonoreerde-verzoeken/).

DISCUSSION

In 2015, the Dutch FSHD Registry was set up according to the recommendations discussed in the trial readiness workshop (2015) and workshop of the European Neuromuscular Centre (ENMC) on the global FSHD registry framework (2016) [11, 12]. The registry has successfully been used to gather cross-sectional and longitudinal data from self-reported questionnaires. Overall, the results showed barely any longitudinal changes on (self-reported) fatigue, QoL, mental status and pain. Furthermore, the registry facilitated targeted patient recruitment for a number of studies, clinical trials and the collection of longitudinal patient-reported outcome measures.

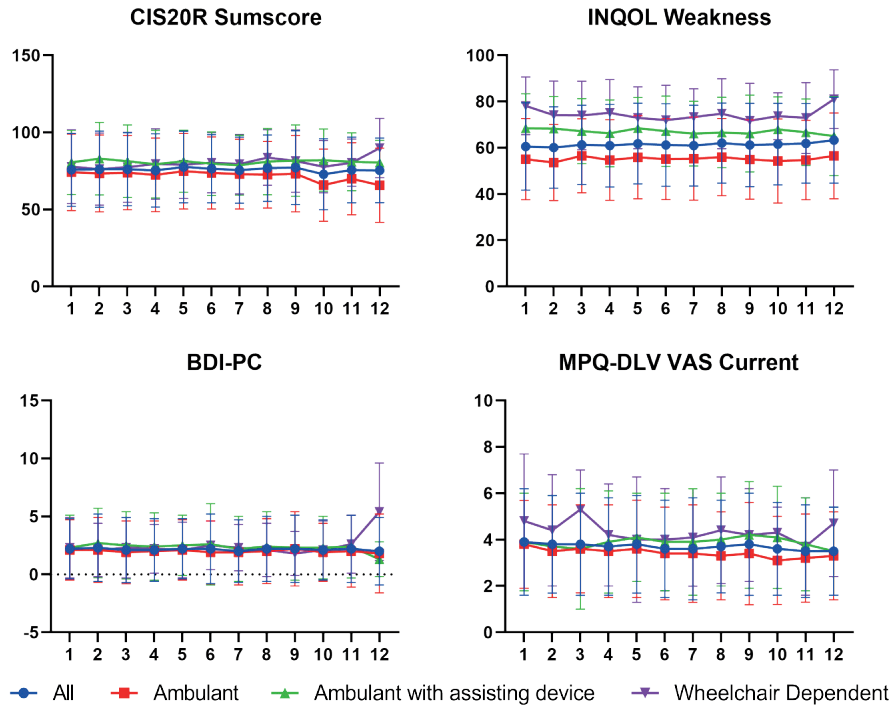

Figure 4. Change in mean (SD) values on questionnaires over time.

The graphs show the mean (SD) of the (sub)questionnaires for all responders and for the subgroups 'ambulant', 'ambulant with assistive device' and 'wheelchair dependent'. On the y-axis the score of each (sub)questionnaire is given, on the x-axis the survey rounds. CIS20R= Checklist Individual Strength, INQoL = Individualized Neuromuscular Quality of Life, QoL = Quality of Life, BDI-PC = Beck Depression Inventory – primary care, MPQ-DLV= McGill Pain Questionnaire – Dutch Language Version, VAS = Visual Analogue Scale

Cohort profile compared with other FSHD registries

So far, 452 FSHD patients were registered within the Dutch FSHD Registry. As the prevalence of FSHD in the Netherlands is estimated at 2,000 individuals, this represents approximately 23% of the Dutch FSHD population [3]. This finding is similar to the French registry (21%), but lower than in the United Kingdom registry (31%) [25, 26]. The Dutch prevalence estimate was based on a capture-recapture calculation, taking into account unobserved persons. Other prevalence estimates were based on observed persons only, resulting in lower prevalence estimates and thus higher registry coverage rates. Therefore, the coverage of the Dutch FSHD registry is probably higher compared to other FSHD registries. Nevertheless, efforts to encourage patients to participate in the registry are ongoing to further improve coverage. Also, we expect a rise of new participants when additional clinical trials will start.

In line with the high level of motivation of the study group, response rates on the half-yearly questionnaires were initially high. Although the response rate did decrease over time, it was still considered relatively high compared to response rates of other surveys [27]. The decrease in response rate was possibly caused by the relatively large time investment for completing all the questionnaires and/or a lack of information about the results. Reducing the number of questionnaires based on usefulness as well as more frequent reporting of the results may be necessary to maintain a high response rate.

Baseline comparison

The baseline scores on the questionnaires were similar to the scores found in other studies. The high CIS20R scores indicating severe fatigue were also observed in a different Dutch study of 135 FSHD patients, reiterating the high prevalence of fatigue symptoms. We do expect these two cohorts to overlap partly, which may account for the similar outcomes [28]. The different subscores of the INQoL corresponded well with the findings reported by the UK FSHD Registry [29].

Interestingly, the Dutch registry cohort scored lower on the Independent, Emotions, Body Image and QoL subcategories, indicating a lower burden, compared with the UK registry population. This may be caused by the slight difference in disease severity between the two cohorts. The UK cohort seemed to have a higher disease severity with 48% of the cohort being ambulant compared with 60% in the Dutch cohort. Additionally, country-specific cultural and healthcare differences may play a part. For example, a large European survey on chronic pain reported a higher use of analgesics (NSAIDS and opioids as well) in the UK compared with the Netherlands

[30]. This corresponds well with the much larger proportion (92%) of UK FSHD patients using analgesics, most commonly NSAIDs or opioids (both roughly 30%), compared with 40% of the Dutch patients using analgesics consisting mostly of paracetamol (24%) or NSAIDs (17.5) [29].

Lastly, the mean BDI score of the FSHD population corresponds well with the mean score found in screening 120 random outpatient clinic patients (2.15 vs 2.18) [31]. Although we cannot say for certain that the 117 (23.6%) FSHD patients who scored ≥4 on the BDI-PC were all affected by a major depressive disorder, this percentage also corresponds well with the outpatient clinic study (24% were diagnosed with a major depressive disorder).

Minimal clinically important difference

The majority of the questionnaires in this study showed no (sub)score changes in persons with FSHD over the course of six years. Based on the currently accepted view that the strength and functionality of moderately affected patients decline relatively fast, we expected the 'ambulant with assistive device' group to show the largest difference over time. However, even in this subgroup almost all (sub)scores remained stable over the six years follow-up. Of the (sub)scores that did show a small change over time, it is highly unlikely that a clinically important difference was reached within this timeframe.

Unfortunately, no data are available on what would be the minimal clinically important difference (MCID) of the questionnaires for FSHD. Barely any data were available on the MCIDs of these questionnaires in other diseases and it is questionable if MCIDs correspond well across diseases. The general MCID of the CIS Fatigue is 10 points, which was not reached in our cohort [32]. The MCID of the pain score (0-10) in chronic pain patients was 0.9-2.7 depending on the calculation method used and could be compared to the VAS scores in the MPQ-DLV questionnaire [33]. However, both scores were stable and no MCID was not reached in our cohort. It is clear that the knowledge base regarding the MCIDs of these questionnaires is small and mostly unavailable for FSHD [34]. A currently ongoing natural history study within this research group will provide more knowledge about the clinical progression of FSHD symptoms over a longer period. Combining the clinical data with the FSHD-registry data may enable us to determine clinically important differences of these questionnaires and provide knowledge about MCIDs in FSHD and the responsiveness of specific PROMS.

Disease progression and QoL

The lack of change in scores on the questionnaires could indicate that: 1) FSHD patients remain stable for a long time, 2) the questionnaires are not sensitive enough to detect the probably small occurring changes, and/or 3) fatigue, QoL, depression and pain are influenced by a wide range of factors and do not directly relate to disease progression. As this study currently does not include sufficient clinical data regarding the disease severity and its changes, we cannot rule out nor confirm any of these hypotheses. However, a longitudinal study in myotonic dystrophy type 1 patients did not find longitudinal changes in the INQoL subscores (or even improvements on some subscores) either, despite worsening of the clinical symptoms in the patients [35]. The authors suggested that quality of life was not directly related to disease progression and could increase by changing external factors (e.g. using assistive devices or a wheelchair when necessary) or internal factors (adaptation of the patient's perspective on what relates to quality of life). Their conclusions point towards the second and third hypothesis. In addition, previous studies pointed to at least mild progressiveness of symptoms within a year, and the Italian FSHD Registry found clinical worsening of disease after five years of follow-up, making it unlikely that the Dutch cohort remained stable over (a maximum of) six year follow-up [36, 37].

Although we cannot completely rule out the usefulness of the questionnaires in clinical trials because the subgroup analysis displayed the ability to discriminate between specific mobility subgroups, the data collected from this cohort seem to suggest a lack of sensitivity to change for all the questionnaires. We are therefore hesitant to recommend the CIS20R, INQoL, BDI-PC and MPQ-DLV to measure drug efficacy in a clinical trial.

Future perspectives

Currently, access to longitudinal clinical outcome assessments has been unavailable. Interpretation of the results of the questionnaires will improve with access to longitudinal clinical data and gives the opportunity to calculate the MCID. Furthermore, it will improve the enrolment process by increasing the possibilities for pre-screening (e.g. based on clinical severity scores or muscle strength scores). Lastly, this will enable to start a range of new studies for example about identifying subtypes of FSHD, establishing genotype-phenotype correlations or investigating the relationship between muscle weakness, psychosocial factors, daily functioning and quality of life. We therefore propose that FSHD registries will be expanded to include clinical outcome assessments, either by performing separate study visits,

combining registry data with already ongoing natural history studies or by linking the registry to parts of the patient files.

As almost all of the (sub)questionnaires remained stable over the course of six years, we recommend reducing the survey frequency. This will lower the burden on the registered patients and is expected to improve the response rate. Furthermore, recently developed questionnaires such as the FSHD-HI and FSHD-RODS may be more sensitive and specific and be useful to include in the registries as well [38, 39]. Together with the Dutch patient advocacy group, we started the process to carefully select which improvements need to be made, what clinical data need to be captured, which questionnaires are to be used and in which frequency, while minimizing the burden on both the participants and clinicians.

In this process, we will make sure that the Dutch registry remains harmonised with other national FSHD registries. Additionally, an effort should be made to combine the data of all the national registries as was originally the aim.

Strengths and limitations

The strengths of this study are the size of the FSHD cohort and the long follow-up period with frequent survey rounds and high response rate, resulting in reliable cross-sectional and longitudinal analysis.

There are several limitations. First, selection bias may be introduced by self-registration, and the registry may therefore not be representative of the entire Dutch FSHD population. However, the demographics of the Dutch Registry population were similar to other studies and FSHD registries. Another limitation of the Registry is the lack of clinical data collection. As mentioned before, clinical data will be useful for interpreting the results of questionnaires, enabling large genotype-phenotype studies, and a more precise preselection of patients for clinical trials. Finally, the process of including the genetical confirmation of the disease was not fully completed at the time of writing. It will become available in the near future to be used for upcoming studies and enable genotype-patient reported phenotype coupling.

Conclusion

The Dutch FSHD Registry has been successfully implemented with a still increasing number of participants. It has been used for fast and selective patient recruitment for several studies and for contacting patients on short notice if important information became available. It will prove to be invaluable for recruitment in

future trials. Although the CIS20R, INQoL, BDI-PC and MPQ-DLV questionnaires do discriminate between specific subgroups of this FSHD cohort, these scores detected minimal or no longitudinal changes in these FSHD patients over a six-year period. These questionnaires may therefore not be useful to monitor disease progression in prognostic studies or clinical trials in patients with FSHD. The inclusion of clinical outcome assessments in FSHD registries should be considered.

Abbreviations

FSHD Facioscapulohumeral Muscular Dystrophy
CIS20R The Checklist Individual Strength
INQoL Individualized Neuromuscular Quality of Life Questionnaire
BDI-PC Beck Depression Inventory – Primary Care
MPQ-DLV McGill Pain Questionnaire – Dutch Language Version
VAS Visual Analogue Scale
NWC-T Number of Words Chosen – Total (part of INQoL scoring)
PRI-T Pain Rating Index – Total (part of INQoL scoring)
MCID Minimal Clinically Important Difference

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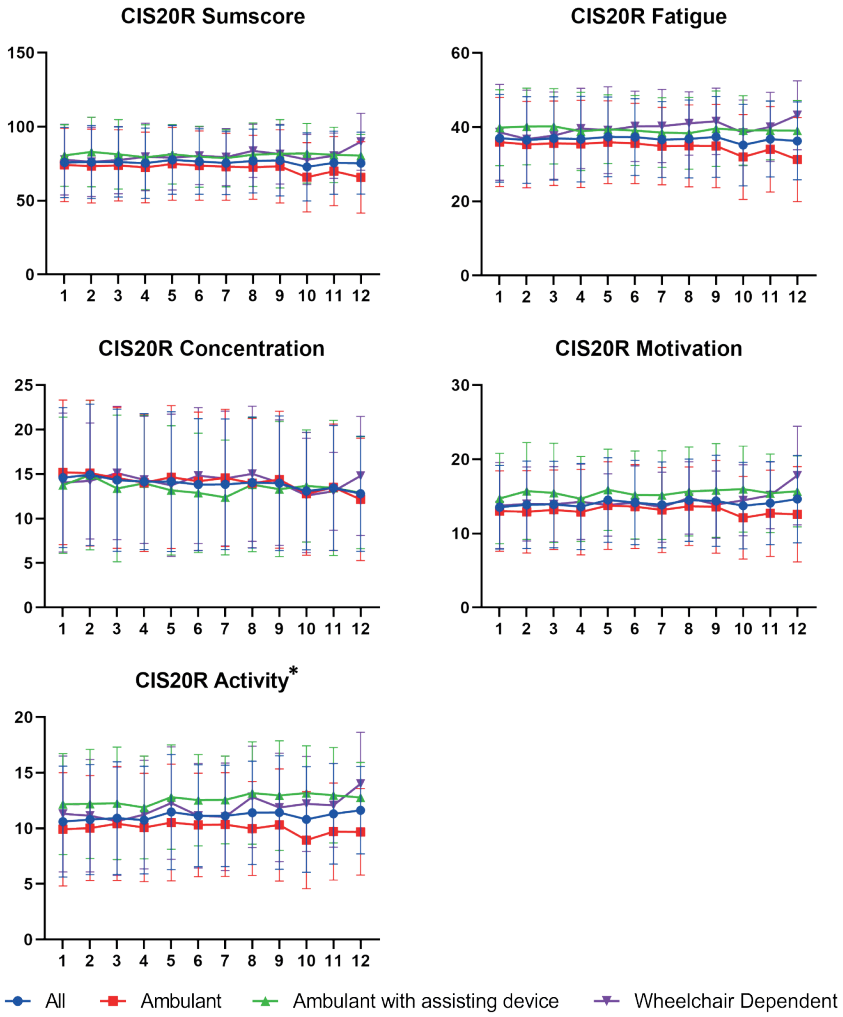
SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2023.10.020.

Appendix A1. Change over time of the CIS20r (sub)questionnaires.

The graphs show the mean (SD) of the CIS20R (sub)questionnaires for all responders and for the subgroups 'ambulant', 'ambulant with assistive device' and 'wheelchair dependent'. On the y-axis the score of each (sub)questionnaire is given, on the x-axis the survey rounds.

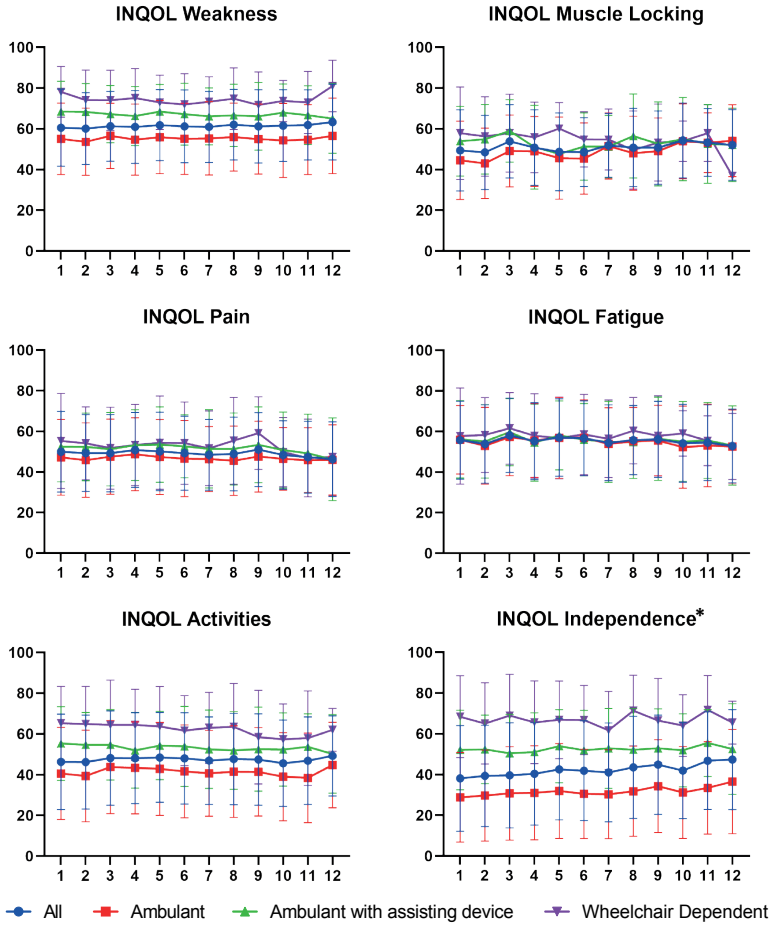
*A statistically significant change over time was found on the Activity subscore when including all responders (p=0.031).CIS20R = Checklist Individual Strength

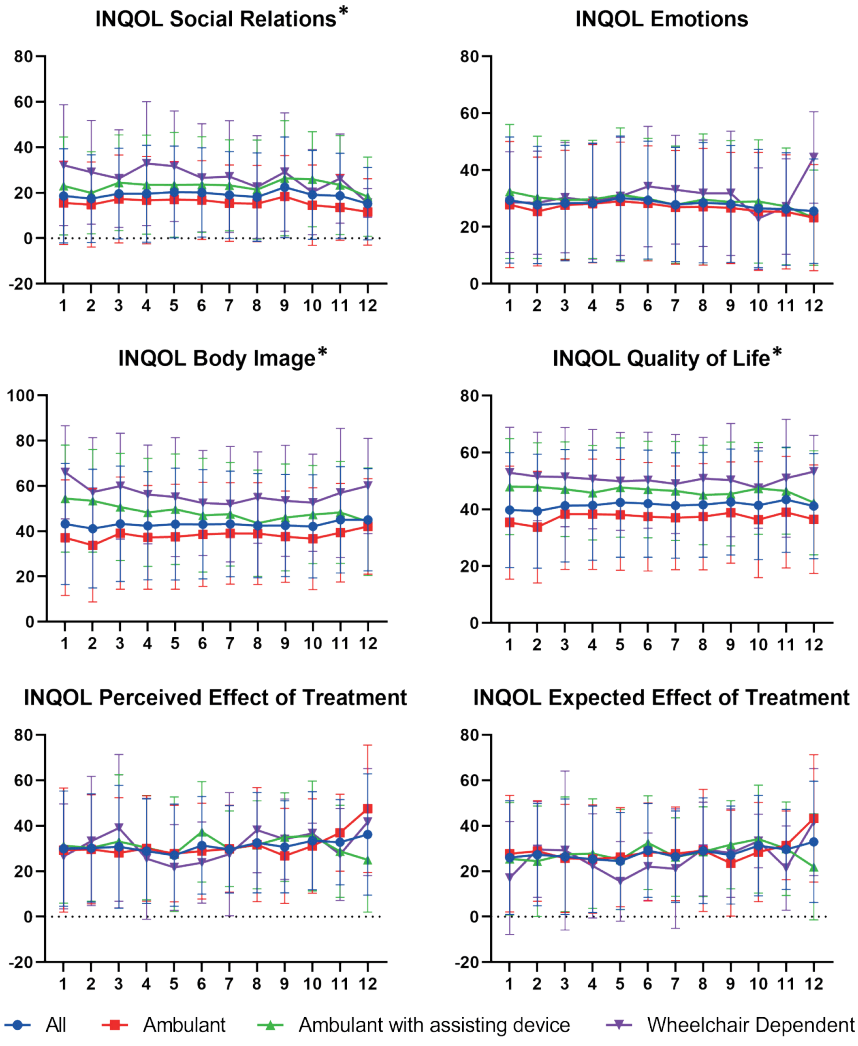


Appendix A2. Change over time of the INQoL subquestionnaires.

The graphs show the mean (SD) of the INQoL subquestionnaires for all responders and for the subgroups 'ambulant', 'ambulant with assistive device' and 'wheelchair dependent'. On the y-axis the score of each (sub)questionnaire is given, on the x-axis the survey rounds.

*A statistically significant change over time was found on the Independence, Social Relations and Quality of Life subscore for all responders (p=0.007, 0.006, 0.024 respectively). For ambulant responder, Social Relations (p=0.010) and Quality of Life (0.002) changed over time. For ambulant with assistive device responders, Body Image (p=0.000) changed significantly over time. INQoL= Individualised Neuromuscular Quality of Life Questionnaire.

