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## Charcot-Marie-Tooth disease in Denmark: a nationwide register-based study of mortality, prevalence and incidence

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# Charcot-Marie-Tooth disease in Denmark: a nationwide register-based study of mortality, prevalence and incidence

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## ABSTRACT

**Objectives:** Charcot-Marie-Tooth disease (CMT) is the most common inherited disorder of the peripheral nervous system, yet no studies have compared the mortality in CMT patients with that of the general population, and prevalence estimates vary considerably. We performed a nationwide register-based study to investigate the prevalence, incidence and mortality of CMT in Denmark.

Design: We used the Danish National Patient Registry to select all records with primary diagnostic codes for CMT between 1977 and 2012 given at a neurologic, neurophysiologic, pediatric or clinical genetic clinic. The prevalence was estimated by December 31, 2012, and the incidence rate was calculated based on data from 1988-2012. We calculated a standardized mortality ratio (SMR) and an absolute excess mortality rate (AER) stratified according to age categories and disease duration.

**Results**: A total of 1534 patients (652 females) were identified. The prevalence proportion was 22.5 per 100,000 (95% confidence interval [CI] 21.2-23.7) and the incidence rate was 0.98 (95% CI 0.93-1.04) per 100,000 person years. The SMR was 1.36 (95% CI 1.21-1.53), and the AER was 4.87 per 1000 person years (95%CI 2.77-6.96). We found a significantly higher SMR in cases below 50 years of age, and in cases with disease duration of more than 10 years.

**Conclusions:** We found a reduced life expectancy among patients diagnosed with CMT. To our knowledge, this is the first study of CMT to use nationwide register-based data, and the first to report a SMR and an AER.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- The first nationwide register based study of Charcot-Marie-Tooth disease.

- Data has been collected form the Danish National Patients Registry; a high quality national registry with prospective data collection, thereby minimizing selection bias.

- The study is based on a large cohort of patients (n=1534) diagnosed with CMT between 1977 and 2012

- The DNPR only includes hospital contacts; therefore CMT patients not admitted and diagnosed at a hospital department are not included, which might be the case for many mildly affected patients,

- We only included patients diagnosed with CMT, any misdiagnosed CMT cases are not included, which might be the case for many patients with atypical CMT and mild CMT.

## INTRODUCTION

The Charcot-Marie-Tooth disease (CMT) is both clinically and genetically heterogeneous. The typical signs are slowly progressive muscle weakness of the extremities, deformities of the feet and hands, loss of tendon reflexes, and mild to moderate sensory loss. However, symptoms and severity as well as age at onset can vary considerably, even within the same family.[1] This heterogeneity makes CMT a great challenge in diagnostics as well as epidemiology. CMT is known as one of the most common hereditary neurological disorders,[2] but prevalence estimates in the literature vary greatly, ranging from 9.7 per 100,000 in Serbia[3] to 82.3 per 100,000 in Norway.[4] In recent years, knowledge of CMT has increased, as more and more CMT associated genes have been discovered owing to the development of massive parallel sequencing technologies. Today, mutations in more than 80 CMT and related neuropathy genes have been identified.[5] In spite of this increase in research, epidemiologic knowledge about CMT is still scarce. The lifespan of patients with CMT is generally assumed to be normal,[2 6] yet to our knowledge, the mortality of CMT patients has never been compared to the mortality in the general population. Recently, Barreto et al reviewed the epidemiologic literature on CMT and reported great variation in methods as well as quality, and stressed the need for further epidemiologic research.[7]

The aim of this study was to perform a nationwide register-based study of the prevalence, incidence and mortality of CMT in Denmark, using data from the Danish National Patients Registry, which is considered one of the finest national health registers in the world.[8] In a previous study we found a high validity of the CMT diagnoses in the DNPR, thus supporting the use of the DNPR in epidemiologic research on CMT.[9]

## METHODS

### Setting and data sources

Denmark is a country with 5.6 million inhabitants. All citizens have free access to tax-funded healthcare from the Danish National Health Service. Since 1968 all citizens have been registered in the Danish Civil Registration System, given a unique 10-digit identification number (CPR number). The Danish Civil Registration System contains information on gender, date of birth and death, and the CPR number enables unambiguous linkage between databases and national registries.[10] The DNPR was established in 1977, and contains information on all non-psychiatric hospital admissions. Outpatient contacts were added in 1995. Data in the DNPR is recorded prospectively, and includes information on discharge diagnosis, diagnosis type (primary, secondary), supplementary diagnoses, hospital department, and admission and discharge dates. Diagnoses are

registered according to the International Classification of Diseases (ICD), from 1977 to 1993 according to the 8th revision (ICD-8), and hereafter according to the 10th revision (ICD-10).[8] In a previous study, the positive predictive value (PPV) of the CMT diagnoses in the DNPR was reported as 88.5%.[9]

The study was approved by the Danish Data Protection Agency (record number 1-16-02-18-12). Ethics committee review is not required for register data studies in Denmark.

**Study population**

The study was based on data from 1977 to 2012. Diagnostic codes consistent with CMT (ICD-10 DG60.0 Hereditary motor and sensory neuropathy and ICD-8 33009 Atrophia mm. neuropathica, Charcot-Marie-Tooth) were identified. Data on all patients with at least one CMT diagnosis was retrieved from the DNPR. To ensure the highest quality of data, we excluded patients not diagnosed at departments of neurology, neurophysiology, clinical genetics or pediatrics, and patients who only had secondary CMT diagnoses. A similar approach was used in the validation study described above.[9] A flowchart of the selection process is shown in figure 1.