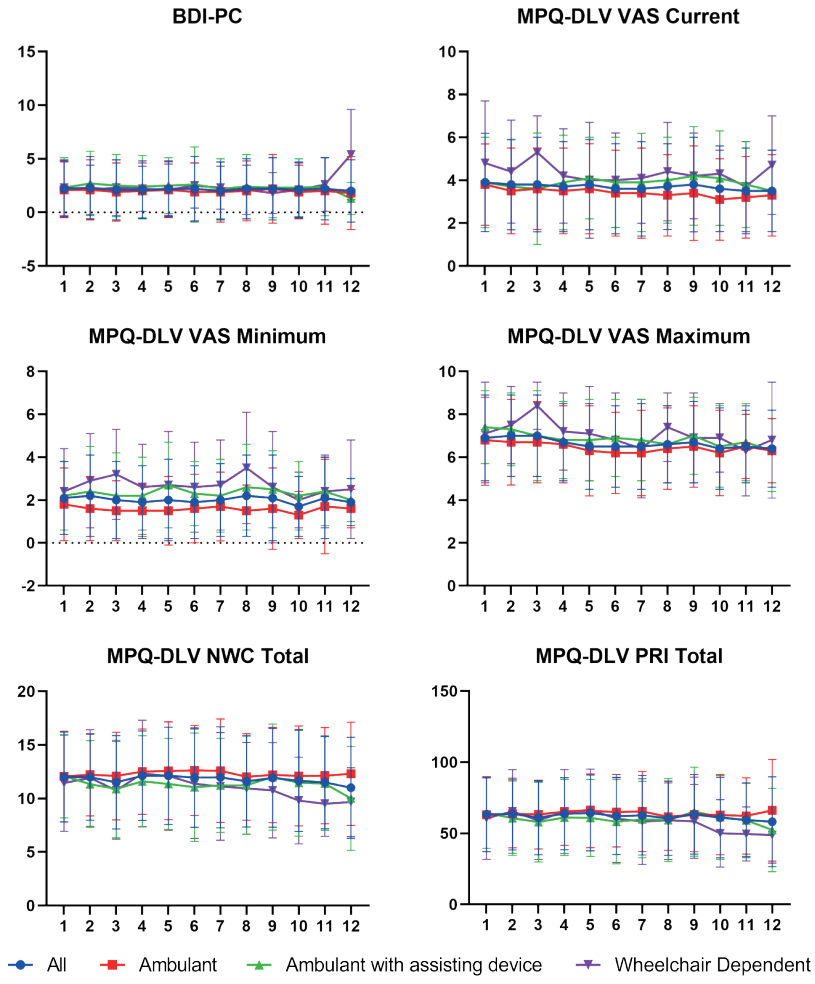



INQOL Social Relations*
INQOL Emotions
INQOL Body Image*
INQOL Quality of Life*
INQOL Perceived Effect of Treatment
INQOL Expected Effect of Treatment
All
Ambulant
Ambulant with assisting device
Wheelchair Dependent

Appendix A3. Change over time of the BDI-PC and MPQ-DLV (sub)questionnaires.

The graphs show the mean (SD) of the INQoL subquestionnaires for all responders and for the subgroups 'ambulant', 'ambulant with assistive device' and 'wheelchair dependent'. On the y-axis the score of each (sub)questionnaire is given, on the x-axis the survey rounds.

BDI-PC = Beck Depression Inventory - Primary Care, MPQ-DLV = McGill Pain Questionnaire – Dutch Language Version, VAS = Visual Analogue Scale, NWC = Number of Words Chosen, PRI = Pain Rating Index.



Supplementary Table S1. P-values of the effect of visit number on the means of the (sub)questionnaires.

Questionnaire	All	Ambulant	Ambulant with assistive device	Wheelchair dependent
CIS20R				
Sumscore	0.866	291	0.698	0.358
Fatigue	0.185	0.04 [b]	0.434	0.195
Concentration	0.317	0.515	0.089	0.615
Motivation	0.197	0.643	0.300	0.775
Activity	0.031 [a]	0.787	0.361	0.019 [b]
INQoL				
Weakness	0.706	0.695	0.233	0.112
Muscle Locking	0.338	0.645	0.148	0.945
Pain	0.78	0.978	0.579	0.541
Fatigue	0.287	0.308	0.492	0.948
Activities	0.14	0.114	0.019 [b]	0.253
Independence	0.007 [a]	0.220	0.496	0.580
Social Relations	0.006 [a]	0.010 [c]	0.452	0.362
Emotions	0.219	0.499	0.357	0.046 [b]
Body Image	0.024 [a]	0.609	0.000 [c]	0.155
Quality of Life	0.492	0.002 [c]	0.466	0.998
Perceived Effect of Treatment	0.62	0.544	0.086	0.122
Expected Effect of Treatment	0.8	0.749	0.316	0.282
BDI-PC	0.799	0.629	0.643	0.399
MPQ-DLV				
VAS current	0.93	0.924	0.775	0.96
VAS Minimum	0.115	0.896	0.219	0.303
VAS Maximum	0.08	0.137	0.461	0.589
NWC-T	0.663	0.931	0.356	0.719
PRI-T	0.644	0.937	0.47	0.81

The p-values of the mixed models are given in the 2nd column. No correction for multiple testing was applied. Number of participants (percentage of total participants) are given in the third column.

a. Statistically significant ($p<0.05$), no correction for multiple testing was applied to the analyses including all responders.

b. Statistically significant ($p<0.05$) before correcting for multiple testing.

c. Statistically significant ($P<0.017$) before and after correcting for multiple testing.

CIS20R = The Checklist Individual Strength, INQoL = Individualized Neuromuscular Quality of Life Questionnaire, BDI-PC = Beck Depression Inventory - Primary Care, MPQ-DLV = McGill Pain Questionnaire – Dutch Language Version, VAS = Visual Analogue Scale, NWC-T = Number of Words Chosen – Total, PRI-T = Pain Rating Index – Total.

Supplementary Table S2. Number of responders per survey round.

Visit	All	Ambulant	Ambulant with assistive device	Wheelchair dependent
1	373	173	92	40
2	308	147	81	35
3	284	143	76	33
4	272	137	78	33
5	258	137	80	30
6	236	130	76	29
7	220	125	71	24
8	198	107	67	24
9	188	99	65	24
10	152	82	55	15
11	121	58	49	14
12	46	19	22	5

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Chapter 9

Living with facioscapulohumeral muscular dystrophy during the first two Covid-19 outbreaks: a repeated patient survey in the Netherlands

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ABSTRACT

Background Patients with facioscapulohumeral dystrophy (FSHD) suffer from slowly progressive muscle weakness. Approximately 20% of FSHD patients end up wheelchair-dependent. FSHD patients benefit from physical activity to maintain their muscle strength as much as possible. The impact of the COVID-19 pandemic on the health of FSHD patients was unknown.

Objective This study assessed changes in daily care received, perceived psychosocial stress, and worsening of FSHD complaints in 2020. Furthermore, we compared COVID-19 infection incidence and severity of symptoms between FSHD patients and non-FSHD housemates.

Methods Three online survey rounds were sent out to all adult participants of the Dutch FSHD registry regarding daily care received, perceived psychosocial stress, COVID-19 infection rate, and COVID-19 symptoms severity. They also included COVID-19-related questions regarding the participants' housemates, which served as control group.

Results Participation rate was 210 (61%), 186 (54%), and 205 (59%) for survey 1, 2, and 3, respectively. Care reduction was reported by 42.7%, 40%, and 28.8% of the participants in the respective surveys. Perceived psychosocial stress increased in 44%, 30%, and 40% of the participants. Compared to the 197 non-FSHD housemates, the 213 FSHD patients reported more possibly COVID-19-related symptoms (27% vs. 39%, p=0.017) of mostly minimal severity (63%). No difference in (possible) COVID-19 infection incidence rates was found (2.0% vs. 2.8%, p=0.527).

Conclusions The COVID-19 pandemic negatively impacted care received and increased perceived psychosocial stress in FSHD patients. However, COVID-19 infection incidence in FSHD patients was similar to their non-FSHD housemates.

Keywords

Neuromuscular diseases, COVID-19, epidemiology, surveys and questionnaires, incidence, registries

Abbreviations

FSHD Facioscapulohumeral muscular dystrophy
COVID-19 Coronavirus disease 2019
NMD Neuromuscular disorder
QoL Quality of life
ENMC European Neuromuscular Centre
MRS Modified Ranking Scale
PSS Perceived Stress Scale

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has affected the health status, daily activities, social participation, care availability, and quality of life of individuals all over the world. In the Netherlands, 6.5 million people tested positive in a registered PCR test, and almost 40,000 people died over the course of 2 years [1, 2]. To slow down the rapid spread of the disease, rigorous restrictions were implemented in March 2020 for a prolonged period of time, such as social distancing, quarantine, and lockdowns [3].

These restrictions resulted in a decrease of physical activity, available healthcare, and an increase in loneliness, anxiety, and depression [4, 5]. For patients with facioscapulohumeral muscular dystrophy (FSHD), a slowly progressive muscle disease, physical activity is crucial to maintain muscular strength, flexibility in joints, and physical endurance to reduce progression of muscle weakness [6, 7]. At the time, the study was initiated in March 2020, it was unknown what the impact of COVID-19, and the restrictions on FSHD patients would be.

In Italy, research on various Neuromuscular Disorders (NMDs) has shown a subjective worsening of the NMD symptoms and a significant worsening of quality of life (QoL) during the pandemic [8, 9]. It is expected that the worsening of disease aspects and QoL will also have occurred in FSHD patients. However, the infection rate and course might differ in FSHD patients. Previous studies hypothesized that the inflammation observed in biopsies and imaging modalities could point to possible alterations in the immune responses [10, 11]. On the other hand, a minority of patients does experience respiratory weakness or weakness in coughing, increasing the susceptibility for infections [12, 13]. It is unknown whether these changes affect the response to the SARS-CoV-2 virus.

The goal of this study was twofold. First, we aimed to assess and describe the physical and mental health of the FSHD patients during the pandemic. Second, we aimed to gain more insight in the COVID-19 incidence rate and severity of symptoms compared to a non-FSHD population.

MATERIALS AND METHODS

Study design

This was an observational questionnaire study, performed in an already existing cohort (i.e., the Dutch FSHD registry cohort). A survey was created to inquire about the impact of the COVID-19 pandemic on care received, perceived psychosocial stress, FSHD complaints, the number of COVID-19 infections, and the severity of corresponding symptoms (Appendix 1 in supplementary material). The survey was electronically sent using CastorEDC to FSHD patients in three rounds in 2020: survey 1 (S1) on May 22nd 2020, survey 2 (S2) on August 26th 2020, and survey 3 (S3) on December 19th 2020 [14].

Study population: the Dutch FSHD registry

The Dutch FSHD registry was set up in 2015 to enable recruitment of FSHD patients for research and to collect patient-reported data about the natural course of the disease, including the core dataset decided upon during the 225th European Neuromuscular Centre (ENMC) workshop [14-16] The registry was originally intended for Dutch-speaking participants only. Other interested people were encouraged to participate in the national registry in their country. Since 2020, people who still wished to enter the Dutch registry despite geographical and language barriers were accepted in the Dutch registry.

All registered FSHD patients aged 16 years and older, the age of consent in the Netherlands regarding medical decisions, were invited for the surveys. The control group consisted of the housemates of the participants who were ≥ 16 years old and did not have FSHD. This enabled comparison of COVID-19 infection incidence rate and severity of possible COVID-19-related symptoms. Housemates were defined as: spouses, children, parents, family, or other. Housemates with FSHD were excluded from the analysis to prevent any accidental duplications in FSHD patients. The data concerning the housemates were reported by the FSHD patients instead of the housemates themselves, because no contact details of housemates were available in the registry. Furthermore, it was a relatively quick process to submit an amendment on the already existing approval of the FSHD registry. Sending

the surveys directly to housemates or other control groups would have required a completely new submission, which would have delayed the study. As time was of the essence during the pandemic, the method for gathering indirect data on housemates was chosen.

Survey

Demographic data regarding age and sex were retrieved from the Dutch FSHD registry. Furthermore, the survey contained a question about risk factors for a more severe COVID-19 disease course known at that time: age >70 years, respiratory problems, chronic heart disease, severely overweight, and immunodeficiency.

The survey consisted of three parts: (1) impact of the pandemic on FSHD complaints and care (2) perceived psychosocial stress, and (3) COVID-19 infection rate and severity of possible symptoms experienced by the FSHD patients and their housemates. Specifically, part one consisted of questions concerning the participants' living arrangement, care received pre-COVID-19, change in received care during the pandemic compared to pre-pandemic care received (yes/no answer with option to elaborate on what changed and the consequences of the changes), and the Modified Ranking Scale (MRS) [17]. The MRS asks about the disease severity as experienced by the participants with 0—'no symptoms' and 5—'severely handicapped, constant need for care'. Participants were asked to report the MRS pre-pandemic and at the time of survey completion.

The second part consisted of questions about the perceived psychosocial stress during the pandemic compared to before (0 'a lot less stress'—5 'a lot more stress'). It included the Perceived Stress Scale (PSS) ranging from 0 'no stress' to 40 'severe stress', which evaluates how unpredictable, uncontrollable, and overloading someone experienced the previous month, and their perceived ability to cope [18]. Furthermore, a set of possible COVID-related stressors used in an ongoing global study were tested on percentage (I do/ do not experience this stressor) and their associated burden if experienced (0 'no burden'—5 'high burden'). Finally, participants were asked to report on any positive effects of the pandemic (yes/no answer with option to elaborate on what positive effect if present) [18-20].

Part three inquired whether participants and housemates experienced COVID-19-related symptoms suggestive of an infection and the severity of these symptoms, as well as if they were tested for COVID-19 and the result of the test.

COVID-19 timeline and survey modifications

Each country reacted differently to the COVID-19 pandemic with restrictions and opportunities changing over time. A timeline with the number of COVID-19 infections and the most important events in the Netherland in 2020 is shown in Fig. 1. During the first months of the pandemic, testing facilities were only available in case hospitalization was needed and primary healthcare availability was limited due to lockdown restrictions. This period coincided with survey 1. From June 2020 on, access to both testing facilities and primary healthcare became available again across the country. Furthermore, barely any restrictions regarding the pandemic were present when survey 2 was sent. At the time of the last survey, new restrictions in the form of a soft lockdown were present and (self)testing on COVID-19 was widespread available. Because of these changes, slight modifications to questions concerning COVID-19 incidence and testing were made in survey 2 and 3 to fit the new situation, mostly concerning questions regarding testing of COVID-19 (Appendix 2 in supplementary material).

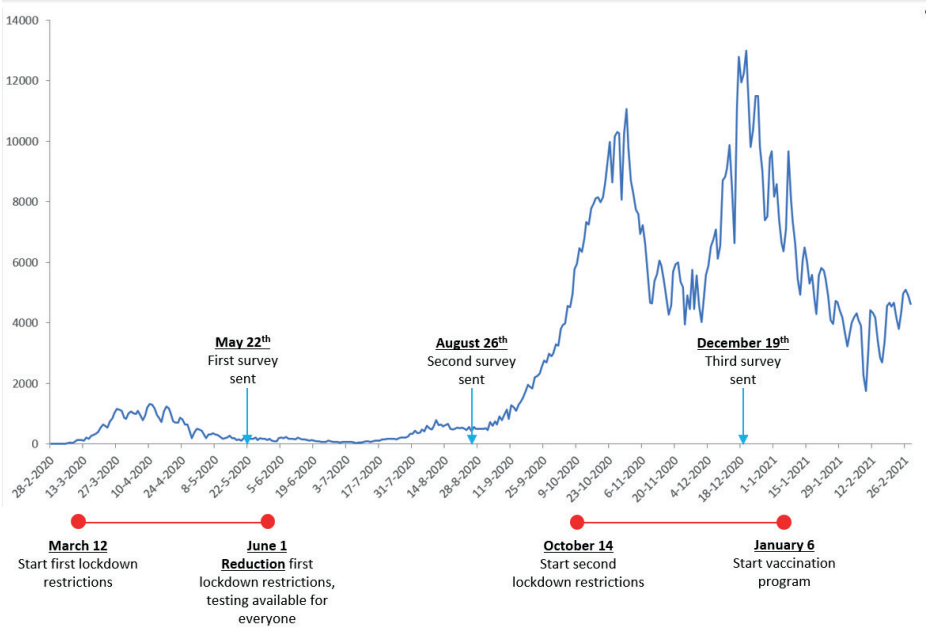

Figure 1. Timeline of the total reported number of cases of COVID-19 infections in the Netherlands during the first year of the pandemic, most important restrictions of the Dutch government, and timepoints of survey acquisition. [21] Dates are given as dd-mm-yyyy.

During survey 1, a large portion of the participants reported reduced physical activity in the comment sections of questions. Therefore, a question was added to capture this in survey 2 and 3.

Data availability and analysis

The data supporting the findings of this study are available on request from the Dutch FSHD registry. The data are not publicly available due to privacy or ethical restrictions [15].

Data were collected in CastorEDC [14]. Analysis of the data was done in R (R Foundation for Statistical Computing, Vienna, Austria) and SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Figures were created using GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, California USA).

Demographics, impact of the pandemic on care, and perceived psychosocial stress are reported using descriptive statistics. The received care pre-pandemic is reported as a pooled group of all unique patients across the three surveys. Data are reported as mean (SD) or median [IQR] depending on normality of the data. Pearson's chi-square was used to test for differences between FSHD patients and the non-FSHD housemates concerning COVID-19 infection rate and severity of the symptoms with a p value < 0.05 considered as statistically signifcant. These analyses were done using only data of survey 3, because for this survey, patients had to report on the whole period since the start of the pandemic, including the timespans of survey 1 and 2. Furthermore, for this comparison, only housemates ≥ 16 years were included.

Ethical approval and informed consent

This study involved clinical research that did not fall within the scope of the Medical Research Involving Human Subjects Act, as declared by the local Medical Ethics Review Committee of the Radboud university medical center (amendment of file 2015-1812 on April 15th 2020). All participants of the FSHD registry provided their written informed consent before they entered the registry. The registry and its databases are in concordance with the General Data Protection Regulation and all other acting laws.

RESULTS

Demographics and clinical features

Of the respectively 339, 341 and 343 invited patients for each for the three surveys, 210 (62%) completed the first, 186 (55%) the second, and 205 (60%) the third survey. In total, 261 participants completed at least one survey. The mean age per survey ranged from 54.6 (14.1) to 56.0 (14.5) years and 39–44% of the population was male (Table 1). Almost half of the participants in each survey (47.6% (S1), 49.5% (S2), and 46.8% (S3)) belonged to one or several risk groups for a severe course of COVID-19 when infected with the SARS-CoV-2 virus.

COVID-19 impact on received care, FSHD complaints, and physical activity

Pre-pandemic care was received by 86 (33%) participants across the three surveys, mostly consisting of care from their partner (18.4%) and/or homecare (12.6%) (Fig. 2). At the time of surveys 1 and 2, 41.7% and 40% of the patients receiving care reported a decrease in care received compared to pre-pandemic care, reducing to 28.8% at the time of survey 3. The following changes were most often reported: home care unavailable, physical therapy unavailable, care personnel having less time, and domestic help unavailable. This reportedly led to a higher burden for informal caregivers, more symptoms, and less activity in general. Although an increase in FSHD-related symptoms was reported by participants, the pre-pandemic MRS did not differ from the MRS at time of the survey [$p = 0.99$ (S1), $p = 0.99$ (S2), and $p = 0.90$ (S3)]. In surveys 2 and 3, 45% and 53% of the participants, respectively, were a little to a lot less active compared to before the pandemic.

Impact of the pandemic on perceived psychosocial stress

Compared to pre-pandemic perceived psychosocial stress (PSS), 44% (S1), 30% (S2), and 40% (S3) of the participants reported a little to a lot more stress. Nevertheless, the perceived stress scores were low, with a median PSS of 11 [6–16] (S1), 9 [6–15] (S2), and 10 [6–15] (S3) (Fig. 3). Stressors most often reported were 'loss of social contact' (86–91.4%) and 'COVID-19 related media coverage' (89.3–90.3%). The stressors that were most burdensome for FSHD patients were 'being unable to attend a funeral of a loved one' (3.06 (1.25) – 3.57 (1.16)) and 'being restricted in visiting family, friends or loved ones in the hospital' (3.03 (1.00) – 3.23 (1.16)) (Appendix 3 in supplementary material).

Table 1. Demographics by survey round.

	Survey 1 (22 May 2020)	**Survey 2 (26 Aug 2020)**	**Survey 3 (19 Dec 2020)**	**Non-FSHD Housemates**
N	210	186	205	204
Age, mean (SD)	54.6 (14.1)	56.0 (14.1)	55.7 (14.5)	49.9 (18.3)
Male	82 (39.0)	78 (41.9)	90 (43.9)	106 (52.0)
Living arrangement[a]				
Independent	169 (80.5)	155 (83.3)	170 (82.9)	
Home care or personal care budget	25 (11.9)	19 (10.2)	24 (11.7)	
Assisted living or care facility	7 (3.0)	5 (2.7)	5 (2.4)	
Other	9 (4.3)	7 (3.8)	6 (2.9)	
Risk factors severe COVID-19				
>70 years old	33 (15.7)	36 (19.4)	36 (17.6)	22 (10.7)
Respiratory problems	27 (12.9)	24 (12.9)	21 (10.2)	5 (2.5)
Chronic heart disease	18 (8.6)	15 (8.1)	12 (5.9)	7 (3.4)
Severely overweight[b]	7 (3.3)	5 (2.7)	6 (2.9)	6 (2.9)
Immunodeficient	7 (3.9)	7 (3.7)	6 (3.0)	1 (0.5)
Other	36 (17.1)	32 (17.2)	34 (16.6)	13 (6.4)
Relation				
Spouse				153 (75)
Parent				10 (5)
Child				14 (7)
Brother/Sister				2 (1)
Other				7 (3)
Missing				17 (8)

Data is shown as N (%) unless given otherwise.
a: Independent – living independently in their own home, by themselves or with their partner/family. Home care – care at home provided by an organization, consisting of healthcare, nursing, domestic help, and guidance in everyday life; Personal care budget - a budget provided by the government with which a patient can buy their own care or assistance; Assisted living or care facility: a house or institution in which the patient lives and is provided with daily care, such as a nursing home.
b: Severely overweight is self-reported, no exact BMI is known.

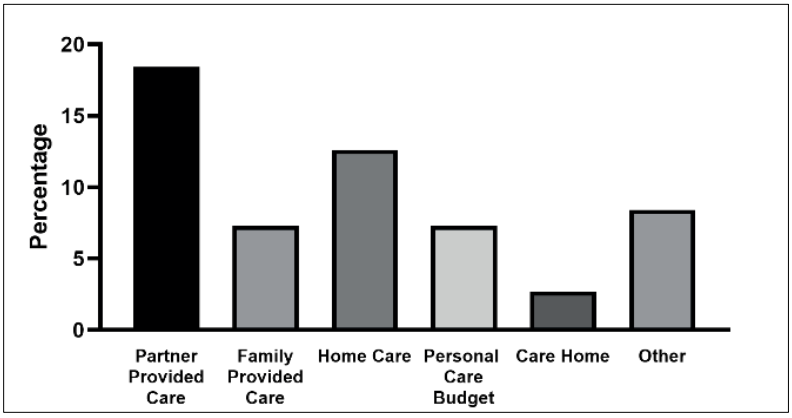

Figure 2. Types of care participants (N=86) reported to receive under normal circumstances.

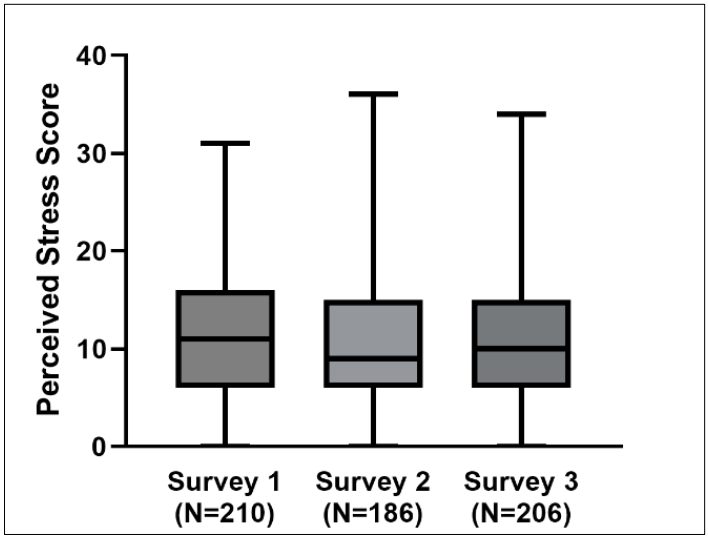

Figure 3. Perceived Stress Scale of participants from three consecutive survey rounds.
A total score of 0-13 is considered low stress, 14-26 moderate stress and 27-40 high stress.

Of the 261 unique responders across the three surveys, 86 (33%) reported that they received care before the COVID-19 pandemic. Partner provided care: partner of patient provides daily care; Family provided care: family provides daily care; Home care: care at home provided by an organization, consisting of healthcare, nursing, domestic help and guidance in everyday life; Personal care budget: a budget provided by the government with which a patient can buy their own care

or assistance; Care home: a house or institution in which the patient lives and is provided with daily care, such as a nursing home.

Positive effects of the pandemic were reported by 32.4% (S1), 26.3% (S2), and 27.8% (S3) of the participants. The most often reported positive effects were fewer social obligations and more time to rest resulting in less pain, less fatigue, less stress, and the opportunity to spend more time with their partners and children.

Comparison FSHD patients and their housemates

In survey 3, 216 housemates were reported on of which 12 housemates were also FSHD patients, resulting in 204 non-FSHD housemates (Table 1). The housemates were significantly younger compared to the FSHD patients [49.9 (18.3) vs. 55.7 (14.5) years old, $p < 0.001$]. The majority of the housemates were the spouse of the FSHD patients (n=153, 75%), followed by their children (n=14, 7%) and parents (n=10, 5%). FSHD patients had more possible COVID-19-related symptoms (38% (n = 80) vs 27% (n = 55), $\chi^2 = 6.73$, p = 0.012). No differences were found in the number of patients and housemates that were tested [34% (n=70) vs 36% (n=74), χ^2=0.203, p=0.68] or tested positive [3% (n = 6) vs. 2% (n = 4), χ^2=0.558 p = 0.53] (Fig. 4). The severity of possible COVID-19-related symptoms differed significantly between patients and their housemates (N=135, χ^2=9.11, p=0.03) (Fig. 5)

DISCUSSION

This study investigated the impact the COVID-19 pandemic had on FSHD patients and the incidence of COVID-19 infections in the Netherlands. The COVID-19 pandemic reduced available care, physical activity, and increased the psychosocial stress in FSHD patients. The COVID-19 infection rate in FSHD patients did not differ from their housemates without FSHD, but they did report more symptoms of minimal severity.

Results are based only on survey 3

FSHD patients reported significantly more possible COVID-19 related symptoms (38.5% vs 27.4%, $\chi 2=5.68$, $p=0.017$). There was no difference between the number of tested participants (regardless of positive or negative result) (33.3% vs 35.5%, $\chi 2=0.219$, $p=0.639$) and number of positive tests (2.8% vs. 2.0%, $\chi 2=0.40$ $p=0.527$).

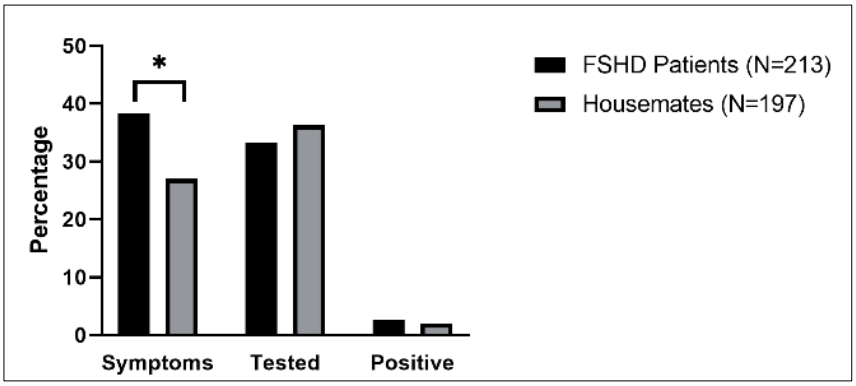

Figure 4. Comparison of possible COVID-19 symptoms, being tested at least once (whether the test was positive or negative) and number of positive tests in FSHD patients versus their housemates

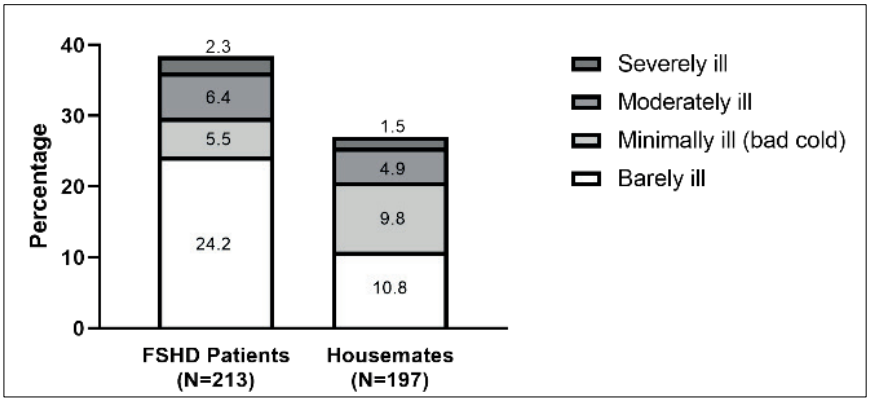

Figure 5. Severity of possible COVID-19 related symptoms in FSHD patients compared to their housemates. The severity differed significantly between the two groups ($N=136$, $\chi 2=10.34$, $p=0.016$).

At surveys 2 and 3, nearly 50% of the patients reported to be less active during the pandemic than before. This is a considerable difference with findings in the general population, where no decline of physical activity was observed [22]. We hypothesize that people without physical challenges can easily change to outdoor activities, which may be harder to do for patients with FSHD or other

NMDs. Since physical activity is known to be an important factor to stay in shape for FSHD patients, it is important to educate and support patients in maintaining their levels of physical activity during another pandemic. Even though face-to-face interactions are preferred by patients, during a pandemic, this might not be possible and telemedicine approaches should be considered for the continuity of physical therapy and rehabilitative care [23-25].

Patients reported to have more psychosocial stress than before the pandemic. This was not reflected by the PSS scores reported in our study, which were low compared to worldwide studies in the general population as well in NMD patients during the pandemic (PSS scores of 15.4 to 17.4) [13, 26, 27]. However, similarly low PSS scores were also reported from the general population in the Netherlands in the same time during the pandemic [22]. The lower stress scores might be due to a higher social security and relatively mild course of the pandemic in the Netherlands compared to other countries. Studies with longer follow-up periods will need to confirm if the stress levels of patients normalize to pre-pandemic levels.

The most prevalent and most burdensome stressors in our study were similar to stressors in healthy individuals (DYNACore-C) and in Parkinson's patients, indicating that the stressors perceived by FSHD patients were not disease-specific [19, 28]. Findings from large studies on these stressors such as the DYNACore-C may therefore be applicable to FSHD patients, which might help with creating therapies to cope with these stressors. Interestingly, more than 25% of the FSHD patients from each survey reported various positive effects of the pandemic, for instance being well rested. A more detailed, possibly qualitative, follow-up on what these positives effects were may help us to improve the quality of life of FSHD patients within as well as outside of a pandemic period.

We did not find a difference in infection incidence rates between FSHD patients and their non-FSHD housemates. One international study in 1243 NMD patients reported a higher infection rate of 8% compared to our findings, but only a minority of those infections (20%) were found in European patients bringing it more in line with our incidence rate [3]. Another international study mentioned an infection incidence of <1% but lacked details [13]. Our data did show a higher incidence of possible COVID-related symptoms in FSHD patients compared to their housemates. However, we suspect that this is due to reporting bias as recalling one's own minimal symptoms is different from identifying and recalling when housemates experienced such symptoms. We also suspect that the higher number of minimal

symptoms in the FSHD patients caused the difference in severity of symptoms between the patients and their housemates.

Due to the limitations of social distancing and lockdowns as well as the lack of contact details of participants' spouses in the registry and limitations in the survey system, the study was limited to data reported by the registry participants, including the data about the housemates. Therefore, a drawback of this method is that the data on housemates is secondhand information and might be more biased. In addition, although we did inquire about the exposure by asking participants about measures taken, we failed to ask about the situation of the housemates. Therefore, we cannot rule out possible exposure differences between participants and housemates.

This study assessed the changes in health(care) during the pandemic. The healthcare system changed after the pandemic, most noticeably in the higher frequency of telemedicine approaches. A study comparing pre- and post-pandemic healthcare received and the satisfaction regarding the new telemedicine approach would be interesting to perform.

Conclusion

This study showed that care received, physical activity, and perceived psychosocial stress were negatively impacted by the COVID-19 pandemic. Although an increase in FSHD complaints was reported by participants, the pre-pandemic MRS did not differ from the MRS at time of the survey. We did not find evidence for a different susceptibility to COVID-19 infections in FSHD patients compared to the control group and differences in the number and severity of possible COVID-19-related symptoms could well be attributable to reporting bias. Since the COVID-19 pandemic is characterized by cyclical outbreaks and given the possibility for other future pandemics, an adequate approach for the support and continuity of care of these patients is essential

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SUPPLEMENTARY DATA

Appendix 1. COVID-19 survey English version 1

FSHD Corona English version

Corona - your situation and occupations
Be careful, do not write down any traceable information

1.1 How is your living situation?
○ Independently
○ Independently with home care or care facilitated by a personal care budget
○ Assisted living (including Fokus)
○ In a care institution
○ Other,…

1.1.1 Describe your other living situation please

1.2 How many people are living in your household, including yourself?

1.3 Are you active in a 'vital job' according to the government rules?
○ No
○ I do not know
○ I do not want to answer
○ Yes, but I am not working
○ Yes and I am working

1.4 Which description suits you (multiple answers possible)?
○ (High) school pupil
○ Studying at a high education facility
○ Independent contractor without staff
○ Independent contractor with staff
○ Under employment
○ Stay-at-home-parent (fulltime or most of the time)
○ Volunteer
○ Retired
○ Unable to work
○ Unemployed
○ Other,…

1.4.1 Please describe your situation

1.5 Do you use personal care on a regular basis, under normal circumstances?
○ Yes
○ No

1.5.1 How is your personal care normally organised?
○ My partner/ residential family or housemates take care of me
○ My family and friends take care of me
○ I receive home care
○ I arrange my personal care via a personal care budget
○ The institution which I am living in arranges my personal care
○ Other, …

1.5.1.1 Please describe your other personal care

1.5.2 Does the personal care differ during the Corona crisis versus normal circumstances?
○ Yes
○ No

1.5.2.1 Describe the changes and consequences in your personal care since the Corona outbreak

Corona- Measurements
2.1 Which of the following alterations did you make due to the Corona outbreak?
○ Staying at home/ working from home
○ 1,5m distance
○ Frequently washing hands with soap
○ Coughing and sneezing in the inner side of the elbow
○ Using paper towels
○ Letting others do your groceries
○ Being in a room with a maximum of two people
○ Using personal protective equipment such as masks, gloves etc.
○ Other,…

2.1.1 Which other measurement did you make?

2.2 Do you consider yourself to be part of one or more risk groups?
○ 70 years old or older
○ Adult with respiratory illness under the treatment of a doctor
○ Adult with chronical heart disease under treatment of a cardiologist
○ Adult with poorly managed diabetes or

diabetes with complications
○ Adult on dialysis or with a donor kidney
○ Adult with diminished immune response against infections caused by medication in connection with auto-immune disease
○ Adult with organ or stem cell transplantation
○ Adult with diminished immune response due to blood diseases
○ Adult with diminished immune response due to spleen removal or disfunction of the spleen
○ Adult with severe immune disfunction, which are treated
○ Adult with cancer, which is treated in the past 3 months with radiation or chemotherapy
○ Adult with HIV infection
○ Adult with severe obesity
○ Other,…
○ No, I do not subject to a risk group

2.2.1 Describe in which other risk group you are, please

2.3 Have you been in voluntary quarantine?
○ Yes
○ No

2.3.1 Please describe your quarantine measurements?

2.3.2 Since when have you been quarantining?

2.4 What are your personal reasons to leave your home (multiple answers are possible)?
○ Going to work
○ Walking my pet
○ Exercise (like jogging or playing sports)
○ Buying groceries for myself or family
○ Going to a pharmacy, hospital or doctor
○ Taking care of others
○ Meeting with friends or family
○ To prevent boredom
○ I just go outside if I want to
○ No particular reason
○ Other, …

2.4.1 Please describe your other reasons to leave your house

2.3.4 Did you stop quarantining in the meantime?
○ Yes
○ No

2.3.3.1 When did you stop quarantining?

2.5 Do you have personal protective equipment (gloves, masks, protective glasses, apron)?
○ No and I do not need them
○ No, but I need them
○ Yes, partly
○ Yes, I have everything I need

2.5.1 Why do you need protective equipment?
○ Because I receive care in my close surrounding
○ Because I have a cold or I am ill
○ Because I have Corona
○ Because I belong to a risk group

2.5.1.1 Please describe why you need protective equipment

Corona - effects and your experience

3.1 How much stress did you experience during the Corona outbreak?
○ Substantially less stress than usual
○ Little less stress than usual
○ As much stress as usual
○ A bit more stress than usual
○ Substantially more stress than usual

How threatening did you find the Corona virus….

3.2 … for yourself?
○ Not threatening at all
○ Not that threatening
○ A little threatening
○ Threatening
○ Really threatening
○ No opinion

3.3 … for your health?
○ Not threatening at all
○ Not that threatening
○ A little threatening
○ Threatening
○ Really threatening
○ No opinion

3.4 … for the health of your family?
○ Not threatening at all
○ Not that threatening
○ A little threatening
○ Threatening
○ Really threatening
○ No opinion

3.5 … for the health of your friends?
○ Not threatening at all
○ Not that threatening
○ A little threatening
○ Threatening

○ Really threatening
○ No opinion

Below, you will find situations in which people could find themselves due to the Corona pandemic. Could you declare if you currently experience or have experienced any of the situations listed down below, and how inconvenient the situation is/was?

3.6 Having Corona symptoms or symptoms that could be related to Corona.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.7 Corona symptoms or symptoms related to Corona in family members, friends, loved ones or colleagues.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.8 Being at increased risk for an infection (e.g., at work).
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.9 Being at increased risk for a serious course of the disease in case of an infection (belonging to a so-called 'risk group').
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.10 Family, friends, or loved ones being at increased risk for a serious course of the disease in case of an infection (they belong to a so-called 'risk group').
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.11 Problems with access to healthcare, medication, or sanitation.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.12 (Feeling) restricted to leave your home.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.13 Loss of social contact and social events.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.14 Family, friends, or loved ones are at the hospital and you are restricted in visiting them.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.15 Unable to attend a funeral of a family member, friend, or loved one.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.16 Having family, friends or loved ones with a vital profession.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient

○ Really inconvenient

3.17 Not being able to perform leisure activities.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.18 Difficulties combining work with childcare.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.19 Tensions at home or family conflict
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.20 Work-related delays/obstacles.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.21 (Threat of) job loss or insolvency of private company.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.22 Problems obtaining basic needs.
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.23 Corona-related media coverage
○ This situation did not occur
○ Not inconvenient
○ Barely inconvenient
○ Somewhat inconvenient
○ Decently inconvenient
○ Really inconvenient

3.24 Does the Corona outbreak have positive consequences for you?
○ Yes
○ No

3.24.1 What positive consequences do you experience?

3.25 How often have you been upset because of something that happened unexpectedly over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.26 How often have you felt that you were unable to control the important things in your life over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.27 How often have you felt nervous and stressed, over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.28 How often have you felt confident about your ability to handle your personal problems over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.29 How often have you felt that things were going your way over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.30 How often have you found that you could not cope with all the things that you had to do, over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.31 How often have you been able to control irritations in your life over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.32 How often have you felt that you were on top of things over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.33 How often have you been angered because of things that happened that were outside of your control l over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

3.34 How often have you felt difficulties were piling up so high that you could not overcome them over the last two weeks?
○ Never
○ Almost never
○ Sometimes
○ Fairly often
○ Very often

Corona- Have you been ill?

4.1 Did you experience the following symptoms, since the start of the Corona outbreak mid-February in the Netherlands?
○ Dry coughing without mucus
○ Coughing with mucus
○ Taste loss
○ Smell loss
○ Flu-like feeling
○ Dizziness
○ Extra exhaustion (more than normal)
○ Feverishness
○ Fever (38 or higher)
○ Headache
○ No appetite
○ Nausea
○ Muscle pain
○ Short of breath
○ Breathing tightness
○ Squeaking breathing
○ Pain in the lungs / with breathing
○ Sore throat
○ Stuffed nose
○ Vomiting
○ Ear pain
○ Eye infection
○ Other, …
○ No symptoms

4.1.1 What other symptoms did you experience?

4.1.2 When did you first get these symptoms (please estimate the date if you don't know precisely)

4.1.3 How bad were your symptoms?
○ Minimal symptoms
○ Few symptoms, having a severe cold but not sick
○ Ill
○ Severely ill

4.2 Were you in contact with someone who presumably has Corona?
○ Yes
○ No

4.1.4 Do you think you have/had Corona?
○ Yes
○ No
○ Maybe

4.3.1 Where do you expect your contamination came from?
○ Yes
○ No

4.3.1.1 Please describe how you were infected (do not report any traceable information)

4.3.2 Did a doctor tell you that you (probably) have Corona/COVID-19 infection?
○ Yes
○ No

4.3.3 Are/ Were you in quarantine?
○ No
○ Yes, at home
○ Yes, in the hospital
○ Other, …

4.3.3.1 Describe your other situation with regard to quarantine, please

4.3.4 What medication (prescribed or not) did you take because of Corona?
○ None
○ Paracetamol
○ Antibiotics
○ Other, …

4.3.4.1 What other medication?

4.3.2.1 Did you get tested for Corona?
○ Yes
○ No
○ I don't know

4.3.2.1.1 When did you test for Corona? (please estimate the date if you don't know precisely)

4.3.2.1.2 How was the test carried out?
○ With a q-tip in the nose
○ With a q-tip in the mouth
○ Via blood test
○ Other, …

4.3.2.1.3 What was the test result?
○ Positive (Corona)
○ Negative (no Corona)
○ Haven't received a result yet
○ I don't know

4.3.2.2 Were you hospitalized?
○ Yes
○ No

4.3.2.2.1 When were you hospitalized? (please provide an estimation if you don't know precisely)

4.3.2.2.2 Are/were you admitted to the ICU?
○ Yes
○ No

4.3.2.2.3 Was your breathing aided?
○ Yes, with oxygen
○ Yes, with a ventilation machine
○ No
○ Other, …

4.3.2.2.3.1 Please describe your other situation with regard to aided breathing

4.3.2.2.4 Were you discharged?
○ Yes
○ No

4.3.2.2.4.1 What is the discharge date? (please estimate the date if you don't know precisely)

4.3.5 Did you recover from the infection and are you in the same condition you were before Corona?
○ Yes, fully recovered
○ No, still recovering
○ No, still ill
○ Other, …

4.3.5.1 Please describe your situation with regard to your recovery (do not use any traceable information)

4.3.6 How many days have you been ill, since the first symptoms?

4.4 What score describes your situation JUST BEFORE the Corona outbreak the best?

This is a standard score which isn't made specially for FSHD patients. This could mean that the descriptions doesn't match your situation exactly. Please pick the option which fits your situation the best.
○ No symptoms
○ No significant disability, despite some symptoms; able to carry out all usual duties and activities
○ Slight disability; unable to carry out all every-day activities, but able to look after own affairs without assistance
○ Moderate disability; requiring some help, but able to walk without assistance
○ Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
○ Severe disability; bedridden, incontinent and requiring constant nursing care and attention

4.5 What score describes your situation AT THE MOMENT the best?
○ No symptoms
○ No significant disability, despite some

symptoms; able to carry out all usual duties and activities
- ○ Slight disability; unable to carry out all every-day activities, but able to look after own affairs without assistance
- ○ Moderate disability; requiring some help, but able to walk without assistance
- ○ Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- ○ Severe disability; bedridden, incontinent and requiring constant nursing care and attention

This is a standard score which isn't made specially for FSHD patients. This could mean that the descriptions doesn't match your situation exactly. Please pick the option which fits your situation the best.