**Statistical Analysis**

The CMT prevalence was calculated as the number of CMT patients alive by the end of 2012 compared to the total population size. Prevalence proportions with 95% confidence limits for each gender and in each of four age categories were derived in a similar way. Information on the total population size by December 31st 2012 categorized by age and gender was obtained from the Statistics Denmark.[11]

An incidence rate with a 95% confidence interval was computed for the period 1988 to 2012 and also for 5-years calendar periods starting in 1988. Patients with a first CMT diagnosis registered in DNPR in the period 1977 to 1987 and the corresponding person-years at risk were excluded from the calculation of incidence rates to minimize the effect of CMT diagnoses that were erroneously classified as a first diagnosis, due to the patient being diagnosed with CMT before the DNPR was established in 1977. CMT incidence rates were computed as the number of new CMT diagnoses in a calendar period divided by the person-years at risk in the same period. Person-years at risk were estimated as the sum of mid-year population sizes for the relevant calendar years using mid-year population sizes obtained from Statistics Denmark.[11]

A PPV-adjusted overall prevalence proportion and overall incidence rate were also obtained. The corresponding confidence intervals accounted for the statistical uncertainty in the PPV estimate.

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The mortality in the CMT cohort was compared to that of the general Danish population in the same period. Each CMT patient was followed from date of first CMT diagnosis in DNPR until December 31st 2012, date of death or date of emigration. Information on death and emigration was obtained from the Danish Civil Registration System by record linkage using the patient's CPR number. The observed number of deaths was compared with the expected number of deaths derived from gender-, age- and period-specific mortality rates for the general population.[12 13] The population rates were obtained from gender-specific life-tables based on 5-years calendar periods and 1 year age categories published by Statistics Denmark.[11] The observed and expected number of deaths was compared by computing a standardized mortality ratio (SMR) and an absolute excess rate (AER) with 95% confidence intervals. The SMR is the ratio of observed to expected number of death and is therefore the relative excess rate plus 1. The AER is the difference between the observed number and the expected number of deaths divided by the person-years at risk. SMR and AER were computed for each gender and 4 age categories and 2 categories of time since first diagnosis (duration). Stata release 13[14] was used for all statistical analyses.

## RESULTS

A total of 2065 patients were registered with a CMT diagnosis in the DNPR between 1977 and 2012, using the selection criteria as described above. In the final study population 1534 patients were included (882 males and 652 females). The selection process is illustrated in figure 1, and the distribution of patients according to selection criteria is shown in table 1. The average age at first diagnosis was 42.5 years (43.2 years in males and 41.5 years in females). The range of age at first diagnosis was 0-91 years, and. the average age at death was 70 years.

| Diagnosis type | Specialized department | | Not specialized department | | All | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| Only primary diagnosis | 1190 | (67.1) | 150 | (51.5) | 1340 | (64.9) |
| Primary and secondary diagnosis | 344 | (19.4) | 37 | (12.7) | 381 | (18.5) |
| Only secondary diagnosis | 240 | (13.5) | 104 | (35.7) | 344 | (16.7) |
| Total | 1774 | (100) | 291 | (100) | 2065 | (100) |

**Table 1:** Distribution of selection criteria among all patients diagnosed with CMT in the DNPR from 1977 to 2012. Specialized department definition: At least one diagnosis given at a neurological, neurophysiological, pediatric or clinical genetic department.

A total of 1258 patients with a CMT diagnosis were alive by December 31st 2012 among 5,602,628 residents in Denmark, corresponding to a prevalence proportion of 22.5 per 100,000 (95%CI 21.2-23.7). The distribution of prevalence according to age and gender is shown in table 2. The highest prevalence (45.2 per 100,000) was found among males in the 70+ years age group. The PPV adjusted prevalence was 19.9 per 100,000 (95%CI 18.2-21.7) when using a positive predictive value (PPV) of 88.5%.[9]

| Age category | Males | 95%CI | Females | 95%CI | Total | 95%CI |
|---|---|---|---|---|---|---|
| 0-29 years | 15.4 | 13.0-17.8 | 12.5 | 10.3-14.7 | 14.0 | 12.3-15.6 |
| 30-49 years | 20.6 | 17.4-23.8 | 20.2 | 17.0-23.4 | 20.4 | 18.1-22.7 |
| 50-69 years | 36.1 | 31.7-40.5 | 28.1 | 24.2-32.0 | 32.1 | 29.1-35.0 |
| 70+ years | 45.2 | 37.3-53.1 | 23.0 | 18.1-27.9 | 32.6 | 28.2-37.0 |
| Total | 25.1 | 23.2-26.9 | 19.9 | 18.2-21.5 | 22.5 | 21.2-23.7 |

**Table 2:** CMT prevalence per 100,000 by December 31st 2012 stratified by age and gender. CI= Confidence Interval.

Our results showed the lowest prevalence in the youngest age group and the highest prevalence in the older age groups. There was a statistically significant higher prevalence in males than females (p<0.001) (Table 2).

As described above, the incidence rate was calculated for the period 1988 to 2012: A total of 1313 patients received their first CMT diagnosis during this period, in which the general population accumulated a total of 133,445,087 person years. The overall incidence rate was 0.98 per 100,000 person years (95%CI 0.93-1.04), 1.12 per 100,000 person years (95%CI 1.05-1.21) for males and 0.85 per 100,000 person years (95%CI 0.78-0.92) for females. The incidence rate in the period 1988-1992 was 0.36 per 100,000 person years (95%CI 0.29-0.44) and the incidence rate in the period 2008-2012 was 1.58 per 100,000 person years (95%CI 1.44-1.73), corresponding to an increase in the incidence by a factor of 4.4 during this 20-year period. The PPV adjusted overall incidence rate was 0.87 per 100,000 person years (95%CI 0.80-0.95). The distribution of new CMT diagnoses in the period 1977 to 2012 is shown in figure 2.

A total of 295 deaths were observed before January 1$^{st}$ 2013 for a total of 15,948 person years. The expected number of

deaths in the matched general population was 216.8. The overall SMR was 1.36 (95%CI 1.21-1.53), and the overall AER was

4.91 (95%CI 2.79-7.02) per 1000 person years. Table 3 shows the SMR and the AER according to gender (only SMR), age

category and disease duration (time from first diagnosis). The SMR decreased with age but increased with disease duration.