4.6 Do you think Corona effects/ effected your FSHD symptoms?
- ○ Yes
- ○ No
- ○ I don't know

4.7 Explain your answer, please.

4.8 Do you want to share other experiences with regards to Corona?
- ○ Yes
- ○ No

4.8.1 Note the experience you want to share, please.

Corona - Housemate 1-6
Down below are questions about your housemates (a maximum of six). You have more than six housemates. Please answer the questions for the six housemates you are the closest in contact with.

5.1 What age is your housemate?

5.2 What is your housemates sex distribution?
- ○ Male
- ○ Female
- ○ Other, …

5.3 Can you ask your housemate how tall he/she is?
- ○ Yes
- ○ No

5.3.1 Length

5.4 Can you ask your housemate what their weight is?
- ○ Yes
- ○ No

5.4.1 Weight

5.5 What is your relationship to your housemate?
- ○ My partner
- ○ My parent
- ○ My kid
- ○ My sister/brother
- ○ Other family member
- ○ Other, …

5.5.1 What is your other relationship to your housemate?

5.6 How often is your housemate at home?
- ○ Whole week
- ○ In the weekends, during the week lives my housemate somewhere else
- ○ During the week, in the weekends live my housemate somewhere else
- ○ Other, …

5.6.1 Please describe what part of the week your housemate is at home.

5.7 Is your housemate part of one or more risk groups?
- ○ 70 years old or older
- ○ Adult with respiratory illness under the treatment of a doctor
- ○ Adult with chronical heart disease under treatment of a cardiologist
- ○ Adult with poorly managed diabetes or diabetes with complications
- ○ Adult on dialysis or with a donor kidney
- ○ Adult with diminished immune response against infections caused by medication in connection with auto-immune disease
- ○ Adult with organ or stem cell transplantation
- ○ Adult with diminished immune response due to blood diseases
- ○ Adult with diminished immune response due to spleen removal or disfunction of the spleen
- ○ Adult with severe immune disfunction, which are treated
- ○ Adult with cancer, which is treated in the past 3 months with radiation or chemotherapy
- ○ Adult with HIV infection
- ○ Adult with severe obesity

○ Other,…
○ No, my housemate doesn't fall into a risk group

5.7.1 Please describe in what other risk group your housemate part of.

5.8 Does your housemate have FSHD?
○ Yes
○ No
○ I don't know

5.8.1 Does your housemate fill in this questionnaire himself/herself (as member of the registry)?
○ Yes
○ No

5.9 Did your housemate experience one of these symptoms down below, since the start of the Corona outbreak in The Netherlands mid-February?
○ Dry cough without mucus
○ Cough with mucus
○ Taste loss
○ Smell loss
○ Flu-like feeling
○ Dizziness
○ Extra exhaustion (more than normal)
○ Feverishness
○ Fever (38 or higher)
○ Headache
○ No appetite
○ Nausea
○ Muscle pain
○ Short of breath
○ Breathing tightness
○ Squeaking breathing
○ Pain in the lungs/ with breathing
○ Sore throat
○ Stuffed nose
○ Vomiting
○ Ear pain
○ Eye infection
○ Other, …
○ No symptoms

5.9.1 What other symptoms did your housemate experience?

5.9.2 When did your housemate first experience any of these symptoms? Please estimate the date if you don't know precisely.

5.9.3 How bad were the symptoms of your housemates?
○ Minimal symptoms
○ Few symptoms, having a severe cold but not sick
○ Sick
○ Severely sick

5.10 Was your housemate in contact with someone with Corona?
○ Yes
○ No

5.9.4 Do you think your housemate has/had Corona?
○ Yes
○ No
○ Maybe

5.11.1 Where does your housemate expect this contamination came from?
○ Yes
○ No

5.11.1.1 Please describe how he/she got infected. (do not use any retraceable information)

5.11.2 Did a doctor tell your housemate that he/she (probably) has Corona/COVID-19 infection?
○ Yes
○ No

5.11.3 Is/ Was your housemate in quarantine?
○ No
○ Yes, at home
○ Yes, in the hospital
○ Other, …

5.11.3.1 Describe your housemates other situation with regard to quarantine, please

5.11.4 What medicine (prescribed or not) did your housemate take because of Corona?
○ None
○ Paracetamol
○ Antibiotics
○ Other, …

5.11.4.1 What other medicine?

5.11.2.1 Did your housemate get tested for Corona?
- ○ Yes
- ○ No
- ○ I don't know

5.11.2.1.1 When did your housemate get tested for Corona? (please estimate the date if you don't know precisely)

5.11.2.1.2 How was the test carried out?
- ○ With a q-tip in the nose
- ○ With a q-tip in the mouth
- ○ Via blood test
- ○ Other, …

5.11.2.1.2.1 Describe how the test was carries out, please

5.11.2.1.3 What was the test result?
- ○ Positive (Corona)
- ○ Negative (no Corona)
- ○ Haven't received a result yet
- ○ I don't know

5.11.2.2 Was your housemate hospitalized?
- ○ Yes
- ○ No

5.11.2.2.1 When did your housemate get hospitalized? (please estimate if you don't know precisely)

5.11.2.2.2 Is/was your housemate hospitalized at the IC?
- ○ Yes
- ○ No

5.11.2.2.3 Does/did your housemate get artificial respiration?
- ○ Yes, oxygen
- ○ Yes, respiration
- ○ No
- ○ Other, …

5.11.2.2.3.1 Describe the other situation with regard to artificial respiration, please

5.11.2.2.4 Did your housemate leave the hospital in the meantime?
- ○ Yes
- ○ No

5.11.2.2.4.1 When did your housemate leave the hospital? (please estimate the date if you don't know precisely)

5.11.5 Did you recover from the infection and are you in the same condition you were before Corona?
- ○ Yes, fully recovered
- ○ No, still recovering
- ○ No, still sick
- ○ Other, …

5.11.5.1 Describe the situation with regard to his/her recovery, please. (don't use any retraceable information)

5.11.6 How many days has your housemate been sick, since the first symptoms?

5.12 What score describes your housemates situation JUST BEFORE the Corona outbreak the best?

This is a standard score which isn't made specially for FSHD patients. This could mean that the descriptions doesn't match your situation exactly. Please pick the option which fits your situation the best.
- ○ No symptoms
- ○ No significant disability, despite some symptoms; able to carry out all usual duties and activities
- ○ Slight disability; unable to carry out all every-day activities, but able to look after own affairs without assistance
- ○ Moderate disability; requiring some help, but able to walk without assistance
- ○ Moderatelysevere disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- ○ Severe disability; bedridden, incontinent and requiring constant nursing care and attention

5.13 What score describes your housemates situation AT THE MOMENT the best?
- ○ No symptoms
- ○ No significant disability, despite some symptoms; able to carry out all usual duties and activities
- ○ Slight disability; unable to carry out all every-day activities, but able to look after own affairs without assistance
- ○ Moderate disability; requiring some help, but able to walk without assistance

- ○ Moderatelysevere disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- ○ Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- ○ This is a standard score which isn't made specially for FSHD patients. This could mean that the descriptions doesn't match your situation exactly. Please pick the option which fits your situation the best.

5.8.2 Do you think Corona effects/ effected your housemates FSHD symptoms?

- ○ Yes
- ○ No
- ○ I don't know

5.8.2.1 Explain your answer, please.

5.14 Does your housemate want to share other experiences with regards to Corona?

- ○ Yes
- ○ No

5.14.1 Note the experience your housemate wants to share, please.

Concluding questions and complement

11.1 Do you want to share any important information about the corona infection or something else?

11.2 What question would you want to ask other participants of the registration?

11.3 Do you have any comments about the questionnaire?

Be careful, it is important that there are no names or other retractable information listed in the questionnaire. Is this the case, please change that before sending the questionnaire. Many thanks.

Dear participants, thank you for your time and participation for this research. We appreciate it a lot.
We would like to point out our second questionnaire, which is send to you about other illnesses besides your FSHD and vaccinations. Your answers to that questionnaire are necessary to translate your answers about Corona into results. We hope that you would fill in that questionnaire as well.

On behalf of the FSHD registration team, Wiecke van de Put, Hanneke Deenen, Anna Greco and Baziel van Engelen.

Appendix 2. Questions added to surveys 2 and 3.

Questions added to Survey 2 and 3.
- Did you complete a previous Corona questionnaire?

o I completed a previous questionnaire
o I am answering this questionnaire for the first time

- Who fills in this questionnaire?
o Me
o Spouse or family
o Other,…

- Who is this other?

- What is your length in cm?

- What is your weight in kg?

- Is this domestic care or (also) personal care?
o Domestic care
o Also personal care (possibly combined with domestic care)

- Was it a voluntary isolation?
o Voluntary isolation
o Mandatory
o Other

- Describe other isolation situation

- How much bodily exercise did you have during the Corona outbreak?
o Substantially less bodily exercise than usual
o Little less bodily exercise than usual
o As much bodily exercise as usual
o A bit more bodily exercise than usual
o Substantially more bodily exercise than usual

- Who carried out the test?
o Test street
o General practitioner
o Night/emergency center for general practice
o Municipal medical assistance organisation
o Regional medical assistance organisation
o Hospital
o Selftest
o Commercial party
o Do not know

Questions added to Survey 3.
- Did you get tested for Corona since the start of the pandemic (early 2020)?
o Yes
o No
o I don't know

- How often were you tested since the start of the pandemic (early 2020)?

- How often was the test positive since the start of the pandemic (early 2020)?

- Was this a re-contamination?
o Yes
o No
o I don't know

- When were you tested the first time and the test result was positive since the start of the pandemic (early 2020)?

- When were you tested the second time and the test result was positive since the start of the pandemic (early 2020)??

- When did you last tested positive since the start of the pandemic (early 2020)?

Questions regarding housemates
- How often was your housemate tested since the start of the pandemic (early 2020)?
- How often was the test positive since the start of the pandemic (early 2020)?
- Was this a re-contamination?
o Yes
o No
o I don't know

- When did your housemate get tested and the test result was positive for the first time since the start of the pandemic (early 2020)?
- When did your housemate get tested the second time and the test result was positive since the start of the pandemic (early 2020)?
- When did your housemate get the last positive test since the start of the pandemic (early 2020)

Appendix Table A1. Frequencies and burden of COVID-19 related stressors.

Stressor	Frequency, N(%)		
	S1	S2	S3
Having COVID-19 symptoms or symptoms that could be related	48 (22.9)	40 (21.5)	52 (25.4)
Having COVID-19 symptoms or symptoms that could be related, in family members, friends, loved ones or colleagues	72 (34.3)	62 (33.3)	101 (49.3)
Being at risk for an infection (e.g. at work, in the supermarket)	117 (55.7)	108 (58.1)	127 (62.0)
Being at risk for a serious course of the disease in case of a COVID-19 infection	97 (46.2)	78 (41.9)	109 (53.2)
Family, friends or loved ones being at risk for a serious course of the disease in case of a COVID-19 infection	133 (63.3)	89 (47.8)	116 (56.6)
Problems with access to healthcare, medication or sanitation	112 (53.3)	100 (53.8)	110 (53.7)
Feeling restricted to leave your home	156 (74.3)	113 (60.8)	138 (67.3)
Loss of social contact and social events [a]	192 (91.4)	160 (86.0)	183 (89.3)
Family, friends or loved ones are at the hospital and you are restricted in visiting them [b]	129 (61.4)	105 (56.5)	129 (62.9)
Unable to attend a funeral of a loved one [b]	59 (28.1)	62 (33.3)	66 (32.2)
Family, friends or loved ones working in vital professions	103 (49.0)	103 (55.4)	108 (52.7)
Less physical activity than usual	141 (67.1)	117 (62.9)	144 (70.2)
Difficulties combining work with childcare	17 (8.1)	12 (6.5)	14 (6.8)
Tensions at home or family conflict	68 (32.4)	57 (30.6)	55 (26.8)
Increased workload or work-related obstacles	55 (26.2)	38 (20.4)	53 (25.9)
(Threat of) job loss, insolvency of a private company, for yourself or someone in your household	20 (9.5)	18 (9.7)	13 (6.3)
Problems obtaining basic needs and services	81 (38.6)	57 (30.6)	66 (32.2)
COVID-19 related media coverage [a]	189 (90.0)	168 (90.3)	183 (89.3)

A: Stressors which had the highest frequency. B: Stressors which had the highest burden. S1 = Survey 1. S2= Survey 2. S3= Survey 3.

Median burden [IQR]			Mean burden (SD)		
S1	**S2**	**S3**	**S1**	**S2**	**S3**
3 [2-4]	3 [2-3]	3 [1-3]	2.87 (1.12)	2.55 (1.08)	2.61 (1.25)
3 [2-3]	3 [2-3]	3 [2-3]	2.79 (1.15)	2.55 (1.07)	2.63 (1.12)
3 [2-3]	3 [2-3]	3 [1-3]	2.77 (1.00)	2.54 (1.09)	2.47 (1.10)
3 [2-4]	3 [2-4]	3 [2-4]	3.17 (1.19)	2.85 (1.30)	2.92 (1.29)
3 [3-4]	3 [2-4]	3 [2-4]	3.21 (1.18)	2.93 (1.19)	2.90 (1.32)
3 [1-3]	3 [2-3]	3 [1-3]	2.56 (1.24)	2.49 (1.09)	2.46 (1.22)
3 [1-4]	2 [1-3]	3 [1-3]	2.56 (1.28)	2.39 (1.08)	2.54 (1.21)
3 [2-4]	3 [2-4]	3 [3-4]	2.89 (1.20)	2.81 (1.09)	3.17 (1.06)
3 [3-4]	3 [3-4]	3 [2-4]	3.23 (1.16)	3.03 (1.00)	3.19 (1.21)
4 [3-4]	3 [2-4]	4 [2-4]	3.57 (1.16)	3.06 (1.25)	3.27 (1.26)
2 [1-3]	2 [1-3]	2 [1-3]	2.43 (1.13)	2.20 (1.05)	2.31 (1.00)
3 [2-4]	3 [2-3]	3 [2-4]	2.87 (1.13)	2.74 (1.08)	2.81 (1.14)
2 [1-3]	3 [1-4]	3 [1-3]	2.06 (1.09)	2.75 (1.29)	2.57 (1.22)
2 [1-3]	2 [1-3]	2 [1-3]	2.10 (1.07)	2.26 (1.17)	2.36 (1.16)
2 [1-3]	3 [2-4]	2 [1-3]	2.27 (1.22)	2.81 (1.27)	2.28 (1.04)
3 [1-4]	3 [2-3]	4 [2.5-4]	2.70 (1.45)	2.44 (0.98)	3.38 (1.33)
2 [1-3]	2 [1-3]	2 [1-3]	2.35 (1.11)	2.11 (1.03)	2.23 (1.05)
2 [1-3]	2 [1-3]	2 [1-3]	2.34 (1.14)	2.21 (1.19)	2.38 (1.16)

Chapter 10

General discussion

This discussion starts with a narrative summary of the empirical results described in the previous chapters. Subsequently, the findings are discussed in light of the current knowledge of the epidemiology of neuromuscular disorders.

NARRATIVE SUMMARY OF THE RESULTS

Neuromuscular disorders in the literature

In 1991, Emery published the first two surveys of the world literature with population frequencies of various inherited neuromuscular disorders (NMDs) [1, 2]. Two and a half decades later, we searched the literature for peer-reviewed articles on the descriptive epidemiology of NMDs published from **1990 to 2014**. Pubmed search terms were 'incidence' and 'prevalence' for 30 disorders. The results were reported in **Chapter 2**. We found incidence rates for 11 NMDs ranging from 0.05 to 9 per 100,000 population per year. No reports on incidence rates were observed for the other 19 disorders. For post-polio syndrome and Charcot-Marie-Tooth disease, we found prevalence rates higher than 10 per 100,000. For 18 other disorders, the prevalence rates were between 1 and 10 per 100,000 population, and four lower than 1 per 100,000. For six disorders, no prevalence rates were presented. On four disorders, no incidence or prevalence information were available at all.

We were able to compare the prevalence rate of ten NMDs with those found by Emery. Three showed stable prevalence estimates over time. Four appeared to have been increased substantially, although the ranges of both observations showed considerable overlap. Our overview yielded nine previously unreported prevalence rates and 11 incidence rates. However, four disorders still remained without any estimates. The sum of the available prevalence rates comprises only the tip of the iceberg, but is already in range with the prevalence of Parkinson's disease. Although individual NMDs are rare, as a group they are not.

With the aim to provide accurate and useful epidemiological information for patients, clinicians, health care managers and researchers, we supplemented the overview in the previous chapter with findings from 26 articles and eight meta-analyses published in the years **2014 to 2023** (**Chapter 3**). We identified prevalence rates for 17 disorders. The rates ranged from 0.3 per 100,000 population for Lambert-Eaton myasthenic syndrome, glycogenosis type 5 and nemaline myopathy to 20 per 100,000 for Charcot-Marie-Tooth disease type 1. We calculated annual incidence rates for eight disorders, ranging from 0.3 per 100,000 population for progressive (spinal) muscular atrophy and facioscapulohumeral muscular atrophy to 1 per 100,000 for Charcot-Marie-Tooth disease type 1 and myotonic dystrophy type 1. This paper showed once again that epidemiological frequencies about neuromuscular diseases are scarce - in particular data on incidence. The mean prevalence estimates based on recently published studies on individual cohorts correspond well with the findings from the sparingly performed meta-analyses.

In Table 1, the expansion of the reported NMD occurrence rates over time that we published in 2015 and 2024, and described in **Chapters 2 and 3**, is summarized. It allows easy access, rapid reference and comparison of the current prevalence and incidence rates.

Table 1 (next page). Summary of prevalence and incidence rates reported in this dissertation.

This table shows the availability and level of the incidence and prevalence rates for a range of NMDs, with Emery's knowledge from 1990 serving as the basis. In this thesis, we added a number of predominantly incidence rate estimates.

	Emery, 1991(2 reviews)	Deenen, 2014 (study)	Deenen, 2015 (review)	Deenen, 2025 (review)	Emery, 1991 (review)	Deenen, 2014 (study)	Deenen, 2015 (review)	Deenen, 2025 (review)	Deenen, 2024 (study)
Anatomical location **Disorder**	**prevalence rateper 100,000 population**				**incidence rateper 100,000 population**				
Anterior horn cells									
Spinal muscular atrophy	1.2		2		4.8		9		
Progressive (spinal) muscular atrophy*				0.5				0.3	0.5
Amyotrophic lateral sclerosis	4.16		5				2		
Post-polio syndrome			60						
Peripheral nerves									
Hereditary motor and sensory neuropathies*	10		20	20				1	
type 1				10					0.5
type 2				9					0.3
Chronic inflammatory demyelinating polyneuropathy*			4	4			0.9	0.7	0.6
Friedreich ataxia			2				4		
Guillain-Barré syndrome					1				
Hereditary neuropathy with liability to pressure palsies			9						
Multifocal motor neuropathy			0.5	0.8				0.6	0.1
Neuropathy with monoclonal gammopathy of unknown significance			3						
Neuromuscular junction									
Myasthenia gravis**	10			10			1		
Lambert-Eaton myasthenic syndrome			0.3	0.3			0.05	0.04	0.06
Muscle									
Duchenne muscular dystrophy	3.2		3		24				
Autosomal recessive (Duchenne-like) muscular dystrophy of childhood	0.5				4				

	Emery, 1991(2 reviews)	Deenen, 2014 (study)	Deenen, 2015 (review)	Deenen, 2025 (review)	Emery, 1991 (review)	Deenen, 2014 (study)	Deenen, 2015 (review)	Deenen, 2025 (review)	Deenen, 2024 (study)
Anatomical location **Disorder**	**prevalence rateper 100,000 population**				**incidence rateper 100,000 population**				
Becker muscular dystrophy	>0.7		2	1	3.6				0.05
Facioscapulohumeral muscular dystrophy*	2	12	4	5	1.7	0.3		0.3	0.4
Limb girdle muscular dystrophy	<4		3		4.4		0.7		
Nemaline myopathy				0.3					0.04
Emery-Dreifuss dystrophy			0.3						
Oculopharyngeal muscular dystrophy*			0.1	0.6					0.07
Myotonic dystrophy*	5		10	10	21				
type 1				10				1	0.9
type 2				2					0.1
Congenital muscular dystrophy			1						
Congenital myotonias	1				1.4				
Non-dystrophic myotonias			1						
Chronic progressive external ophtalmoplegia			3						
Glycogen storage disease type 2 or Pompe disease*				0.3					0.2
Glycogen storage disease type 5 or McArdle disease				0.7					0.03
Polymyositis			7				2		
Dermatomyositis			8				0.9		
Inclusion body myositis*			2	3			0.4	0.4	0.3

*including population-based incidence distribution maps; **Emery combined myasthenia gravis with familial motor neuron disease.