The highest SMR was observed in males in the 0-29 year age group (6.01 (95%CI 3.00-12.01)). The AER increased with both

age and disease duration.

| Gender | Age category | | | | Duration category | | Total |
|---|---|---|---|---|---|---|---|
| | 0-29 years | 30-49 years | 50-69 years | 70-99 years | 0-9 years | 10+ years | |
| **Males** | | | | | | | |
| Observed | 8 | 12 | 63 | 113 | 104 | 92 | 196 |
| Expected | 1.33 | 6.18 | 40.35 | 96.74 | 89.13 | 55.48 | 144.6 |
| SMR | 6.01 | 1.94 | 1.56 | 1.17 | 1.17 | 1.66 | 1.36 |
| 95%CI | (3.00;12.01) | (1.10;3.43) | (1.22;2.00) | (0.97;1.40) | (0.96;1.41) | (1.35;2.03) | (1.18;1.56) |
| | | | | | | | |
| **Females** | | | | | | | |
| Observed | 2 | 15 | 21 | 61 | 53 | 47 | 99 |
| Expected | 0.43 | 2.49 | 15.68 | 53.57 | 44.3 | 27.86 | 72.16 |
| SMR | 4.66 | 6.04 | 1.34 | 1.14 | 1.17 | 1.69 | 1.37 |
| 95%CI | (1.17;18.63) | (3.64;10.01) | (0.87;2.05) | (0.89;1.46) | (0.89;1.54) | (1.27;2.25) | (1.14;1.68) |
| | | | | | | | |
| **Total** | | | | | | | |
| Observed | 10 | 27 | 84 | 174 | 156 | 139 | 295 |
| Expected | 1.76 | 8.66 | 56.03 | 150.31 | 134.43 | 83.34 | 216.76 |
| SMR | 5.68 | 3.12 | 1.50 | 1.16 | 1.17 | 1.67 | 1.36 |
| 95%CI | (3.06;10.55) | (2.14;4.55) | (1.21;1.86) | (1.00;1.34) | (1.00;1.37) | (1.41;1.97) | (1.21;1.53) |
| | | | | | | | |
| Risktime (y) | 3992.02 | 4667.34 | 4963.88 | 2325.02 | 10524.5 | 5423.77 | 15948.27 |
| AER/1000y | 2.06 | 3.93 | 5.63 | 10.19 | 2.14 | 10.26 | 4.91 |
| 95%CI | (0.51;3.62) | (1.75;6.11) | (2.02;9.25) | (-0.93;21.31) | (-0.18;4.47) | (6.00;14.52) | (2.79;7.02) |

**Table 3:** Standardized mortality ratio (SMR) and an absolute excess rate (AER) stratified according to age category and time

since first diagnosis. SMR is also stratified according to gender. CI= confidence interval, y=years.


**DISCUSSION**

In this nation wide study, we used national register data from the DNPR to identify 1534 patients diagnosed with CMT during a 35-year period. We report a 36% higher mortality among patients diagnosed with CMT as compared to the general population. We found a prevalence of 22.5 per 100.000 and a more than 4 fold increase in the incidence from 1988 to 2012. The DNPR is a high-quality health registry. Selection bias is minimized due to the universal nature of the Danish healthcare system and the nationwide coverage and prospective data collection of the DNPR.[8] We have previously reported a high validity of the CMT diagnoses, supporting the use of the DNPR in epidemiological research on CMT.[9] However, the CMT population in our study is not complete, as the DNPR only covers patients with hospital contact since 1977. Patients with milder signs and symptoms, or patients to whom CMT is already a well-known part of their family history, might never be referred to a hospital department. Other patients with mild or atypical symptoms may be misdiagnosed, and an unknown number of individuals with CMT or latent CMT will have died before the diagnosis could be established. Patients diagnosed before 1977 who have not received a second diagnosis, are missing from our study. The selection of patients based on department and diagnosis type, may also have excluded an unknown number of CMT patients. The DNPR does not include a categorization according to CMT subtype. We did not attempt to gather information from genetic or neurophysiologic evaluations, and thus cannot present an estimate of the distribution of subtypes.

Based on the missing CMT cases in our data, as described above, the prevalence in our study are likely to be underestimated, and should be regarded as a minimum estimate. On the other hand, the PPV values used to derive the PPV adjusted prevalence and incidence might be underestimated, as we have previously reported trends for a higher PPV in cases diagnosed between age 30 and 49 years, cases diagnosed after year 2000 and among females.[9]

The increase in incidence seen since the early 1990's, is most likely an effect of changes in the organization of the Danish National Health Service and in the DNPR: In 1992 the first genetic analysis for CMT became available to clinicians, and since then the number of genes available for analysis, as well as the general awareness of hereditary disorders, has increased steadily. In 1994 the classification system changed from ICD-8 to ICD-10, and in 1995 outpatient data was added to the DNPR.[8] The higher incidence early in the study period is most likely due to the inclusion of CMT cases diagnosed before the DNPR was established in 1977. To avoid false first diagnoses, we calculated incidence rate from 1988, yet the incidence is still likely to be overestimated, as approximately half of the patients alive had not received a second diagnosis after 15 years of follow up (data not shown).

Prevalence estimates in the literature vary greatly. In a recent review, Barreto et al assessed the quality and results of epidemiologic studies of CMT worldwide. Prevalence estimates were found within a range from 9.7-82.3 per 100,000.[3 4]

Medical record review was used in data collection in the majority of the studies, although methodology otherwise varied considerably.[7] To our knowledge, the present study is the first to use nationwide register-based data, which gives us the advantage of a large population, but limits the detail in information; unlike many other studies, we do not have data on CMT subtypes. Our prevalence result is similar to studies from Sweden (20.1/100,000)[15] and the UK (18.1/100,000).[16]

The highest and most frequently cited prevalence estimates have been reported in Norway.[2 4] In both these studies meticulous effort was put into the search for undiagnosed relatives with CMT, which may be part of the explanation for the high prevalence estimates.[4 7] In our study we did not attempt to identify undiagnosed family members. As argued above, our CMT population is not complete, and our calculated prevalence is likely to be underestimated.