Neuromuscular disorders under epidemiological surveillance in the Netherlands

Neuromuscular disorders encompass many different diseases with typically small patient populations. Patient registries serve to overcome the research limitations that are inherent in the study of rare diseases. This was one of the reasons to initiate the Dutch nationwide Computer Registry of All Myopathies and Polyneuropathies (CRAMP) in 2004 [3]. It was developed to register individuals who were newly diagnosed with a NMD in the Netherlands.

Based on the first eight years of data collection by CRAMP in the Netherlands (with a population size of 16.7 million in 2012), we presented real-world epidemiological information on 20,000 patients covering 30 neuromuscular disorders in **Chapter 4**. The number per diagnosis varied from nine individuals with Emery–Dreifuss muscular dystrophy to 2057 persons with amyotrophic lateral sclerosis. The proportion of men ranged from 38% for post-polio syndrome to 68% for progressive spinal muscular atrophy. The lowest median age at diagnosis was found for Duchenne muscular dystrophy (10 years), while inclusion body myositis showed the highest median age at diagnosis (70 years). These data may be helpful in the diagnostic process in clinical practice and trial readiness.

For the benefit of patients and public health we have provided in **Chapter 5** the first neuromuscular atlas of the Netherlands with maps for eight neuromuscular disorders: myotonic dystrophy, progressive (spinal) muscular atrophy, chronic inflammatory demyelinating polyneuropathy, FSHD, inclusion body myositis, hereditary motor and sensory neuropathy, Pompe disease and oculopharyngeal muscular dystrophy. Considerable regional variation was observed between these diseases, particularly for myotonic dystrophy and FSHD. This may be due to CRAMP being incomplete, or because some participating centres have contributed more than others. Still, the patterns displayed by the different disorders are not consistent, in contrast to what is expected in case of asymmetrical contribution of centres. Geographical mapping of the specific disorders is expected to provide valuable insights into clustering of these conditions, which points to possible environmental and genetical determinants.

Capture-recapture approach to adjust for unregistered patients

CRAMP enabled registration of a vast number of rare NMDs, of which facioscapulohumeral muscular dystrophy (FSHD) was expected to occur at a relatively high frequency. To study the completeness of the registered FSHD data we applied a 3-source capture-recapture approach. It allowed us to estimate the

number of non-registered individuals with FSHD, thus enabling to calculate a more valid estimate. This method requires the use of multiple registries. To that issue, we used, in addition to CRAMP, a patient association membership database and a genetic database from an expert centre to determine the number of unregistered individuals. Using these three data sources, we estimated in **Chapter 6** the annual number of newly diagnosed individuals with FSHD, including those not registered in any of the three sources. Multiplication of incidence and disease duration yielded the prevalence estimate. On average, 52 persons were diagnosed annually, resulting in an annual incidence rate of 0.3 per 100,000 population in the Netherlands. The prevalence rate for FSHD was 12 per 100,000, corresponding to 2,000 affected individuals. This was higher than prevalences found since the introduction of genetic confirmation: on average 5/100,000. Our calculated prevalence estimate was more than twice as high. The study showed that the total number of symptomatic persons with FSHD in the population may well be underestimated and a considerable number of affected individuals remained undiagnosed. This suggests that FSHD is one of the most prevalent neuromuscular disorders.

Next, we applied a 2-source capture-recapture method to the CRAMP dataset and the patient association-based *Spierziekten Nederland* dataset to calculate the incidence for 15 NMDs. In **Chapter 7** we reported that the annual incidence rates per 100,000 population varied from 0.03 (95% CI: 0.00 to 0.06) for glycogenosis type 5 to 0.9 (95% CI: 0.7 to 1.0) for myotonic dystrophy type 1. Nine of the incidence rates provided were previously unavailable, three were similar to those reported in literature, and three were higher compared with previous findings, although with overlapping confidence intervals. This study provides nationwide incidence rates for 15 neuromuscular disorders predominantly diagnosed in adult life, nine of which previously unavailable. 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.

Use of a disease-specific neuromuscular registry

The FSHD registry in the Netherlands was initiated in 2015 by the Dutch FSHD Foundation and the national expertise centre for FSHD (Radboud university medical center and Leiden University Medical Center). The aim was to raise awareness of the disease, to identify patients who are potential participants for future trials, and to collect data on various characteristics of FSHD. The registry provided data for the studies described in **Chapters 8 and 9**.

As listed in **Chapter 8**, participants were invited to complete a digital survey on patient and disease characteristics: the Checklist Individual Strength (CIS20R, sumscore [20 - 140]), the Individualised Neuromuscular Quality of Life Questionnaire (INQoL, multiple scores [0 - 100]), the Beck Depression Index – Primary Care (BDI-PC, sumscore [0-21], and the McGill Pain Questionnaire-Dutch Language Version (MPQ-DLV, including multiple sumscores).

Up to March 2021, 373 patients completed the longitudinal sets of surveys administered every six months. At baseline, fatigue and muscle weakness were the most common symptoms (median CIS20R sumscore 77 [interquartile range IQR: 60 - 92], median INQoL fatigue score 58 [IQR: 42 - 68] and median INQoL weakness score 58 [IQR: 42 - 68]). Pain was most often experienced in the head and shoulder region (52%). At five-year follow-up no significant changes on 19 of the 23 questionnaire (sub)scores was found. Although these scores do discriminate between specific subgroups of this FSHD cohort, they detected minimal or no longitudinal changes in these FSHD patients over the six-year follow-up period. The applied questionnaires may therefore not be useful to monitor disease progression in prognostic studies or clinical trials in patients with FSHD. Further, the registry has successfully been used for fast and selective patient recruitment for several studies and for contacting patients on short notice if important information became available and it will continue to be invaluable for recruitment in future trials.

Within the FSHD registry framework, another study was conducted in 2020-2021, specifically applied on patient trajectories following a SARS-CoV-2 infection (**Chapter 9**). We assessed the severity of FSHD symptoms, daily care received and perceived psychosocial stress. Furthermore, we compared the incidence and symptoms of COVID-19 infection between the FSHD patients and household members without FSHD. The participation rate in all surveys was 60%. Reduction of care was reported by more than 40% of the respondents, and an increase in perceived psychosocial stress by 40% of the participants. Compared to 197 household members without FSHD, the 213 FSHD patients reported more possibly COVID-19-related symptoms (39% vs. 27%, p=0.02) of mostly minimal severity (63%). No difference was found in cumulative incidence rates of (possible) COVID-19 infection (2.8% vs. 2.0%, p=0.53). This study thus contributed evidence on how COVID-19 negatively impacted care received and about increased perceived psychosocial stress in FSHD patients, and provided early insights regarding COVID-19 infection incidence in FSHD patients, that appeared to be similar as in their non-FSHD housemates.

REFLECTIONS ON THE FINDINGS

The primary objective of this thesis was to provide information on the occurrence of neuromuscular disorders in the population. In Chapters 2 and 3, the descriptive epidemiology of a large number of neuromuscular disorders was studied, using comprehensive search terms and based on the information available in the literature. We experienced that the extensive NMD literature review we initially had planned would be too laborious. The search strategy was therefore restricted to a limited set of search terms. MesH terms were omitted. Only the most commonly used names were retained, leaving out a list of (near-)synonyms. Reviews and other relevant studies were not examined for useful references. The search strategies nevertheless retained their systematic character. Concise inclusion and exclusion criteria served as quality assessment tool instead of applying diverse risk of bias checks. After data extraction, we presented basic summary information on incidence, prevalence, and age and sex distribution for the 30 most common NMDs. For these disorders, we reported the order of magnitude rather than seemingly precise numerical findings.

The primary motivation for the work was to compare the incidence and prevalence rates we aimed to derive from the nationwide CRAMP registry with the findings from elsewhere. The project resulted in our 2015 paper entitled 'The epidemiology of neuromuscular disorders: a comprehensive overview of the literature' (Chapter 2).

During the analysis of the CRAMP data (Chapter 7) we ended up with disease frequencies of five NMD (sub-)types which we had not previously studied in Chapter 2. In addition, new findings had become available in literature. This motivated us to repeat our method to revise the disease frequency estimates from Chapter 2 to a partially new set of NMDs as presented in Chapter 3.

We also identified the first eight meta-analyses on the occurrence of NMDs, which were not available in 2015. These meta-analyses mainly included pooled prevalence rates, just one also presented a pooled incidence rate. Plotting the pooled prevalence estimates from the meta-analyses against the calculated mean of the prevalence estimates from our extended search of individual studies, resulted in a scatter diagram with points that oscillated only slightly around the diagonal (see Figure 1, taken from Chapter 3, page 61). It was concluded that in the absence of level 1 evidence from meta-analysis these more simply derived disease frequency estimates serve well as basic material for comparison.

The updated review of the literature (Chapter 3) showed once again that the prevalence rates for the more or less commonly seen disorders in neuromuscular practice are low. They range from 0.3 per 100,000 population to 20 per 100,000. The annual incidence rates range from 0.3 per 100,000 population to 1 per 100,000. It was also noted that incidence estimates are still relatively often unavailable, especially compared to the prevalence estimates. This is intriguing, because deriving incidence estimates from disease registries is much more straightforward than is the derivation of prevalence estimates. Fortunately, more and more disease registries are being set up and increased knowledge on incidence is to be expected to become available in the near future.

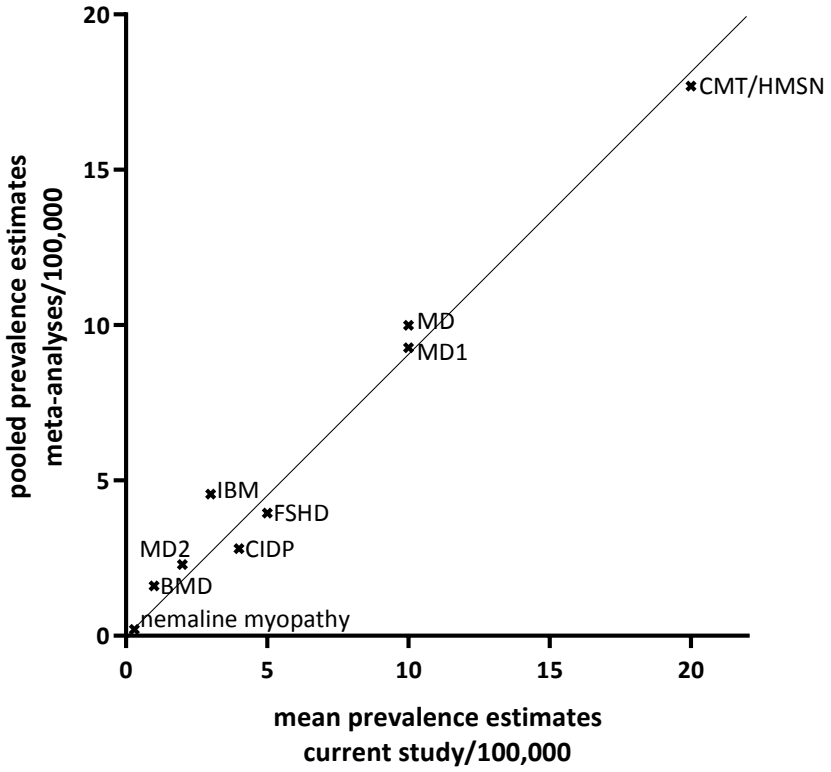

Figure 1. Comparison between pooled prevalence rates of NMDs from meta-analyses and mean prevalence rates calculated from individual studies.

BMD – Becker muscular dystrophy; CIDP – chronic inflammatory demyelinating polyneuropathy; CMT – Charcot-Marie-Tooth disease or hereditary motor and sensory neuropathy; HMSN – hereditary motor and sensory neuropathy; FSHD – facioscapulohumeral muscular dystrophy; IBM – inclusion body myositis; MD – myotonic dystrophy, types 1 and 2 [4-11].

In this era of treatment options emerging for rare diseases, it is also important to realise that incidence and prevalence rates will change as new treatments become available. It brings individuals to the attention of clinicians which previously have been out of sight – a common phenomenon in NMDs with limited treatment options. In addition, (mono-)genetic diseases incorporated in newborn screening programs will detect affected individuals (much) earlier, and potentially even individuals who would never develop the disorder clinically. Possibly, prenatal screening can be implemented, which will also change incidence and prevalence. Furthermore, as prevalence is a combination of incidence and disease duration, prevalence will be affected by changes in disease duration. This especially concerns diseases with a limited life expectancy. In addition, the mechanisms mentioned for the incidence will also affect prevalence estimates.

For completeness, we would like to mention one last factor regarding the size of the disease frequencies. With a population of 16.7 million people in 2012, recently the Netherlands reached the 18 million inhabitants in 2024. This, together with the ageing effect and increased life expectancy, will ensure a different composition of the population. All this affects the incidence and prevalence estimates, which justifies an updating of disease frequencies say every 5 or 10 years. As according to Netherlands Statistics, a significant part of the population increase is due to immigration, including people with a different genetic background, other diseases will appear in the firmament. This is an additional reason for regularly updating the descriptive epidemiology of NMD. It shows that descriptive epidemiology is a chronic, continuous task.

NEUROMUSCULAR DISORDERS UNDER EPIDEMIOLOGICAL SURVEILLANCE

Most medical articles start with a presentation of what is known about the frequency of the disease. It is the opening scene regardless of the subject of the article: disease mechanism, diagnostics, clinical course, treatment options, prevention or public health aspects. More often than not, the age and sex distributions follow shortly. It implies that this kind of knowledge is readily available and reliable, which however is not always the case, especially not for (ultra-)rare diseases.

Chapters 4 to 7 of this thesis focus on applications of a registry for multiple neuromuscular disorders. CRAMP was the first of its kind and registered a multitude of neuromuscular disorders combined in one registry. It contains a wealth of

previously unavailable information about age and sex distributions for many neuromuscular disorders.

We initially assessed the completeness of CRAMP by obtaining the numbers of individuals who were newly in care for neuromuscular disorders according to the Dutch reimbursement information systems of all Dutch hospitals in 2010. It showed that CRAMP contained at least 75% of the total number of new diagnoses in one of the eight university medical centres. There was no reason to expect that the unregistered adult persons would have a very different age and sex pattern than those registered in CRAMP. Therefore, we extracted and organised the data into easily accessible lists, tables and figures for future reference in the literature. In doing so, we provided extensive information on the sex distribution for 30 disorders, eleven of which were previously unavailable in the literature. The newly found information on age from CRAMP was similar to what was already known from literature, with 13 out of the 30 disorders lacking previously published information on age.

Incidence, prevalence and disease duration

Next, we focused on collecting information on disease occurrence calculated in the population: incidence and prevalence. Both incidence and prevalence have two different forms: an absolute form (counts) and a population-related form (rates or risks). The design of the CRAMP database turned out to be very suitable to provide incidence rates, i.e., the number of newly diagnosed patients for a specific (group of) disorder(s) within a certain time period standardised to the size of the population from which the patients came. To describe a (chronic) disorder correctly in epidemiological terms, we need to know three entities: its incidence, its prevalence and its (mean) disease duration [12]. CRAMP readily provided one of these three frequency measures: the incidence of newly diagnosed patients per year in the catchment area of the Netherlands. If an incidence registry like CRAMP has been in use long enough, it can also provide prevalence data, although it takes decades (lifespan) to reach this point and it must correctly record mortality as well. It is certainly possible to find all living persons with a specific disease (by means of population screening for example), but especially for chronic disorders without a (curative) treatment, it is very challenging to find all patients, or put in other words: to be complete.

Another way to derive prevalence numbers is to use information of the (average) disease duration. Under steady state assumptions, incidence, prevalence and disease duration are linearly related [12]. For non-life-threatening chronic diseases,

disease duration is on average the number of years a person is expected to live (life expectancy) minus the age at onset. As the prevalence of a disease is a function of incidence and disease duration, the prevalence can be approximated by multiplying incidence by duration. CRAMP does not record symptom onset because this variable is subject to a lot of bias. Instead, CRAMP registers age at diagnosis which can serve as a proxy for age at onset. This allows the average disease duration to be derived. Next, by applying the linearity described by Freeman and Hutchison, the prevalence can be estimated [12]. This is shown in Chapter 6, with the first paper we published on CRAMP data.

The first neuromuscular atlas of the Netherlands with incidence rates

In Chapter 5, we plotted incidence rates for eight NMDs across two-digit postal code areas in the Netherlands and covering an eight-year registration period. These maps demonstrated a useful application of registry data for health care planning and research into etiological questions. In the near future (more) complete nationwide data are expected to become available via automated data collection systems. Then, easily accessible information will be generated for patients, clinicians and other health care providers with searchable devices, similar to the Cancer Atlas of the Netherlands Comprehensive Cancer Organisation, and the Australian Cancer Atlas [13, 14].

The method we used to design the NMD maps, although simple and straightforward, can generate increased incidence rates. Low population numbers in smaller geographical areas combined with just a few extra cases can easily result in a potential outlier. This risk was reduced by using not-too-small geographical areas and an observation period of eight years. A more comprehensive approach for future research would be to apply a Bayesian approach to the calculations, taking into account the incidence rates of the surrounding areas. This statistical method uses Bayes' theorem to calculate and update disease probabilities after obtaining new data.

The method can be explained narratively. First, differences between the incidence of the different postal code areas that are due to differences in the age and sex composition of the population are adjusted to the expected numbers based on the age- and sex-specific incidence rates of all postal code areas taken together. It might be clear that, for example, in two areas with an unchanged risk of NMD in periods of similar duration, and with an identical population structure and risk of NMD, we will not observe equal numbers of patients due to random effects. Since our interest is not in the observed (potentially biased) incidence but in the

true underlying incidence, we need to address the calculated incidence estimate. For that issue, the incidences of the neighbouring areas give a good impression of the underlying incidence. Thus, the incidence in a certain area is corrected by the average incidence of the neighbouring areas. The actual calculations are made with statistical software that applies a Poisson model for the random occurrence of diseases into a Bayesian analysis incorporating the incidence of the neighbouring areas [15, 16].

DYNAMICS OF A REGISTRY ON MULTIPLE NEUROMUSCULAR DISORDERS

The capture-recapture method for accurate patient numbers

When our epidemiological research started in 2010, CRAMP was known to be incomplete. The database setup was a first-ever nationwide registry of multiple-neuromuscular disorders. It could collect its data at least partly in a semi-automatic way from existing hospital information systems, thereby reducing the workload of neurologists at the participating centres. To address the incompleteness of the incidence data due to under-ascertainment of patients, we applied the capture-recapture method. This way of calculating population sizes originates from biology. Biologists have been using it for more than a century to accurately estimate the size of the fauna living in a certain area or period (see illustration box in Chapter 1, page 4). Huisman, *et al.*, successfully deployed a similar approach to assess the epidemiology of amyotrophic later sclerosis. [17]

Capture-recapture methodology not only provided us with the tools to assess the completeness of CRAMP data, but also the opportunity to correct for incompleteness by estimating the number of unrecorded persons. This allowed us to derive adjusted incidence (and by extension, prevalence) estimates. We needed at least two 'catches' or captures of the disease(s) under investigation. This was achieved with the help of the patients association for people with NMDs in the Netherlands: *Spierziekten Nederland*. After anonymising the individual data, their member database served as the second registry of NMDs. To start the capture-recapture procedure, we produced tallies of the number of patients present in the CRAMP database, in the *Spierziekten Nederland* database, and in both. Based on the method described in Chapters 6 and 7, the capture-recapture procedure was used to calculate the number of individuals who did not appear in any of the (two or three) sources. In this way, an overall estimate could be made of all patients with a specific disorder in the Netherlands.

Assumptions and methods limitations of the capture-recapture approach

Although the capture-recapture method to calculate population size is simple in nature, it is accompanied by a number of assumptions (Chapters 6 and 7). It is clear that at least some of these assumptions are violated when applied to epidemiological questions on valid disease frequency. By taking a number of measures we minimized the effects of the possible violations.

The first assumption is about correct patient matching. In our capture-recapture study this was certainly at risk because available patient data were pseudonymised or anonymised. Only a limited number of identifiers were available, none of which were unique identifiers. For practical reasons we applied a procedure whereby a possible match (not all matching variables completely similar) was counted as a match, unless there was clear evidence of the contrary (e.g., two very different diagnoses that are unlikely to be confused in the clinic).

Usually, the second assumption on the stability of the population size is approximated by keeping the time period to obtain patients short. In our situation this turned out to be difficult because for many disorders we would identify too few cases within a very short time frame. The compromise was to set the data collection period to eight years, which is a rather long time period with respect to the necessity to approximate a closed population, but long enough to collect sufficient numbers of patients to allow capture-recapture calculations.

The third and fourth assumptions, i.e., the need for equal probability of being captured and the need for non-dependency of sources, are known to be intertwined [18]. In capture-recapture calculations it is impossible to assess all levels of dependency between the sources. However, when more than two sources are applied, it is possible to assess some of the mathematical interactions. In case of a three-source capture-recapture method, first-level interactions can be evaluated, because there are three variables and three mathematical equations based on log-linear modelling that mathematically can be solved. As soon as a second-level interaction term is added (interaction term of all three registries), we will end up with four variables and three equations, leaving us with one unsolvable variable. Nevertheless, the three-source capture-recapture method provides adequate information about possible dependencies between registries.