Results on incidence and prevalence of CMT in Denmark have previously been presented by Werdelin & Keiding.[17] Their study included 126 cases with hereditary ataxias (defined as cerebellar ataxia, Friedreich's ataxia, hereditary spastic paraplegia and CMT) from the Danish island of Zealand in the period from 1961 to 1975. The study included 46 cases with CMT with an age between 10 and 50 years at first diagnosis. Werdelin and Keiding used probands to estimate incidence rates and found highest incidence at ages below 30 years. Prevalence was estimated from incidence and mortality information using methodology based on a stationary population assumption. This approach was clearly not appropriate for the present study and we therefore estimated the prevalence directly from the number of CMT cases alive by the end of 2012.

Apart from the study by Wedelin and Keiding, we have not been able to find other reports on the incidence of CMT.

Based on the limitations in our study population as discussed above, the mortality may have been overestimated if many of the assumed missing cases were mildly affected individuals (given that mortality is linked to the severity of CMT). Another aspect that may have influenced the mortality outcome was the use of age at first diagnosis as time of disease onset. Age at onset is extremely difficult to establish in a slowly progressive disorder such as CMT, and many patients are diagnosed long after onset of symptoms. However, since patients were identified at the date of first diagnosis in the DNPR, follow-up must start at this date to avoid survival bias.

Survival of patients with CMT was studied by comparing the mortality in the study population with the mortality in the general population. The excess mortality was described using both a multiplicative model (SMR) and an additive model (AER) for the mortality rate. The two descriptions complement each other and together provide a more complete picture of how the excess mortality depends on age and time since first diagnosis (i.e. duration of disease). We found similar trends with age and duration in excess mortality for males and females. Regarding the age dependence we found that the AER increased with age, whereas the SMR, and therefore also the relative excess rate, decreased with increasing age. This pattern shows that

the excess mortality rises with age, but not as fast as the mortality of the general population. The higher SMR values in the younger age categories probably reflect the low general mortality in young people rather than a high excess mortality. We also calculated separate SMR and AER values for two categories of duration of disease. Interestingly, we observed an increasing excess mortality both in absolute and relative terms. The decreasing SMR with age that would imply a lower relative excess mortality in the highest duration category was apparently counteracted by an increased mortality with time since diagnosis, suggesting that co-morbidities or general frailty accumulates and leads to higher excess mortality.

Some CMT subtypes are known to be more severe than others, and could have a higher mortality than other subtypes.[2 3] Especially X-linked CMT in males, and certain CMT2 and CMT4 subtypes have a more severe disease course, with very early onset and sometimes involving diaphragm paralysis.[18 19] The latter may be associated with higher risk of pulmonary morbidity and early mortality as addressed by Abboud et al.[20] Unfortunately, due to the limitation of our data we were unable to investigate if certain CMT subtypes were associated with a higher mortality than others.

To our knowledge, no prior studies on CMT have reported SMR or AER estimates; hence our results cannot be directly compared with other studies. The issue of survival in CMT has been addressed in a study by Mladenovic et al, who reported a cumulative probability of a 15-year survival in a population of 161 CMT patients. Unlike our study, Mladenovic et al used internal comparison, however, similar to our study, they found an unfavorable prognostic factor for younger age at onset.[3] The study of Werdelin & Keiding presents survival curves corrected for delayed entry. However, they do not compare survival (or mortality) of patients with that of the general population and their results are therefore not directly comparable with our results.

Until now it has been generally assumed that the lifespan of CMT patients was unaffected.[2 6] However, our study of a large group of patients diagnosed with CMT, reveals a significant increase in mortality. This finding brings to light a new set of intriguing questions and areas for further research to what causes this increase in mortality. One important question in terms of intervention is whether the increased mortality is caused by an accumulation of comorbidities, or is explained by the CMT disease itself. Being a chronic progressive disorder, CMT patients have needs for long-term and continuous medical and social support. Further understanding of the excess mortality in CMT, could help target the research and public health resources to the areas of greatest effect.

**CONTRIBUTORS**

## COMPETING INTERESTS

The authors report no conflicts of interest in this work.

## FUNDING

## ETHICS APPROVAL

The study was approved by the Danish Data Protection Agency (record number 1-16-02-18-12). Ethics committee review is not required for register data studies in Denmark.

## DATA SHARING STATEMENT

Additional data are available on request by emailing vaeth@dadlnet.dk

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**FIGURE LEGENDS**

**Figure 1:** Flowchart of study population selection. CMT= Charcot Marie Tooth. DNPR= Danish National Patients Registry. CMT case definition: At least one of ICD8 33009 or ICD10 DG60.0. Specialized department definition: At least one diagnosis given at a neurological, neurophysiological, pediatric or clinical genetic department.

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4    **Figure 2:** Distribution of first CMT diagnoses per year in the DNPR from 1977 to 2012 in males and females.
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CMT cases in the DNPR
**N=2065**

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Excluded
**N=291**

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6 Specialized department
7 **N=1774**
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10 Excluded
11 **N=240**

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13 At least one primary diagnosis
14 **N=1534**
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# BMJ Open

## Charcot-Marie-Tooth disease in Denmark: a nationwide register-based study of mortality, prevalence and incidence

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# Charcot-Marie-Tooth disease in Denmark: a nationwide register-based study of mortality, prevalence and incidence

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## ABSTRACT

**Objectives:** Charcot-Marie-Tooth disease (CMT) is the most common inherited disorder of the peripheral nervous system, yet no studies have compared the mortality in CMT patients with that of the general population, and prevalence estimates vary considerably. We performed a nationwide register-based study to investigate the prevalence, incidence and mortality of CMT in Denmark.

Design: We used the Danish National Patient Registry to select all records with primary diagnostic codes for CMT between 1977 and 2012 given at a neurologic, neurophysiologic, pediatric or clinical genetic clinic. The prevalence was estimated by December 31, 2012, and the incidence rate was calculated based on data from 1988-2012. We calculated a standardized mortality ratio (SMR) and an absolute excess mortality rate (AER) stratified according to age categories and disease duration.

**Results**: A total of 1534 patients (652 females) were identified. The prevalence proportion was 22.5 per 100,000 (95% confidence interval [CI] 21.2-23.7) and the incidence rate was 0.98 (95% CI 0.93-1.04) per 100,000 person years. The SMR was 1.36 (95% CI 1.21-1.53), and the AER was 4.87 per 1000 person years (95%CI 2.77-6.96). We found a significantly higher SMR in cases below 50 years of age, and in cases with disease duration of more than 10 years.

**Conclusions:** We found a reduced life expectancy among patients diagnosed with CMT. To our knowledge, this is the first study of CMT to use nationwide register-based data, and the first to report a SMR and an AER.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- The first nationwide register based study of Charcot-Marie-Tooth disease.

- Data has been collected from the Danish National Patients Registry (DNPR); a high quality national registry with prospective data collection, thereby minimizing selection bias.

- The study is based on a large cohort of patients (n=1534) diagnosed with CMT between 1977 and 2012

- The DNPR only includes hospital contacts; therefore CMT patients not admitted and diagnosed at a hospital department are not included, which might be the case for many mildly affected patients,

-  Misdiagnosed cases due to atypical CMT symptoms and signs are missing in this study, as we only included patients who are registered with a CMT diagnosis in the DNPR.

## INTRODUCTION

The Charcot-Marie-Tooth disease (CMT) is both clinically and genetically heterogeneous. The typical signs are slowly progressive muscle weakness of the extremities, deformities of the feet and hands, loss of tendon reflexes, and mild to severe sensory loss. However, symptoms and severity as well as age at onset can vary considerably, even within the same family.[1] This heterogeneity makes CMT a great challenge in diagnostics as well as epidemiology. CMT is known as one of the most common hereditary neurological disorders,[2] but prevalence estimates in the literature vary greatly, ranging from 9.7 per 100,000 in Serbia[3] to 82.3 per 100,000 in Norway.[4] In recent years, knowledge of CMT has increased, as more and more CMT associated genes have been discovered owing to the development of massive parallel sequencing technologies. Today, mutations in more than 80 CMT and related neuropathy genes have been identified.[5] In spite of this increase in research, epidemiologic knowledge about CMT is still scarce. The lifespan of patients with CMT is generally assumed to be normal,[2 6] yet to our knowledge, the mortality of CMT patients has never been compared to the mortality in the general population. Recently, Barreto et al reviewed the epidemiologic literature on CMT and reported great variation in methods as well as quality, and stressed the need for further epidemiologic research.[7]

The aim of this study was to perform a nationwide register-based study of the prevalence, incidence and mortality of CMT in Denmark, using data from the Danish National Patients Registry, which is considered one of the finest national health registers in the world.[8] In a previous study we found a high validity of the CMT diagnoses in the DNPR, thus supporting the use of the DNPR in epidemiologic research on CMT[9].

## METHODS

### Setting and data sources

Denmark is a country with 5.6 million inhabitants. All citizens have free access to tax-funded healthcare from the Danish National Health Service. Since 1968 all citizens have been registered in the Danish Civil Registration System, given a unique 10-digit identification number (CPR number). The Danish Civil Registration System contains information on gender, date of birth and death, and the CPR number enables unambiguous linkage between databases and national registries.[10] The DNPR was established in 1977, and contains information on all non-psychiatric hospital admissions. Outpatient contacts were added in 1995. Data in the DNPR is recorded prospectively, and includes information on discharge diagnosis, diagnosis type (primary, secondary), supplementary diagnoses, hospital department, and admission and discharge dates. Diagnoses are

registered according to the International Classification of Diseases (ICD), from 1977 to 1993 according to the 8th revision (ICD-8), and hereafter according to the 10th revision (ICD-10).[8] In a previous study, the positive predictive value (PPV) of the CMT diagnoses in the DNPR was reported as 88.5%.[9]

The study was approved by the Danish Data Protection Agency (record number 1-16-02-18-12). Ethics committee review is not required for register data studies in Denmark.

**Study population**

The study was based on data from 1977 to 2012. Diagnostic codes consistent with CMT (ICD-10 DG60.0 Hereditary motor and sensory neuropathy and ICD-8 33009 Atrophia mm. neuropathica, Charcot-Marie-Tooth) were identified. Data on all patients with at least one CMT diagnosis was retrieved from the DNPR. To ensure the highest quality of data, we excluded patients not diagnosed at departments of neurology, neurophysiology, clinical genetics or pediatrics, and patients who only had secondary CMT diagnoses. A similar approach was used in the validation study described above[9]. A flowchart of the selection process is shown in figure 1.

**Statistical Analysis**

The CMT prevalence was calculated as the number of CMT patients alive by the end of 2012 compared to the total population size. Prevalence proportions with 95% confidence limits for each gender and in each of four age categories were derived in a similar way. Information on the total population size by December 31st 2012 categorized by age and gender was obtained from the Statistics Denmark.[11]

An incidence rate with a 95% confidence interval was computed for the period 1988 to 2012 and also for 5-years calendar periods starting in 1988. CMT diagnoses could not be identified prior to the establishment of DNPR in 1977. Therefore, early in the study period, some patients who had their first CMT diagnosis registered in DNPR may have been diagnosed with CMT before 1977. The first diagnosis in DNPR would then erroneously be identified as the patient's first diagnosis of CMT, causing a spurious increase of the incidence. To minimize this problem patients with a first CMT diagnosis registered in DNPR in the period 1977 to 1987 and the corresponding person-years at risk were excluded from the calculation of incidence rates. CMT incidence rates were computed as the number of new CMT diagnoses in a calendar period divided by the person-years at risk in the same period. Person-years at risk were estimated as the sum of mid-year population sizes for the relevant calendar years using mid-year population sizes obtained from Statistics Denmark.[11]