In our study on FSHD frequency estimates, we applied a three-source capture-recapture method based on CRAMP, *Spierziekten Nederland*, and a third dataset

from Leiden University Medical Center that covers all Dutch clinical genetic diagnoses for FSHD (Figure 2). Contrary to what we expected, we found nearly no dependency between the three datasets, i.e., the capture overlap by one dataset is not dependant of the sizes and overlaps of the other datasets. We therefore think that the fourth assumption was met. Furthermore, we did not apply the Chapman estimator of sample sizes, the most commonly used estimator for two-source capture-recapture calculations. Instead, we applied Chao's estimator, which is less biased in its mathematical properties, has a better confidence interval coverage and is less sensitive to deviations from equal catchability [19]. Thus, even if the assumptions of equal catchability or non-dependence are not fully met, applying Chao's estimator will further minimise the effects of the deviations.

Generally, if the first and second assumption are not met, overestimation of the number of cases may occur. If the third or fourth assumption is violated, this will result in underestimation. However, by taking the specific precautions described above, we expect to have mitigated the impact of the violations on the estimates. In Chapter 7, the population-based incidence rates of the 15 neuromuscular disorders were analysed with a nationwide two-source capture-recapture study. We conclude to have achieved an adequate approximation of the total number of patients and as a consequence more valid disease estimates than when based on the CRAMP data alone or a simple combination of the CRAMP and *Spierziekten Nederland* data.

Epidemiology as a useful tool in the diagnostic process

Epidemiological data are used in clinical practice to order lists of differential diagnoses. This is usually based on prevalence estimates obtained in (outpatient) clinic. However, collecting valid prevalence estimates in rare diseases is complex. (Inter)national registries are (being) set up to accurately assess disease frequencies. These counts, however, tend to be based on incidence findings in newly diagnosed patients. Therefore, using incidence rather than prevalence is preferred in processes like for instance the ordering of differential diagnoses. Additionally, incidence is less influenced by disease duration, which is an advantage in the near future when more and more treatment options are expected to become available influencing disease duration (and thus the prevalence of a disorder).

This does not imply that there is no longer a need for prevalence estimates. On the contrary, in order to correctly describe a disease in terms of disease frequency, we need to have at least two of its three component estimators: incidence, prevalence and disease duration. In addition, health care planners like the European Medicines Agency work with prevalence and incidence, as they have to plan for patients

who are already in care and for those who are expected to enter into care in the future. Nevertheless, in literature one still observes prevalence estimates highly outnumbering incidence estimates. Again: prevalence is not enough to fully characterise a disease and incidence measures may form a better basis for a list of differential diagnoses, especially in rare diseases. There is still a need for more incidence data, preferably pooled ones from systematic reviews and meta-analyses.

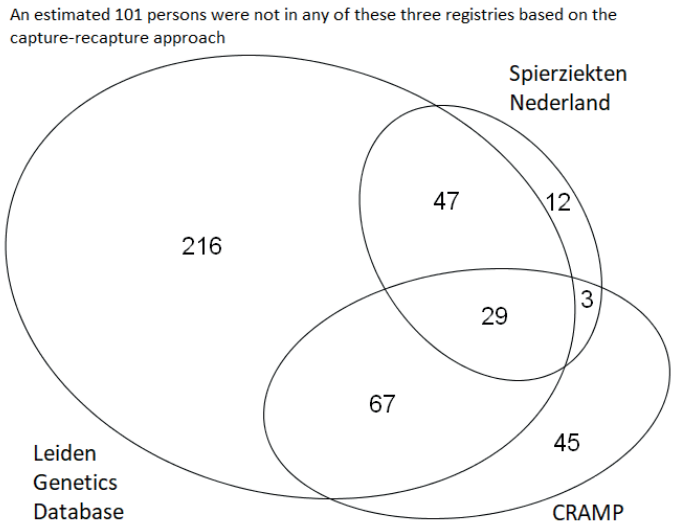

Figure 2. Area-proportional Euler diagram with numbers of individual patients.

The diagram depicts sets of absolute numbers of symptomatic individuals with FSHD for each of the three registries and their overlap as registered for a ten-year period. By applying a capture-recapture approach we estimated there were 101 individuals with FSHD who were not registered in any of these three registries. They were added to present the total number of newly diagnosed individuals with FSHD. The graph was created with EulerAPE [20].

UTILISATION OF A DISEASE-SPECIFIC NEUROMUSCULAR REGISTRY

Registries as a framework to initiate clinical and public health studies

In addition to obtaining valid disease frequencies, registries also enable rapid patient recruitment for clinical trials. This asset facilitates cross-sectional and longitudinal data collection aiming to inform about specific (groups of) patients. Items can be: 1) the natural history and clinical course of the (untreated) disease, 2) post-marketing functions, 3) newsletters content in a fast manner, 4) returning previously collected patient-reported outcomes at a personalised as well as at group level, and 5) potential (research) questions that participants may be interested in. Many of these items are related to trial readiness. The concept of trial readiness refers to the availability of (clinically) validated research instruments and knowledge of the natural history of the disease that are needed for the design of clinical trials [21]. With these aims in mind, the FSHD registry was established in 2014. Where CRAMP provided the robust foundation to obtain disease frequencies in a comprehensive and accurate manner, the FSHD registry provided the framework to collect more extensive data using patient-reported surveys in a flexible way (Figure 3).

In addition to the primary aims, adequately designed and maintained patient registries can serve as suitable frameworks to help answering research questions. This was illustrated in Chapter 5 on the design of maps showing the geographical distribution of several NMDs across the country based on CRAMP data. In addition, FSHD data were used to initiate two patient studies: Chapter 8 presenting representative patient profiles and clinical trajectories of FSHD, and Chapter 9 displaying characteristics on a current topic, i.e., the impact of COVID-19 on FSHD patients.

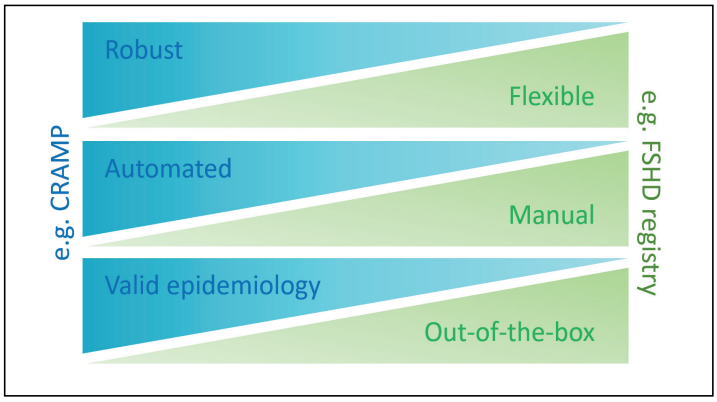

Figure 3. Registries with different purposes showing a trade-off in registry characteristics.

Output and impact of the FSHD questionnaires

As indicated in Chapter 8, we sent out questionnaires twice a year for a period of six years. These validated questionnaires were expected to be suitable to detect slow deteriorations often observed in FSHD. It turned out that the questionnaires indeed could distinguish between patients with a clearly different level of mobility. Here, mobility level was used as a proxy for disease severity, as currently there is no severity score available in the Dutch FSHD registry. Nevertheless, the used questionnaires noted no or just a very limited change over the period of six years in this large FSHD cohort. This illustrates that the set of questionnaires is less useful for trials, although it may be applicable as a stratification tool. It remains unknown whether the lack of change in this cohort was due to lack of deterioration, a limited sensitivity to change of the questionnaires or whether the deterioration was modified by other factors that we have not measured.

Another study based on clinical data from a different FSHD patients cohort showed a limited deterioration over a time period similar to our study cohort (unpublished results). The questionnaires used in the FSHD registry seem to be of limited value for follow-up purposes. The use of our mandatory item list is further under debate, because participants have to answer the same questions over and over again. The possible replacement with different questionnaires is also discussed, as well as a different (lower) frequency of data collection. If we were to stop using the current questionnaires now, we would have to start again from scratch with new questionnaires for the entire cohort of over 500 participants.

Apart from the way forward with the current questionnaires, the FSHD-RODS questionnaire will be added to the protocol and sent out at least once a year [22]. The

RODS disability scale is a general disability scale validated with the Rasch method. It was specifically designed for patients with FSHD, which is an advantage over all previously used validated questionnaires. In addition, the use of the Rasch method converted the originally ordinal scale into a scale with measurable intervals. This provides a more detailed basis for assessing severity-related research questions.

Furthermore, we used the registry (among other contact-routes) to find and inform patients about the opportunity to be vaccinated against COVID-19 months ahead of the general population [23]. This was clinically motivated by considering that individuals with FSHD (and other neuromuscular disorders) could be more vulnerable to severe outcomes of a COVID-19 infection. In contrast to other risk groups, such as patients with severe obesity who were invited even earlier by their general practitioners, patients with neuromuscular disorders were considered 'hard to find' through other channels. Both CRAMP and the FSHD registry were instrumental in reaching patients all over the country in a rapid way.

Another example of the use of registry data was a study investigating the socioeconomic burden of FSHD [24]. Here, available data from the registry were combined with specifically collected data. These new data were added to the registry database and thus became available for future reference and use. The study showed that FSHD was associated with substantial direct and indirect socioeconomic costs as well as a reduction in health-related quality of life. In turn, this knowledge may be used for the allocation of research funds and the assessment of cost-effectiveness of novel therapies.

A final example of the registry being instrumental, was a study concerning the psychosocial outcomes of facial weakness and reduced facial function in FSHD [26]. For this study, not only participants were requested but also data on their pre-COVID psychosocial functioning, as the study was conducted during the first COVID-19 outbreak in 2020. By comparing the scores of the Beck Depression Inventory for Primary Care before and during the outbreak, the researchers assessed the influence of the outbreak on their psychosocial functioning. Depression scores before and during the COVID-19 pandemic were available for 55% of the participants. The depression scores from the FSHD registry showed no difference: the rate of depressive feelings before mid-February 2020 was 12%; from February 2020 onwards it was 13%, with 9% of the patients reporting depressive feelings in the pre-pandemic period as well as during the pandemic. The registry data turned out to be a valuable asset to retrospectively put the researched information into perspective.

Table 2. Changes in characteristics of the three CRAMP versions over the period 2004-2024.

Characteristic	CRAMP 1.0	CRAMP 2.0	CRAMP 2.1
Period	2000 - 2015	2016 - 2023	2024 - onwards
Design	stand-alone	online	online
Software	MS dBase	custom-built DHD	custom-built DHD
Data collection	at the discretion of the participating neuromuscular neurologist	based on compulsory financial administrative data from the Dutch hospital register	based on compulsory health care administrative data from the Dutch hospital register
Number of included disorders	≈1400 (Rowland classification)[25]	≈180 disorders based on Kortbeek classification	≈100 diagnoses
Allows registry undiagnosed individuals	yes, based on symptoms	-	-
System-based deduplication	-	partly	yes
Mapping options	-	yes, limited to absolute numbers	yes, limited to absolute numbers
Options to select data from specific groups	-	yes, with some limitations	yes, with more limitations than CRAMP 2.0
Data description and accessible//findable information	yes, for the participating neurologists	yes, but limited information	more info than for CRAMP 2.0, yet remains incomplete and not readily available

In summary, the FSHD registry not only provided the basis for studies about the natural history and implications of COVID-19 infections, it also provided the opportunity to quickly contact participants. The registry has served as a starting point for more than a dozen studies, for which either participants, data or a combination of both were requested; see the list of accepted research applications [27]. These are just a few examples of the use of a registry. There are many other ways to use registries, such as post-market surveillance, and more will likely be initiated in the years to come. By building a registry in a modular way, it can be expanded with new options based on demand and availability.

FUTURE PERSPECTIVES: REGISTRIES IN PROGRESS

After the initial version of CRAMP became operational in the first decade of this century, it was evaluated by the *Prinses Beatrix Spierfonds* in 2013 [28]. Based on the recommendations of the evalauation, the Dutch Hospital Data (DHD) cooperative group designed a new system version (CRAMP2.0) was launched in 2016. This (fairly) new system collects data in a fully automated way based on data from the Dutch Landelijke Basisregistratie Ziekenhuiszorg healthcare information system [29]. In 2023, an updated version became available, informally called CRAMP2.1, which is very similar to the recently launched OrphaViewer (also by DHD). A comprehensive overview of the three CRAMP versions is presented in Table 2.

Although CRAMP as such is known among neuromuscular neurologists, many appear to be unaware of the specifics of the current system and full potential of the registry. There is a need for a campaign propagating its features and potential for the future, and readily-accessible information about new developments in CRAMP. This thesis may help to increase awareness and applicability of the CRAMP system. Advantages of the updated system are:

i. CRAMP2.0 is fully automated and based on data which are already delivered for quality or financial purposes. It is outsourced to an organisation that is specialised in collecting and processing data in a safe way, including necessary rules and regulations.
ii. It is operating nationwide, currently in university medical centres, where the majority of rare neuromuscular disorders is diagnosed.
iii. By its set-up it is the 'safest bet' of gathering complete epidemiological information. It is a large asset compared to other registries.
iv. To some extent, the CRAMP data are Interoperable and Reusable by design (based on the FAIR acronym, referring to being Findable, Accessible, Interoperable and Reusable [30, 31]). The Findability and Accessibility still need work. CRAMP would benefit from an evaluation of the current FAIRness, using FAIRmetrics and a subsequent improvement trajectory[32].

Suggestions for new developments of the system (CRAMP 3.0) are:

a. A readily available description of the system is a prerequisite. This includes procedures on how data are collected, how changes in diagnosis are made, how patients are referred from one centre to another, how to prevent double diagnoses within one person, and how consent rules are applied.
b. For the system to work properly, it is necessary that participating centres have procedures in place that facilitate the workflow of the diagnostic process. For example, a module in the electronic health system that changes initial-probability diagnoses to confirmed diagnoses.
c. To check whether data collection and processing are organised correctly, verification of the data in the system is needed.
d. A clear request procedure for data and patient-recruitment is needed, which must be easily findable and accessible.
e. European and regional legislators should be aware that current privacy laws are at odds with the need for comprehensive epidemiological data. This calls for solutions facilitating the collection of the required data, while privacy matters still remain protected. The opt-out procedures as proposed for the European Health Data Space are a good development.
f. Currently, not all NMDs are collected by CRAMP2.1. It is limited to circa 100 diagnoses, leaving out many rare to ultra-rare disorders. This hampers trial readiness for the patients affected and this in turn calls for separate registries for these disorders, which is not the preferred way. A workable yet less limiting solution should be pursued here.
g. Preferably, data collection should be extended to all Dutch hospitals and rehabilitation centres, which is a challenge considering the 61 hospital organisations and eight university medical centres [33].
h. If the CRAMP data could be connected with the Personal Records Database (PRD), this would enable future ascertainment of prevalence estimates. The PRD contains date of death, which is needed to assess which patients are alive and correct estimation of prevalence numbers [34]. Also, the current address where individuals are registered is known, ensuring correct data and fast contacting options.
i. For more functional use of the data, population-based estimates are needed rather than providing simple tallies. Age- and sex distribution-stratified population sizes are readily available from Statistics Netherlands and updated on a yearly basis.
j. If CRAMP could serve as a basis in the future where modalities could be connected to or be built upon, this would combine the best of both registry types.

The CRAMP2.0 initiative was part of a pilot to incorporate its collectively gathered information into the Euro-NMD registry set up by the European Reference Network for Rare Neuromuscular diseases [35]. This is a federated infrastructure designed with FAIR principles of the highly-specialised hospital units involving NMD in the European Union, and is in contrast to the CRAMP1.0 project where all datasets were assembled and aligned at one location. Collaborating patient registries at European and global level will further improve data availability and maintenance of the NMD data. In addition, it will facilitate identification and recruitment of patients for future clinical trials, and launch projects on newly emerging situations and insights [36]. By the time a collective system like the Euro-NMD registry will be fully functioning, a local specific registry such as the FSHD registry may become redundant, provided that the collective system is flexible enough to facilitate the full research life cycle. If this central registry could serve as a basis for new modular functionalities, this would allow for the reuse of already collected data while following the progress in knowledge.

At the time of the FSHD registry initiative in 2015, all collected data, except from the genetic diagnosis, were patient-reported. This enabled a wide reach of the registry with limited efforts for data collection for the involved physicians, but at a considerable burden for the participant. In the meantime, knowledge on FSHD has been extending and clinical trials have commenced. It seems to be the right moment to extend the data collection towards pre-specified clinical information. Possibly by first combining registry items with data from other research projects on FSHD, and starting with registry participants who consented to do so. In addition, data extraction from the electronic health records in combination with formalised visit contents will make it possible to closely monitor disease progression, stabilisation or even recovery when treatment options become available (Figure 4).

After 10 years of limited data collection, the way forward will be a comprehensive data gathering, ranging from clinical assessments to the use of wearables. Preferably, analysis should be accomplished in an automated way, and use artificial intelligence applications to extract, organize and analyse relevant items where appropriate. In addition, it would really be beneficial for patients as well as clinicians if participants from disease-specific registries could have access to their own longitudinal data. Using these findings, they could assess how they are doing, preferably displayed in view of group data. This could help them substantiate challenges they are facing in everyday life in the consultation room. It is time for the development of a framework specifically directed at registry building rather than trying to use data management platforms designed for clinical trials.

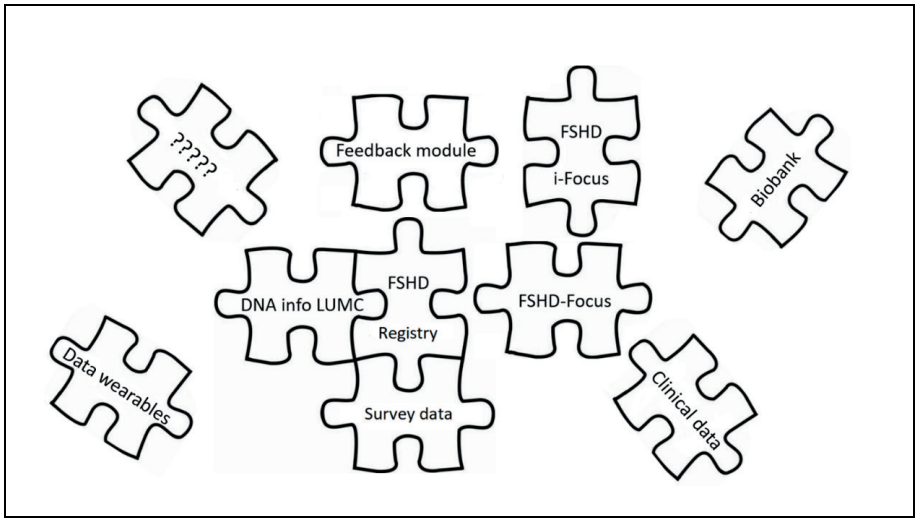

Figure 4. Graphic representation of the FSHD registry functionalities depicting its current and possible future modules.

This thesis is all about numbers, frequencies and rates of NMDs. Studying numbers can teach us that there are differences between diseases, within diseases, and from person to person. In this way, epidemiology can contribute to personalized medicine. In the end, epidemiology is all about patients. Each number in my thesis represents a group of patients, who try to live their most optimal life and hope for treatments that make life easier. This is illustrated by Nynke's testimonial in Chapter 1, which is now continued in the box below.

Finally, the studies described in this thesis gathered specific information on disease frequency for clinical and basic researchers, patients, healthcare workers and others alike. Based on different, but complementary, nationwide registry systems, this thesis delivered elements for the neuromuscular descriptive epidemiology that previously were lacking. It was supplemented with practical demonstrations of how to make use of registries with various objectives, with the overall aim to alleviate the needs of persons with a neuromuscular disorder.

Box 1 – Continued conversation with Nynke, on future perspectives

Nynke, what is still missing as far as you are concerned?

"That's not a difficult question: further treatment options and medication, even if FSHD could only be slowed down or stopped. It would be even better if there would also be improvements. For myself, of course, but especially for the younger people who are on the same road as me. I very much hope that their decline can be slowed down.

Another thing is that it is sometimes difficult to belong to an exceptional group within FSHD (namely with a severe course). Much research is focused on or concerns the 'average' person with FSHD. It would be nice if more information became available, tailored to the group of people with a more severe course. A good example is that research has shown that training, to some extent, is beneficial to people with FSHD. However, I already use my energy to the maximum of my capabilities, leaving no room for physical exercise. Nevertheless, becoming aware of particular muscles I have and focusing on their use helped me very much. For example, the examination of facial weakness and the associated conversations with a speech therapist gave me the insight to use certain small muscles in my cheeks to create more expression in my face. It raised awareness: I still have those muscles, I just have to find ways to use them. That is a form of training that is feasible for me. Sometimes a slightly different approach is needed for certain groups. In my experience, people with a severe form also encounter more and more complex problems compared with the average FSHD patient. For example, with regard to always being in a wheelchair or being dependent on care 24 hours a day, this should receive more attention in my opinion.

I am also very curious whether it is possible to conduct further research into the role of hormones. FSHD often shows more deterioration in adolescence and during menopause, but not much research has been done on the influence of hormones. Could these aspects be looked at more closely, possibly through the use of the registry? There are still plenty of questions and the registry is a means to make us findable as patients with FSHD, but also to gather our ideas and experiences."