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4     A PPV-adjusted overall prevalence proportion and overall incidence rate were also obtained. The corresponding confidence
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6     intervals accounted for the statistical uncertainty in the PPV estimate.
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8     The mortality in the CMT cohort was compared to that of the general Danish population in the same period. Each CMT
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10    patient was followed from date of first CMT diagnosis in DNPR until December 31st 2012, date of death or date of emigration.
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12    Information on death and emigration was obtained from the Danish Civil Registration System by record linkage using the
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14    patient's CPR number. The observed number of deaths was compared with the expected number of deaths derived from
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16    gender-, age- and period-specific mortality rates for the general population.[12 13] The population rates were obtained from
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18    gender-specific life-tables based on 5-years calendar periods and 1 year age categories published by Statistics Denmark.[11]
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20    The observed and expected number of deaths was compared by computing a standardized mortality ratio (SMR) and an
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22    absolute excess rate (AER) with 95% confidence intervals. The SMR is the ratio of observed number of death to expected
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24    number of death and is therefore the relative excess rate plus 1. The AER is the difference between the observed number
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26    and the expected number of deaths divided by the person-years at risk. SMR and AER were computed for each gender and 4
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28    age categories (0-29, 30-49, 50-69 and 70-99 years) and 2 categories of time since first diagnosis (duration) (0-9 and >10
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30    years). Stata release 13[14] was used for all statistical analyses.
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34    **RESULTS**
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36    A total of 2065 patients were registered with a CMT diagnosis in the DNPR between 1977 and 2012, using the selection
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38    criteria as described above. In the final study population 1534 patients were included (882 males and 652 females). The
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40    selection process is illustrated in figure 1, and the distribution of patients according to selection criteria is shown in table 1.
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42    The average age at first diagnosis was 42.5 years (43.2 years in males and 41.5 years in females). The range of age at first
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44    diagnosis was  0-91 years, and. the average age at death was 70 years.
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| Diagnosis type | Specialized department | | Not specialized department | | All | |
| --- | --- | --- | --- | --- | --- | --- |
| | Number | % | Number | % | Number | % |
| Only primary diagnosis | 1190 | (67.1) | 150 | (51.5) | 1340 | (64.9) |
| Primary and secondary diagnosis | 344 | (19.4) | 37 | (12.7) | 381 | (18.5) |
| Only secondary diagnosis | 240 | (13.5) | 104 | (35.7) | 344 | (16.7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Total | 1774 | (100) | 291 | (100) | 2065 | (100) |

**Table 1:** Distribution of selection criteria among all patients diagnosed with CMT in the DNPR from 1977 to 2012.

Notes: Specialized department = At least one diagnosis (ICD8 33009 or ICD10 DG60.0) given at a neurological, neurophysiological, pediatric or clinical genetic department.

A total of 1258 patients with a CMT diagnosis were alive by December 31st 2012 among 5,602,628 residents in Denmark, corresponding to a prevalence proportion of 22.5 per 100,000 (95%CI 21.2-23.7). The distribution of prevalence according to age and gender is shown in table 2. The highest prevalence (45.2 per 100,000) was found among males in the 70+ years age group. The PPV adjusted prevalence was 19.9 per 100,000 (95%CI 18.2-21.7) when using a PPV of 88.5%.[9]

| Age category | Males | 95%CI | Females | 95%CI | Total | 95%CI |
|---|---|---|---|---|---|---|
| 0-29 years | 15.4 | 13.0-17.8 | 12.5 | 10.3-14.7 | 14.0 | 12.3-15.6 |
| 30-49 years | 20.6 | 17.4-23.8 | 20.2 | 17.0-23.4 | 20.4 | 18.1-22.7 |
| 50-69 years | 36.1 | 31.7-40.5 | 28.1 | 24.2-32.0 | 32.1 | 29.1-35.0 |
| 70+ years | 45.2 | 37.3-53.1 | 23.0 | 18.1-27.9 | 32.6 | 28.2-37.0 |
| Total | 25.1 | 23.2-26.9 | 19.9 | 18.2-21.5 | 22.5 | 21.2-23.7 |

**Table 2:** CMT prevalence per 100,000 by December 31st 2012 stratified by age and gender.
Abbreviation: CI, Confidence Interval.

Our results showed the lowest prevalence in the youngest age group and the highest prevalence in the older age groups. There was a statistically significant higher prevalence in males than females (p<0.001) (Table 2).

As described above, the incidence rate was calculated for the period 1988 to 2012: A total of 1313 patients received their first CMT diagnosis during this period, in which the general population accumulated a total of 133,445,087 person years. The overall incidence rate was 0.98 per 100,000 person years (95%CI 0.93-1.04), 1.12 per 100,000 person years (95%CI 1.05-1.21) for males and 0.85 per 100,000 person years (95%CI 0.78-0.92) for females. The incidence rate in the period 1988-1992 was 0.36 per 100,000 person years (95%CI 0.29-0.44) and the incidence rate in the period 2008-2012 was 1.58 per 100,000 person years (95%CI 1.44-1.73), corresponding to an increase in the incidence by a factor of 4.4 during this 20-year period.

The PPV adjusted overall incidence rate was 0.87 per 100,000 person years (95%CI 0.80-0.95). The distribution of new CMT diagnoses in the period 1977 to 2012 is shown in figure 2.

A total of 295 deaths were observed before January 1st 2013 for a total of 15,948 person years. The expected number of deaths in the matched general population was 216.8. The overall SMR was 1.36 (95%CI 1.21-1.53), and the overall AER was 4.91 (95%CI 2.79-7.02) per 1000 person years. Table 3 shows the SMR and the AER according to gender (only SMR), age category and disease duration (time from first diagnosis). The SMR decreased with age but increased with disease duration. The highest SMR was observed in males in the 0-29 year age group (6.01 (95%CI 3.00-12.01). The AER increased with both age and disease duration.

| Gender | Age category | | | | Duration category | | Total |
|---|---|---|---|---|---|---|---|
| | 0-29 years | 30-49 years | 50-69 years | 70-99 years | 0-9 years | 10+ years | |
| **Males** | | | | | | | |
| Observed | 8 | 12 | 63 | 113 | 104 | 92 | 196 |
| Expected | 1.33 | 6.18 | 40.35 | 96.74 | 89.13 | 55.48 | 144.6 |
| SMR | 6.01 | 1.94 | 1.56 | 1.17 | 1.17 | 1.66 | 1.36 |
| 95%CI | (3.00;12.01) | (1.10;3.43) | (1.22;2.00) | (0.97;1.40) | (0.96;1.41) | (1.35;2.03) | (1.18;1.56) |
| | | | | | | | |
| **Females** | | | | | | | |
| Observed | 2 | 15 | 21 | 61 | 53 | 47 | 99 |
| Expected | 0.43 | 2.49 | 15.68 | 53.57 | 44.3 | 27.86 | 72.16 |
| SMR | 4.66 | 6.04 | 1.34 | 1.14 | 1.17 | 1.69 | 1.37 |
| 95%CI | (1.17;18.63) | (3.64;10.01) | (0.87;2.05) | (0.89;1.46) | (0.89;1.54) | (1.27;2.25) | (1.14;1.68) |
| | | | | | | | |
| **Total** | | | | | | | |
| Observed | 10 | 27 | 84 | 174 | 156 | 139 | 295 |
| Expected | 1.76 | 8.66 | 56.03 | 150.31 | 134.43 | 83.34 | 216.76 |
| SMR | 5.68 | 3.12 | 1.50 | 1.16 | 1.17 | 1.67 | 1.36 |
| 95%CI | (3.06;10.55) | (2.14;4.55) | (1.21;1.86) | (1.00;1.34) | (1.00;1.37) | (1.41;1.97) | (1.21;1.53) |
| | | | | | | | |
| Risktime (y) | 3992.02 | 4667.34 | 4963.88 | 2325.02 | 10524.5 | 5423.77 | 15948.27 |
| AER/1000y | 2.06 | 3.93 | 5.63 | 10.19 | 2.14 | 10.26 | 4.91 |
| 95%CI | (0.51;3.62) | (1.75;6.11) | (2.02;9.25) | (-0.93;21.31) | (-0.18;4.47) | (6.00;14.52) | (2.79;7.02) |

**Table 3:** Standardized mortality ratio (SMR) and an absolute excess rate (AER) stratified according to age category and time since first diagnosis. SMR is also stratified according to gender.

Abbreviations: CI, confidence interval; y, years.

## DISCUSSION

In this nation wide study, we used national register data from the DNPR to identify 1534 patients diagnosed with CMT during a 35-year period. We report a 36% higher mortality among patients diagnosed with CMT as compared to the general population. We found a prevalence of 22.5 per 100,000 and a more than 4 fold increase in the incidence from 1988 to 2012. The DNPR is a high-quality health registry; selection bias is minimized due to the universal nature of the Danish healthcare system and the nationwide coverage and prospective data collection.[8] We have previously reported a high validity of the CMT diagnoses, supporting the use of the DNPR in epidemiological research on CMT[9]. However, the CMT population in our study is not complete, as the DNPR only covers patients with hospital contact since 1977. Patients with milder signs and symptoms, or patients to whom CMT is already a well-known part of their family history, might never be referred to a hospital department. Other patients with mild or atypical symptoms may have been misdiagnosed, e.g. as having another neurological disorder, and an unknown number of individuals with CMT or latent CMT will have died before the diagnosis could be established. Patients diagnosed before 1977 who have not received a second diagnosis, are missing from our study. Before 1995, the DNPR only included data from hospital admissions, therefore any CMT diagnosis given at an outpatient contact before 1995 is missing from our data. However, the health care system in Denmark has changed considerably during the study period; many hospital admissions from before 1995 would probably be performed as outpatient contacts today. The selection of patients based on department and diagnosis type, may also have excluded an unknown number of CMT patients also. Although we only included specialized departments presumed to have considerably experience with diagnosing CMT, we cannot exclude incorrect CMT diagnosis in some cases. However, as mentioned earlier, in a previous study we found that the validity of the CMT diagnosis is high in the DNPR.[9] The DNPR does not include a categorization according to CMT subtype. We did not attempt to gather information from genetic or neurophysiologic evaluations, and thus cannot present an estimate of the distribution of subtypes.

Based on the missing CMT cases in our data, as described above, the prevalence in our study are likely to be underestimated, and should be regarded as a minimum estimate. On the other hand, the PPV used to derive the PPV adjusted prevalence and incidence might be underestimated, as we have previously reported trends for a higher PPV in cases diagnosed between age 30 and 49 years, cases diagnosed after year 2000 and among females.[9]

The increase in incidence seen since the early 1990's, is most likely an effect of changes in the organization of the Danish National Health Service and in the DNPR: In 1992 the first genetic analysis for CMT became available to clinicians, and since

then the number of genes available for analysis, as well as the general awareness of hereditary disorders, has increased steadily. In 1994 the classification system changed from ICD-8 to ICD-10, and in 1995 outpatient data was added to the DNPR.[8] The higher incidence early in the study period is most likely due to the inclusion of CMT cases diagnosed before the DNPR was established in 1977. To avoid false first diagnoses, we calculated incidence rate from 1988, yet the incidence is still likely to be overestimated, as approximately half of the patients alive had not received a second diagnosis after 15 years of follow up (data not shown).