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NEDERLANDSE SAMENVATTING

In 1991 publiceerde A.E. Emery de eerste twee overzichten van de wereldliteratuur met betrekking tot populatiefrequenties van verschillende erfelijke neuromusculaire aandoeningen (NMA). Vijfentwintig jaar later doorzochten wij de literatuur naar peer-reviewed artikelen over de beschrijvende epidemiologie van NMA gepubliceerd van 1990 tot 2014. De Pubmed zoektermen waren 'incidentie' en 'prevalentie' voor 30 aandoeningen. Wij vonden incidentiecijfers voor 11 NMA variërend van 0,05 tot 9 patiënten per 100.000 inwoners per jaar. Voor de andere 19 aandoeningen werden geen publicaties over incidentiecijfers gevonden. Voor het postpoliosyndroom en de ziekte van Charcot-Marie-Tooth vonden wij prevalentiecijfers hoger dan 10 per 100.000. Bij 18 andere aandoeningen lagen de prevalentiecijfers tussen 1 en 10 per 100.000 inwoners, en bij vier lager dan 1 per 100.000. Voor zes aandoeningen werden geen prevalentiecijfers gevonden. Voor vier van de 30 aandoeningen waren helemaal geen incidentie- of prevalentiegegevens beschikbaar.

Wij konden de prevalentie van tien NMA vergelijken met die gevonden door Emery. Drie vertoonden stabiele prevalentieschattingen. Vier bleken aanzienlijk hoger te zijn, hoewel de range van beide observaties aanzienlijke overlap vertoonde. Ons overzicht leverde negen nog niet eerder gerapporteerde prevalentiecijfers op en 11 incidentiecijfers. Vier aandoeningen bleven echter zonder schattingen. De som van de beschikbare prevalentiecijfers omvat slechts het topje van de ijsberg, maar komt al in de buurt van de prevalentie van de ziekte van Parkinson. Hoewel de individuele NMA zeldzaam zijn, zijn zij dat als groep niet.

Om nauwkeurige en bruikbare epidemiologische informatie te verstrekken aan patiënten, clinici, managers in de gezondheidszorg en onderzoekers, hebben wij vervolgens het overview-artikel aangevuld met bevindingen uit 26 artikelen en acht meta-analyses die in de jaren 2014 tot 2023 zijn gepubliceerd. Wij identificeerden prevalentiecijfers voor 17 aandoeningen. De cijfers varieerden van 0,3 per 100.000 inwoners voor het Lambert-Eaton myastheen syndroom, glycogenose type 5 en nemaline myopathie, tot 20 per 100.000 voor de ziekte van Charcot-Marie-Tooth type 1. We berekenden jaarlijkse incidentiecijfers voor acht aandoeningen, variërend van 0,3 per 100.000 inwoners voor progressieve (spinale) musculaire atrofie en facioscapulohumerale spierdystrofie (FSHD), tot 1 per 100.000 voor de ziekte van Charcot-Marie-Tooth type 1 en myotone dystrofie type 1. Hieruit bleek eens te meer dat epidemiologische frequenties over neuromusculaire ziekten schaars zijn - in het bijzonder gegevens over incidentie. De gemiddelde prevalentieschattingen op basis

van recent gepubliceerde studies over individuele cohorten kwamen goed overeen met de bevindingen uit de spaarzaam uitgevoerde meta-analyses.

Neuromusculaire aandoeningen omvatten veel verschillende ziekten met doorgaans kleine patiëntpopulaties. Patiëntregisters dienen hierbij om de onderzoeksbeperkingen te overwinnen die inherent zijn aan studies van zeldzame ziekten. Dit was een van de redenen in 2004 om de Nederlandse landelijke Computer Registry of All Myopathies and Polyneuropathies (CRAMP) te starten. Het werd ontwikkeld om individuen te registreren die een diagnose NMA kregen.

Op basis van de eerste acht jaar aan gegevensverzameling door CRAMP in Nederland (met een bevolkingsomvang van 16,7 miljoen in 2012), presenteerden wij real-world epidemiologische informatie over 20.000 patiënten met 30 neuromusculaire aandoeningen. Het aantal per diagnose varieerde van negen personen met een Emery-Dreifuss spierdystrofie tot 2057 personen met amyotrofische laterale sclerose. Het aandeel mannen varieerde van 38% voor het postpoliosyndroom tot 68% voor progressieve spinale musculaire atrofie. De laagste mediane leeftijd bij diagnose werd gevonden voor Duchenne spierdystrofie (10 jaar), terwijl inclusion body myositis de hoogste mediane leeftijd bij diagnose liet zien (70 jaar). Deze gegevens kunnen behulpzaam zijn bij het diagnostische proces in de klinische praktijk en bij de voorbereiding van therapeutische trials.

Ten behoeve van patiënten en voor de volksgezondheid hebben we de eerste neuromusculaire atlas van Nederland samengesteld met kaarten voor acht neuromusculaire aandoeningen: myotone dystrofie, progressieve (spinale) spieratrofie, chronische inflammatoire demyeliniserende polyneuropathie, FSHD, inclusion body myositis, erfelijke motorische en sensorische neuropathie, de ziekte van Pompe en oculofaryngeale spierdystrofie. Er werd aanzienlijke regionale variatie waargenomen tussen het optreden van deze ziekten, met name voor myotone dystrofie en FSHD. Dit kan komen doordat de CRAMP-registratie onvolledig is of doordat sommige deelnemende centra meer hebben bijgedragen dan andere. Toch waren de patronen van de verschillende aandoeningen niet consistent, in tegenstelling tot wat verwacht wordt bij een asymmetrische bijdrage van centra. Het geografisch in kaart brengen van specifieke aandoeningen zal naar verwachting waardevolle inzichten opleveren voor clustering van aandoeningen, wat wijst op mogelijke omgevings- en genetische determinanten.

CRAMP maakte registratie mogelijk van een groot aantal zeldzame NMA, waarvan verwacht werd dat facioscapulohumerale spierdystrofie (FSHD) relatief vaak zou

voorkomen. Om de volledigheid van de geregistreerde FSHD-gegevens te bestuderen hebben wij een zogenaamde 3-bronnen capture-recapture aanpak toegepast. Hiermee konden wij ook het aantal niet-geregistreerde individuen met FSHD schatten, waardoor een meer valide schatting van de aantallen te schatten was. Deze methode vereist het gebruik van meerdere registers. Daarom gebruikten wij, naast CRAMP, een database van de Nederlandse patiëntenvereniging voor NMA en een genetische database van een expertisecentrum in Leiden om het aantal niet-geregistreerde personen te bepalen. Met deze drie gegevensbronnen hebben wij een schatting gemaakt van het totale jaarlijkse aantal nieuw gediagnosticeerde personen met FSHD. Vermenigvuldiging van incidentie en ziekteduur leverde een prevalentieschatting op. Gemiddeld werden jaarlijks 52 personen gediagnosticeerd, wat overeenkomt met een jaarlijkse incidentie van 0,3 per 100.000 inwoners in Nederland. Bij een gemiddelde en stabiele ziekteduur van 39 jaar is de prevalentie van FSHD 12 per 100.000, wat overeenkomt met 2.000 getroffen personen. Dit was hoger dan prevalenties die sinds de introductie van genetische bevestiging werden gevonden, namelijk gemiddeld 5/100.000. De studie toonde verder aan dat het totale aantal symptomatische personen met FSHD in de bevolking mogelijk wordt onderschat en dat een aanzienlijk aantal patiënten niet gediagnosticeerd blijft. Dit suggereert dat FSHD een van de meest voorkomende neuromusculaire aandoeningen is.

Vervolgens pasten wij een 2-bronnen capture-recapture methode toe op de CRAMP-dataset en de gegevensverzameling van Spierziekten Nederland om daarmee de incidentie voor 15 NMA te berekenen. Wij rapporteerden dat de jaarlijkse incidentie per 100.000 inwoners varieerde van 0,03 (95% betrouwbaarheidsinterval (BI): 0,00 tot 0,06) voor glycogenose type 5 tot 0,9 (95% BI: 0,7 tot 1,0) voor myotone dystrofie type 1. Negen van de gevonden incidentiecijfers waren niet eerder beschikbaar, drie waren vergelijkbaar met die gerapporteerd in de literatuur en drie waren hoger vergeleken met eerdere bevindingen, hoewel met overlappende betrouwbaarheidsintervallen. Om de hiaten in de kennis van ziektefrequenties aan te vullen, is er behoefte aan schattingen vanuit een geautomatiseerd, verplicht gegevensverzamelingssysteem van cumulatief gediagnosticeerde en nieuw gediagnosticeerde patiënten met neuromusculaire aandoeningen.

De FSHD-registratie in Nederland is in 2015 geïnitieerd door de Nederlandse FSHD Stichting, *Spierziekten Nederland*, het Radboud universitair medisch centrum en het Leids Universitair Medisch Centrum. Het doel was om meer bekendheid te geven aan de ziekte, om patiënten te identificeren die potentiële deelnemers zijn voor toekomstige onderzoeken en om gegevens te verzamelen over de verschillende kenmerken van FSHD.

Deelnemers uit de FSHD-registratie werden uitgenodigd om een digitale enquête in te vullen over patiënt- en ziektekenmerken zoals de Checklist Individual Strength (CIS20R, somscores van 20 tot 140), de Individualised Neuromuscular Quality of Life Questionnaire (INQoL, meerdere scores van 0 tot 100), de Beck Depression Index Primary Care (BDI-PC, somscore van 0 tot 21) en de McGill Pain Questionnaire-Dutch Language Version (MPQ-DLV, inclusief meerdere somscores).

Tot maart 2021 hebben 373 patiënten de longitudinale sets vragenlijsten ingevuld die elke zes maanden werden verstuurd. Bij baseline waren vermoeidheid en spierzwakte de meest voorkomende symptomen (mediane CIS20R somscore 77 met interkwartielafstand IQR 60-92), mediane INQoL vermoeidheidsscore 58 en IQR: 42-68, alsmede een mediane INQoL zwakte score van 58 met IQR 42-68). Pijn werd het vaakst ervaren in de hoofd- en schouderregio (52%). Bij vijf jaar follow-up werden geen significante veranderingen op 19 van de 23 vragenlijst(sub)scores gevonden. Hoewel deze scores wel onderscheid konden maken tussen specifieke subgroepen van dit FSHD-cohort, detecteerden ze nauwelijks of geen longitudinale veranderingen bij deze FSHD-patiënten gedurende de zes jaar follow-up. De toegepaste vragenlijsten zijn daarom mogelijk niet bruikbaar om ziekteprogressie te monitoren bij prognostische studies of klinische onderzoeken bij patiënten met FSHD. Verder is de registratie met succes gebruikt voor snelle en selectieve werving van patiënten voor verschillende onderzoeken en voor het contacteren van patiënten op korte termijn als belangrijke informatie beschikbaar kwam, en het zal van grote waarde blijven voor werving in toekomstige onderzoeken.

In het kader van de FSHD-registratie werd in 2020-2021 nog een ander onderzoek uitgevoerd, specifiek gericht op patiënttrajecten na een SARS-CoV-2 infectie. Wij beoordeelden hierbij de ernst van de FSHD-gerelateerde symptomen, de ontvangen dagelijkse zorg en de ervaren psychosociale stress. Verder vergeleken wij de incidentie en symptomen van COVID-19 infectie tussen de FSHD-patiënten en andere leden van het huishouden zonder FSHD. Het deelnamepercentage aan alle onderzoeken was 60%. Vermindering van zorg werd gerapporteerd door meer dan 40% van de respondenten en een toename van ervaren psychosociale stress door 40% van de deelnemers. Vergeleken met 197 huisgenoten zonder FSHD, rapporteerden de 213 FSHD-patiënten meer mogelijke COVID-19-gerelateerde symptomen (39% vs. 27%, p=0,02) van meestal minimale ernst (63%). Er werd geen verschil gevonden in cumulatieve incidentie van (mogelijke) COVID-19-infecties (2,8% vs. 2,0%, p=0,53). Deze studie droeg zo bij aan kennis over hoe COVID-19 de ontvangen zorg negatief beïnvloedde en over toegenomen ervaren psychosociale stress bij FSHD-patiënten. Het verschafte vroege inzichten over de incidentie van

COVID-19-infectie bij FSHD-patiënten, die vergelijkbaar bleek te zijn met die bij hun niet-FSHD-huisgenoten.

In de algemene discussie hielden wij de toegepaste methodes om incidentie en prevalentie te schatten tegen het licht, bespraken wij uitkomsten en tekortkomingen en deden wij een aantal voorstellen ter verbetering van zowel toegepaste methodes als de gebruikte registraties van multi-specifieke en ziektespecifieke zeldzame aandoeningen.

APPENDIX

Research Data Management
List of Publications
Portfolio
Dankwoord
Curriculum Vitae

RESEARCH DATA MANAGEMENT

This thesis reports on the results of medical research based on two projects. The first project concerns the nationwide Computer Registry of All Myopathies and Polyneuropathies (CRAMP). CRAMP was discussed with the local Medical Ethics Review Committee of the Radboud university medical center (file No. 2011-397). Participant consent was not required in case of use of anonymised data for quality purposes and epidemiological analysis (based on the then current COREON guidelines). The study did therefore not fall within the scope of the Medical Research Involving Human Subjects Act.

The second project, the facioscapulohumeral muscular dystrophy (FSHD) registry (officially named "FSHD-Databank"), involved data collection and analyses of longitudinal patient reported outcome measures and was deemed medical research that did not fall within the scope of the Medical Research Involving Human Subjects Act either. This was declared by the same local Medical Ethics Review Committee of the Radboud university medical center (amendment of file No. 2015-1812 on April 15th 2020 based on the original decision with the file No. 2013/403 on August 28th 013). All participants of the FSHD registry provided their written informed consent before they entered the registry. The registry and its databases are in concordance with the General Data Protection Regulation and all other acting laws.

These projects are stored on the Radboud university medical center neurology department server (managed by Managementsupport (secretariaatstaf.neuro@radboudumc.nl):
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0
H:\Cramp
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\FSHD registratie
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\FSHD registratie data opslag.

The paper informed consent forms and other documentation for the FSHD registry are stored in the department archive closet (Radboud university medical center, room M352.04.139). All digital versions of the paper informed consent forms are located at \Umcn.nl\nas\APP\NEURO_ONDERZOEK\FSHD registratie\ Datamanagement\Informed consent\.

All data were either entered into the computer using Castor Electronic Data Capture (CastorEDC), MS dBase, MS Excel, MS Word, SPSS (SPSS Inc., Chicago, Illinois, USA), SAS software (version 9.2/9.4), EulerAPE or RStudio, or by participants

through responding to surveys where their answers were directly entered into CastorEDC databases.

Data management and analysis were performed with the mentioned software packages. An audit trial was initiated for data in CastorEDC to provide evidence of the activities that have altered the original data. The privacy of the participants in this study is warranted by the use of encrypted and unique individual codes in the data analyses files. The code, if applicable (for CRAMP we did not have a code file with personal details), was stored separately from the study data.

The data used in **chapters 2 and 3** of this thesis consists of scientific literature obtained with two systematic searches of bibliographic databases. The extracted data for the analyses is stored on the departments' drive:
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\literatuur\
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\data\Bestanden dataverzameling\Bevindingen\artikel 1 Overview\
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\artikelen\artikel 1 overview artikel\
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\artikelen\artikel 2 extended overview 17 disorders\.

All data used in **chapter 4** is stored in on the departments' drive:
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\data\Bestanden dataverzameling\Bevindingen\artikel 2 Numbers\
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\artikelen\artikel 3 age at onset and sex distribution\

All data used in **chapter 5** is stored in on the departments' drives:
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\data\Bestanden dataverzameling\Bevindingen\artikel 4 FSHD\
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\artikelen\artikel 4 incidence FSHD three source capture recapture\

All data used in **chapter 6** is stored in on the departments' drives:
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\data\Bestanden dataverzameling\Bevindingen\artikel 3 Capture-recapture 50 disorders\
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\artikelen\artikel 5 capture-recapture\

All data used in **chapter 6** is stored in on the departments' drives:
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\data\Bestanden dataverzameling\Bevindingen\artikel 6 Geographical distributions\
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\CRAMP1.0\artikelen\artikel 6 geographical distribution\

All data used in **chapters 7** and **8** is stored in on the departments' drives:
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\FSHD registratie\
\\Umcn.nl\nas\APP\NEURO_ONDERZOEK\FSHD registratie data opslag\

The data from **chapters 4-7** are also stored for 15 years in the Radboud Data Repository at:
DOI: https://doi.org/10.34973/0r4e-fa24

The data from **chapters 8-9** are also stored for 15 years in the Radboud Data Repository at:
DOI: https://doi.org/10.34973/dxge-bp38
For the CRAMP data there is no time limitation on data saving.

For the FSHD data there is in basis no time limitation outside a small group of participants whom consented using V4 and V5. For these 44 people, their data need to be either deleted or anonymised within 15 years of entering the registry. There are plans to ask for re-consent to fix this and other new needs regarding data.

Using the FSHD data in future research is only possible after renewed permission by the Steering Committee of the FSHD registry. The datasets analysed for the studies reported in this thesis are available from the corresponding author upon reasonable request.

"Gedragscode Gezondheidsonderzoek." Retrieved June 24, 2024, 2024, from https://www.coreon.org/gedragscode-gezondheidsonderzoek/.

LIST OF PUBLICATIONS

Part I

Deenen JC, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The epidemiology of neuromuscular disorders: A comprehensive overview of the literature. J Neuromuscul Dis. 2015;2:73-85.

Deenen JC, Verbeek AL, Verschuuren JJ, van Engelen BG, Voermans NC. Prevalence and incidence rates of 17 neuromuscular disorders: An updated review of the literature. J Neuromuscul Dis. 2025; in press.

Part II

Deenen JC, van Doorn PA, Faber CG, van der Kooi AJ, Kuks JB, Notermans NC, Visser LH, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The epidemiology of neuromuscular disorders: Age at onset and sex distribution in the Netherlands. Neuromuscul Disord. 2016;26:447-452.

Deenen JCW, Verbeek ALM, van Doorn PA, Faber CG, van der Kooi AJ, Notermans NC, Verschuuren JJGM, van Engelen BGM, Voermans NC. Geographical distribution of eight neuromuscular disorders in the Netherlands based on a nationwide registry. Rare. 2025; in press.

Part III

Deenen JC, Arnts H, van der Maarel SM, Padberg GW, Verschuuren JJ, Bakker E, Weinreich SS, Verbeek AL, van Engelen BG. Population-based incidence and prevalence of facioscapulohumeral dystrophy. Neurology. 2014;83:1056-1059.

Deenen JCW, Horlings CGC, Voermans NC, van Doorn PA, Faber CG, van der Kooi AJ, Kuks JBM, Notermans NC, Visser LH, Broekgaarden RHA, Horemans AMC, Verschuuren JJGM, Verbeek ALM, van Engelen BGM. Population-based incidence rates of 15 neuromuscular disorders: a nationwide capture-recapture study in the Netherlands. Neuromuscul Disord. 2024;42:27-35.

Part IV

Kools J, **Deenen JC**, Blokhuis AM, Verbeek AL, Voermans NC, van Engelen BG. The Dutch registry for facioscapulohumeral muscular dystrophy: Cohort profile and longitudinal patient reported outcomes. Neuromuscul Disord. 2023;33:964-971.

Deenen JCW, Kools J, Greco A, Thewissen R, van de Put W, Lanser A, Joosten LAB, Verbeek ALM, van Engelen BGM, Voermans NC. Living with facioscapulohumeral muscular dystrophy during the first two COVID-19 outbreaks: a repeated patient survey in the Netherlands. Acta Neurol Belg. 2024;124:559-566.

Other publications:

van de Geest-Buit WA, Rasing NB, Mul K, **Deenen JCW**, Vincenten SCC, Siemann I, Lanser A, Groothuis JT, van Engelen BG, Custers JAE, Voermans NC. Facing facial weakness: psychosocial outcomes of facial weakness and reduced facial function in facioscapulohumeral muscular dystrophy. Disabil Rehabil. 2023;45:2507-2516.

Blokhuis AM, **Deenen JCW**, Voermans NC, van Engelen BGM, Kievit W, Groothuis JT. The socioeconomic burden of facioscapulohumeral muscular dystrophy. J Neurol. 2021;268:4778-4788.

Stunnenberg BC, Raaphorst J, **Deenen JCW**, Links TP, Wilde AA, Verbove DJ, Kamsteeg EJ, van den Wijngaard A, Faber CG, van der Wilt GJ, van Engelen BGM, Drost G, Ginjaar HB. Prevalence and mutation spectrum of skeletal muscle channelopathies in the Netherlands. Neuromuscul Disord. 2018;28:402-407.

Tanck E, **Deenen JC**, Huisman HJ, Kooloos JG, Huizenga H, Verdonschot N. An anatomically shaped lower body model for CT scanning of cadaver femurs. Phys Med Biol. 2010;55:N57-62.

PhD portfolio of Johanna Cornelia Wilhelmina Deenen

Department: **Neurology**
PhD period: **01/06/2010 – 30/09/2024**
PhD Supervisor(s): **Prof. B.G.M. van Engelen, Prof. A.L.M. Verbeek, Prof. J.J.G.M. Verschuuren, Prof. N.C. Voermans**

Training activities	Hours
Courses	
Radboudumc - Introduction day (2010)	6.00
RIHS - Introduction course for PhD candidates (2011)	15.00
RU - Scientific Writing for PhD candidates (2011)	48.00
BROK cursus (2011)	12.00
RU - Presentation Skills (2012)	42.00
Capture recapture course (2012)	16.00
Qualitative Research Methods in Health Care (2016)	28.00
RU - Grant Writing and Presenting for Funding Committees (2018)	18.00
Brok herregistratie (2018)	16.00
RU - The Art of Finishing Up (2020)	10.00
RU - Design and Illustration (2020)	26.00
Radboudumc - eBROK course (2020)	42.00
R (2020)	28.00
Radboudumc - Scientific integrity - VRIJSTELLING (2024)	0.00
Seminars	
SCN Retraite (2021) Sheets & breakout sessions (online)	4.00
Werkbijeenkomst Spierziekten Centrum Nederland (2024) attendance plenary part	4.00
Conferences	
Muscles2Meet 2016 (2016) Poster	8.00
Muscles2Meet 2017 (2017) Poster	12.00
TGDOC Registry Curators Meeting & Treat-NMD congress Freiburg 2017 (2017) attendance	16.00
TGDOC Registry Curators Meeting (invited speaker) & Treat-NMD congress Leiden 2019 (2019) Oral	16.00
2020 IRC (International Research Congress FSHD society (Poster) (2020)	8.00
2022 IRC - International Research Congress FSHD Society(Poster) (2022)	6.00
Kick-off meeting 3 kinderspiercentra (2023) attendance & breakout sessions	8.00
Other	
Yearly updates at patient association Spierziektecongres 2014-2019 (posters)	18.00
Meeting with CEOs FSHD Society (2023) oral	4.00
Meeting with CEOs Spieren voor Spieren foundation (2023)	2.00
Teaching activities	
Supervision of internships / other Student-assistant for preliminary writing process Covid-19 paper	12.00
Total	**425.00**

&

DANKWOORD

Iedereen die mij kent weet dat ik een mens van veel woorden ben. Zo ook dit dankwoord, niet alleen door die eigenschap maar ook vanwege de lange, lange lijst mensen die ik graag wil bedanken, maak je borst maar nat…

Nadat ik mijn master Biomedische Wetenschappen had behaald, was mijn enige wens om aan de slag te kunnen in een daarbij passend werkveld. Na een paar keer bijna aangenomen te zijn bij 'gewone' sollicitaties, waarna het dan toch afketste omdat ik niet 36 uur per week kon werken naast mijn onbezoldigde 'disability management'-baan, zakte de moed me in de schoenen. Op een gegeven moment hoorde ik via twee verschillende mensen van een database die lag te wachten op analyse, waarop ik een open sollicitatiebrief schreef aan ene professor Van Engelen. Van hem had ik ooit een uurtje les gehad over neuromusculaire aandoeningen, waarbij ik het direct met hem aan de stok kreeg over een aantal kenmerken van SMA. Tot mijn verbazing mocht ik op gesprek komen. Tijdens dat gesprek ontschoot mij voor ik er erg in had het commentaar dat het acroniem CRAMP (Computer Registry of All Myopathies and Polyneuropathies) helemaal niet alle neuromusculaire aandoeningen omvatte ook al deed CRAMP dat blijkbaar wel. Ondanks dat mocht ik mee komen schrijven aan een projectvoorstel voor de analyse van CRAMP en zo kwam het dat ik na het toekenning hiervan aan een promotietraject mocht beginnen, dat ik nu na 15 jaar eindelijk kan afronden.

Allereerst ben ik heel veel dank verschuldigd aan alle betrokken patiënten, in het bijzonder de mensen die lid werden van de FSHD-registratie, voor hun uitleg, hun geduld, hun enorme uithoudingsvermogen om elke keer weer ellenlange vragenlijsten te beantwoorden. De mensen die de computer niet (meer) zelf konden bedienen en via mij aan de telefoon antwoord voor antwoord aan de registratie toevertrouwden. Alle mensen die vragen stelden, en vervolgens mijn vragen beantwoordden, mij uitlegden hoe hun leven er in de praktijk uitzag, zo een doorkijkje gevend in de gevolgen van hun spierziekte. Mensen die hun toch al beperkte energie hiervoor steeds weer opnieuw beschikbaar stelden.

In het bijzonder waren er de mensen van de diagnosewerkgroep van Spierziekten Nederland, die bergen werk verzetten als vrijwilligers, daarbij een professionaliteit aan de dag leggend waar sommige 'professionals' nog een puntje aan kunnen zuigen. Anke Lanser, waarvan ik meer geleerd heb over FSHD dan van wie dan ook, altijd klaarstaand om mee te denken, om problemen aanhangig te maken en nieuwe ideeën uit te werken, Anke, enorm bedankt! En Nynke de Waard, die

ik ooit als tiener al kort ontmoette op een JIG-weekend, waar ze alleen een dagje naar toe kwam omdat het hele weekend te veel was. Iets waar ik toen nog heel makkelijk over dacht, wat ik intussen wel heb afgeleerd. Je deelde je ervaringen om in mijn proefschrift mensen met FSHD een gezicht te geven, tussen alle cijfertjes en methodologische overwegingen door, de gesprekken die wij voerden heb ik enorm gewaardeerd, dank je wel voor je hulp. Jij en ik weten dat we niks kunnen en hoeven vergelijken, maar ik zou elke dag kiezen voor SMA, zeker als de andere keuze FSHD zou zijn. Het plannen van een verdedigingsdatum met zes hoogleraren en een aantal artsen was een flinke kluif. Hierbij belandde mijn verdediging ongemerkt in jouw vakantie, iets waar ik nog steeds enorm van baal. Hopelijk tref ik jou na mijn verdediging om eindelijk jullie kampeeroplossing te komen bewonderen. Dit zijn twee mensen die ik met naam en toenaam mag en kan noemen, maar ook aan alle anderen die ik sprak tijdens mijn werk voor de FSHD-registratie: dank voor al jullie inzet.

Dan mijn promotie-team, zij drukken altijd een stempel op een PhD-traject. Maar in dit geval geldt dit dubbel en dwars omdat jullie mij niet alleen een promotieplek boden, maar ook de ruimte die ik zowel letterlijk als figuurlijk nodig heb om te kunnen functioneren. Baziel, je stak je nek uit door mij deze plek te bieden. Je zag in de loop van de tijd dat het hebben van werk van cruciaal belang is in mijn leven en je bood me de kans om dit vorm te geven op een manier die mij paste. Als ik weer eens (te) hard toewerkte naar het afronden ervan, was jij het die me herinnerde dat je me dan niet kon blijven voorzien van een aanstelling. En zo kwam het dat mijn proefschrift nu niet over één, maar over twee spierziekte-registraties gaat, waaraan ik allebei een bijdrage mocht leveren. Jouw oog voor mensen, je altijd opbouwende coaching, de uitstapjes in onze gesprekken over Frankrijk, reizen, sporten en zeilen, je interesse voor de mensen om je heen, onze (zeldzame!) gesprekken over SMA, de verre van zeldzame gesprekken over zaken rond het hebben van een beperking (omdat die zich nu eenmaal altijd opdringen in mijn leven, ook als ik dat niet wil) heb ik enorm gewaardeerd. Jammer genoeg moest je de laatste twee jaar meer afstand nemen om je met je eigen gezondheid bezig te houden, maar ook in die tijd dook je geregeld op met een kleine bemoediging of een onmisbaar commentaar of relativering van zaken. En al die tijd beleed je niet alleen met de mond je standpunten over inclusie, je voegde de daad bij het woord en was zo bijna 14 jaar mijn baas. Een mens (in ieder geval dit mens) kan zich geen betere baas wensen.

André, je stak je nek al voor me uit toen ik nog op de opleiding Biomedische wetenschappen zat. Ik mocht bij jou aan de slag voor mijn tweede master-

stage. Om prompt na drie weken weer af te haken omdat ik het presteerde mijn beide bovenbenen te breken in één val. Zo schoof de hele stage zomaar zes maanden vooruit. Niet getreurd, we gingen gewoon opnieuw aan de slag. Met een iets ander onderwerp, nog steeds binnen een van jouw aandachtsvelden, de borstkankerscreening. Het was mijn eerste ervaring met het ontwerpen van een vragenlijst. Ondanks dat ik je vooral in het begin lang niet altijd begreep, was jij een van de twee mensen die mij op CRAMP wees. En zo begonnen de gesprekken, waarbij jij samen met Baziel boomde over sport (bij voorkeur hardlopen) en sportonderzoek (of het nu het fysiologie-onderzoek tijdens de Vierdaagse was of sport-gerelateerde behandeling van FSHD en de voortvloeisels daaruit), waarna we vervolgens soms kort en soms lang het werk rond CRAMP en later de FSHD-registratie bespraken. In de laatste jaren ontpopte je je meer en meer als dagelijks begeleider. Als steun en toeverlaat bij alle hobbels die een PhD-student tegenkomt. Steeds weer opnieuw onvermijdelijke vertragingen vriendelijk accepterend, zonder klacht of afkeuring. Je liet vrijwel altijd wel op een of andere manier merken dat je jouw begeleiding niet als verplichting voelde, dat je het sparren over allerlei zaken leuk vond. Soms onbegrijpelijk voor mij, maar vooral de laatste twee jaar heb ik met name aan dat sparren heel veel plezier beleefd. Indirect ook veel dank aan je familie, omdat ik jouw begeleiding en expertise steeds weer opnieuw mocht lenen, ook al was je al lang met pensioen. Jouw begeleiding was en is een voorrecht!

Nicol, ik wil jou graag ook bedanken. Voor je hulp bij mijn eerste zoektocht om de diagnoses uit de diverse registratiesystemen correct te combineren, wat de basis heeft gevormd voor al mijn andere CRAMP-gerelateerde werkzaamheden. En later, toen je in afwezigheid van Baziel zijn werkzaamheden overnam en je aansloot bij mijn promotie-team. Dank voor je altijd razendsnelle reacties en de continue verbeterslagen die je me hebt laten maken, ze verbeterden de papers die ik in samenwerking met jou samen schreef enorm. Jan Verschuuren, je was degene die vanuit het LUMC (aan de andere kant van het land) op de achtergrond meedacht. Met je uitgebreide kennis over CRAMP en over neuromusculaire aandoeningen heb je me meer dan eens een zetje in de goeie richting gegeven en ook jij hebt dit project van begin tot het eind volgehouden. Dank daarvoor!

Ook bedank ik heel graag de manuscript-commissie voor hun werk, hun verbeteringen en goedkeuring van mijn proefschrift!

Er waren vele collega's die me verder hielpen. Waaronder Corinne Horlings, je nam na het koppelen van de diagnoses het klinische advieswerk over. Heel veel dank voor je lange adem en je geduld bij het nemen van beslissingen over het

ontdubbelen en matchen van mensen in de diverse registraties. Door gebruik te mogen maken van jouw klinische kennis over neuromusculaire aandoeningen kon ik vooruit met het toepassen van de capture-recapture methodes. Wim Lemmens, je hielp me regelmatig weer op weg als ik vastliep in een SAS-gerelateerd script-probleem. Altijd met dezelfde vriendelijkheid, steeds de tijd nemend om mijn (meestal uitgebreide) verhaal aan te horen, om dan met een even simpele als praktische oplossing aan te komen. Wat heb ik je gemist toen je van je welverdiende pensioen ging genieten!

Toen ik begon bij de afdeling belandde ik op de kamer van Berna Rood en Paul van Keeken. Dank voor het opschuiven in jullie kantoor en alle hulp en gezelligheid in die eerste jaren! Vervolgens kwam het onderzoeksbureau neurologie bij ons inhuizen, te beginnen met Annet Geerlings. Annet, mede door jouw toedoen mocht ik meedenken over de opzet van de FSHD registratie, in de samenwerking met jou heb ik veel van je geleerd. 'k Heb met heel veel plezier met je samengewerkt en we hebben de basis mogen leggen voor een veel gebruikt systeem dat nog steeds in iets andere vorm in gebruik is. Dank je wel!

Later volgden onder andere Marlies van Nimwegen, Hanneke Nuy en Janneke Prudon. Er werd hard gewerkt en tegelijkertijd was het een gezellige boel. Na een tijd in de marge van de afdeling te hebben gebivakkeerd, verhuisden we in 2016 naar het hart van de afdeling: de staflaag op de vijfde verdieping. Daar moesten we flink indikken, maar ook dit lukte allemaal. Het was het begin van meer contact met collega's, makkelijker betrokken raken bij projecten en jammer genoeg ook het afscheid van het net opgezette onderzoeksbureau. In die tijd stapte de FSHD-registratie over naar Castor, dat gebruiksvriendelijker was voor zowel de registratie-medewerker als voor de deelnemer. Daarbij, en ook met alle daaropvolgende uitdagingen die Castor met zich meebracht, ben ik uitgebreid geholpen door Remco den Ouden, de lokaal beheerder van Castor in het Radboudumc. Er waren periodes dat ik elke paar weken wel een uur aan de telefoon hing. En altijd was je bereid om mee te denken en me (opnieuw) te informeren over de ins en outs van Castor. Over de mogelijkheden en de onmogelijkheden ervan. Je was altijd bereid om mee te denken hoe we dit systeem, ontworpen voor trials, konden inzetten voor iets heel anders: een registratie. Het bracht me niet alleen kennis, maar ook veel werkplezier, dank je wel!

In deze periode kwam ik ook in contact met mensen van de FSHD Stichting, van Spierziekten Nederland, van het Prinses Beatrix Spierfonds, en later ook met mensen van Spieren voor Spieren. In eerste instantie stuiterend van de zenuwen

verslag doend van alles wat er nog niet was rond mijn promotie en later de FSHD-registratie. Van lieverlee werd het een fijne samenwerking waarin ik veel ruimte kreeg van velen en ook hier weer veel heb opgestoken. Ellen Sterrenburg, Simone van den Berge, Kees van der Graaf, Rob Staartjes, Annette Menheere, Nicole Voet, wederom Anke Lanser en Nynke de Waard, Marcel Timmen, Ria Broekgaarden, Ingeborg Meijer en vele anderen, dank voor alles.

Rond die tijd leerde ik ook Yvonne Krom (nu Meijer-Krom) kennen, ik denk op het eerste Treat-NMD congres waar ik heen ging (in Freiburg)? Je was ook met registraties bezig en wat was het fijn om met iemand van gedachten te wisselen en door te praten over oplossingen en verbeteringen. Later werd die spar-groep uitgebreid en werkten we samen met Hilde Braakman en Fay-Lynn Asselman aan het voorbereiden van het registratieproject voor Spieren voor Spieren. Het was leuk om hier alle kennis die we gezamenlijk hadden verzameld te bundelen. Ik hoop dat die informatie zijn beslag zal krijgen in de toekomst. Ik heb in ieder geval met veel plezier met jullie samengewerkt, erg bedankt daarvoor!

Anna Zielman, je was in 2018 de eerste onderzoeker die een dataverzoek deed voor de FSHD-registratie. Met een combinatie van al verzamelde gegevens en nieuwe vragenlijsten schreef je een paper over de sociaal-economische belasting van FSHD. Een super mooie testcase voor de bruikbaarheid van de FSHD-registratie. De learning curves waren steil, het hele proces was super leerzaam. Zo fijn dat de registratie gebruikt ging worden! En wat vond ik het leuk dat ik tweede auteur mocht zijn van jouw paper! Je zou later nog een keer meeschrijven aan een paper over de registratie zelf. Heel veel dank voor al je hulp en de fijne samenwerking.

In 2019 verkasten we nog een keer, waarbij het Parkinson onderzoek grotendeels op een andere verdieping belandde en de kamer jammer genoeg om allerlei, deels verdrietige redenen, leeg liep. Gelukkig kwam er ook een nieuwe collega bij: Rinske. Na even de kat uit de boom gekeken te hebben werd het met zijn tweeën ook fijn simultaan werken (want we werkten altijd aan andere projecten). Begin 2020 volgden verschillende verhuizingen naar werkplek “at home”, vanwege de Covid-pandemie. Een tijd waarin ik eindelijk toe kwam aan leren werken met R (want elk nadeel heeft nu eenmaal zijn voordeel). En toen we tussen de golven door terug waren op de werkvloer, startten we direct een onderzoek naar de ervaringen van de deelnemers van de FSHD-registratie gedurende de Covid-pandemie. Anna Greco, het was fijn om hier samen mee aan de slag te gaan en zo een heel klein beetje kijk te krijgen op de risico’s die mensen met FSHD liepen door corona. Hoewel de methode misschien beter had gekund, roeiden we met de riemen die we hadden

en het leverde op korte termijn inzicht in de situatie van voor ons zo belangrijke patiënten. Erg bedankt voor deze samenwerking en heel veel succes met het verdedigen van je eigen promotie, die een paar dagen na die van mij gepland staat.

Het eerste auteurschap van de twee laatste papers deelde ik met Joost Kools. Ik vond en vind het schrijven van een paper een hele klus en wat was ik blij dat jij wilde aanschuiven om het schrijf- en analyseerwerk van de papers over de registratie samen te doen. Heel veel dank voor al het verzette werk en de open en opbouwende samenwerking. Het maakte dat mijn promotie-werk na de corona-dip weer op gang kwam en dat ik ook weer zin kreeg in het schrijven van de drie laatste CRAMP-papers. Ook was het fijn om af en toe even te sparren met iemand die ook in de eindsprint zat. Erg bedankt!

Ook heb ik de gesprekken met Peter-Bram 't Hoen, Nawel Lalout en het mogen aansluiten bij de biijeenkomsten voor ERN registratiehouders erg gewaardeerd. Hier vond ik de tweede groep gelijkgestemde mensen die met dezelfde zaken bezig waren en waar ik mijn licht op kon steken over zaken die ik nog niet eerder had uitgevoerd. Tot slot waren de laagdrempelige gesprekken die ik jaar in jaar uit mocht voeren met de functionaris gegevensbescherming, Léon Haszing en zijn collega's als ik vragen had rond privacy of regelgeving naast een bron van kennis ook altijd plezierig en opbouwend. Zeker toen ik over de schouders van andere registratiehouders mee keek, zag ik pas hoe kort de lijntjes bij ons in huis waren. Ook aan jullie: hartelijk dank!

Uiteindelijk verhuisde ik een laatste keer, met de afdeling mee naar het nieuwe hoofdgebouw. Een heel ander soort werkomgeving maar ook hier heb ik fijn gewerkt. Ik kwam dichter in de buurt te zitten van wat intussen management support heette. Zo sprak ik Ingrid en ook je collega's regelmatig, je stond altijd klaar om iets uit te zoeken en even mee te denken als ik weer eens met gekke vragen kwam. Ook veel dank aan Ilse en Fran, voor jullie hulp en samenwerking rond het vinden en informeren van nieuw-gediagnosticeerde mensen met FSHD.

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tijdens mijn promotie en diegenen die er niet fysiek bij kunnen zijn, zijn er vast in gedachten bij of gluren door een luikje ergens vanuit het firmament mee.

Geert Jan, je staat als het erop aankomt altijd voor me klaar. Je kinderen, mijn neefjes (euh, neven) Mees en Brent en inmiddels bonusneef en -nicht Just en Karlijn, samen met Linda, jullie brengen me veel plezier, zijn nooit te belabberd voor een knuffel, gaan gewoon mee een Zuid-Franse rivier op als die gekke tante achterop een waterfiets wil. De traditie van ge-wel-di-ge sinterklaas surprises is jullie met de paplepel ingegoten en het is een feest om dat met jullie elk jaar gekker en gekker te maken. Dank jullie wel! Ik hoop nog vele jaren van en met jullie te mogen genieten van al het leuks dat er te doen valt.

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CURRICULUM VITAE

About the author

Johanna Cornelia Wilhelmina Deenen (Hanneke) was born in Amsterdam on the 5th of August, 1975. She completed her secondary education at OSG Het Baken in Almere in 1993. She obtained a Bachelor of Science degree as a building engineer at HAN University of Applied Sciences in Arnhem in 1998. Hereafter, she worked at the municipality of Ede as a building permit officer, completing necessary job-related courses while on the job and became a senior officer in 2000. She resigned from this much appreciated job in 2001 to follow her other big interest: health and disease.

From 2001 to 2008, she studied Biomedical Sciences at Radboud University Nijmegen, where she specialised in both epidemiology and human movement sciences. Three internships were part of obtaining a Master of Science degree. One at Integraal Kankercentrum Oost, Nijmegen (part of the Netherlands Comprehensive Cancer Organisation, Utrecht), where she researched differences in clinical features and survival between patients with nodal vs. extranodal non-Hodgkin lymphoma. A second internship at the Orthopaedic Research Laboratory regarding the determination of densities using QCT - a pilot study for Predicting fracture risk in patients with metastatic bone defects. The third internship was completed at the department of Health Evidence at the Radboud university medical center, where she looked into increasing breast cancer incidence and if this could be attributable to changing risk factor prevalences like mammographic densities. This Masters' degree was completed *bene meritum* in 2008. She registered as Epidemiologist A through the Netherlands Epidemiology Society.

Shortly after finishing her education, she started working as a junior researcher at the Neurology department of Radboud university medical center in Nijmegen in 2009. In 2010, she started her PhD project regarding an area at the crossroads of her interests: descriptive epidemiology and neuromuscular disorders, analysing a large but incomplete database containing a wealth of information about the occurrence of neuromuscular diseases (supervisors: prof. B.G.M. van Engelen, prof. A.L.M. Verbeek and prof. J.J.G.M. Verschuuren and prof. dr. N.C. Voermans). She also started working on a second project alongside her PhD-project in 2014, helping out with setting up the Dutch FSHD registry, a disease-specific registry for people with facioscapulohumeral muscular dystrophy. At first this was limited to assisting her colleague Annet Geerlings (head of the Trial unit of the Neurology department), later on she became curator of the registry, under supervision of prof. B.G.M. van

Engelen and since 2023 also under supervision of prof. Nicol Voermans. With completing her PhD, she will obtain her Epidemiologist Researcher degree at PhD level (Epidemiologist B).

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