Prevalence estimates in the literature vary greatly: In a recent review, Barreto et al assessed the quality and results of epidemiologic studies of CMT worldwide. Prevalence estimates were found within a range from 9.7-82.3 per 100,000.[3 4] Medical record review was used in data collection in the majority of the studies, although methodology otherwise varied considerably.[7] To our knowledge, the present study is the first to use nationwide register-based data, which gives us the advantage of a large population, but limits the detail in information; unlike many other studies, we do not have data on CMT subtypes. Our prevalence result is similar to studies from Sweden (20.1/100,000)[15] and the UK (18.1/100,000).[16]

The highest and most frequently cited prevalence estimates have been reported in two studies from Norway.[2 4] In both Norwegian studies meticulous effort was put into the search for undiagnosed relatives with CMT, which may be part of the explanation for the high prevalence estimates.[4 7] In our study we did not attempt to identify undiagnosed family members. As argued above, our CMT population is not complete, and our calculated prevalence is likely to be underestimated. We found a significantly higher prevalence of males diagnosed with CMT as compared to females. Similar findings have been reported by Mladenovic et al and Gudmundsson et al,[3 17] however, Braathen et al reported a higher prevalence in females[4] and Morocutti et al found no difference in prevalence between the sexes.[18]

Results on incidence and prevalence of CMT in Denmark have previously been presented by Werdelin & Keiding.[19] Their study included 126 cases with hereditary ataxias (defined as cerebellar ataxia, Friedreich's ataxia, hereditary spastic paraplegia and CMT) from the Danish island of Zealand in the period from 1961 to 1975. The study included 46 cases with CMT with an age between 10 and 50 years at first diagnosis. Werdelin and Keiding used probands to estimate incidence rates and found highest incidence at ages below 30 years. Prevalence was estimated from incidence and mortality information using methodology based on a stationary population assumption. This approach was clearly not appropriate for the present study and we therefore estimated the prevalence directly from the number of CMT cases alive by the end of 2012.

Apart from the study by Wedelin and Keiding, we have not been able to find other reports on the incidence of CMT.

Based on the limitations in our study population as discussed above, the mortality may have been overestimated if many of

the assumed missing cases were mildly affected individuals (given that mortality is linked to the severity of CMT). Another

aspect that may have influenced the mortality outcome was the use of age at first diagnosis as time of disease onset. Age at

onset is extremely difficult to establish in a slowly progressive disorder such as CMT, and many patients are diagnosed long

after onset of symptoms. However, since patients were identified at the date of first diagnosis in the DNPR, follow-up must

start at this date to avoid survival bias.

Survival of patients with CMT was studied by comparing the mortality in the study population with the mortality in the

general population. The excess mortality was described using both a multiplicative model (SMR) and an additive model (AER)

for the mortality rate. The two descriptions complement each other and together provide a more complete picture of how

the excess mortality depends on age and time since first diagnosis (i.e. duration of disease). Overall, the excess mortality was

modest, but statistically significant; we found 295 deaths where 217 deaths were expected, giving a SMR of 1.36. This SMR is

slightly smaller than the SMR describing the excess mortality seen for males relative to females in Denmark.[20] We found

similar trends with age and duration in excess mortality for males and females. Regarding the age dependence we found that

the AER increased with age, whereas the SMR, and therefore also the relative excess rate, decreased with increasing age.

This pattern shows that the excess mortality rises with age, but not as fast as the mortality of the general population. The

higher SMR values in the younger age categories probably reflect the low overall mortality in young people rather than a high

excess mortality. This interpretation is further supported by the fact that the AER is quite small for the youngest age

category.  We also calculated separate SMR and AER values for two categories of duration of disease. Interestingly, we

observed an increasing excess mortality both in absolute and relative terms. The decreasing SMR with age that would imply a

lower relative excess mortality in the highest duration category was apparently counteracted by an increased mortality with

time since diagnosis, suggesting that co-morbidities or general frailty accumulates and leads to higher excess mortality.

Some CMT subtypes are known to be more severe than others, and could have a higher mortality than other subtypes.[2 3]

Especially X-linked CMT in males, and certain CMT2 and CMT4 subtypes have a more severe disease course, with very early

onset and sometimes involving diaphragm paralysis.[21 22] The latter may be associated with higher risk of pulmonary morbidity

and early mortality as addressed by Abboud et al.[23] Unfortunately, due to the limitation of our data we were unable to

investigate if certain CMT subtypes were associated with a higher mortality than others.

To our knowledge, no prior studies on CMT have reported SMR or AER estimates; hence our results cannot be directly

compared with other studies. The issue of survival in CMT has been addressed in a study by Mladenovic et al, who reported a

cumulative probability of a 15-year survival in a population of 161 CMT patients. Unlike our study, Mladenovic et al used

internal comparison, however, similar to our study, they found an unfavorable prognostic factor for younger age at onset.[3]

The study of Werdelin & Keiding presents survival curves corrected for delayed entry. However, they do not compare survival

(or mortality) of patients with that of the general population and their results are therefore not directly comparable with our

results.

Until now it has been generally assumed that the lifespan of CMT patients was unaffected.[2 6] However, our study of a large

group of patients diagnosed with CMT, reveals a significant increase in mortality. This finding brings to light a new set of

intriguing questions and areas for further research to what causes this increase in mortality. One important question in terms

of intervention is whether the increased mortality is caused by an accumulation of comorbidities, or is explained by the CMT

disease itself. Being a chronic progressive disorder, CMT patients have needs for long-term and continuous medical and

social support. Further understanding of the excess mortality in CMT, could help target the research and public health

resources to the areas of greatest effect.

## CONTRIBUTORS

SV and UBJ were responsible for the acquisition of data. SV was responsible for data management and initial drafting of the

manuscript. MV was responsible for the statistical analysis and contributed to the data management and the initial drafting

of the manuscript. SV, MV, HA, RC and UBJ contributed to the research idea, study design and critical revision of the

manuscript. All authors have read and approved the final manuscript.

## COMPETING INTERESTS

The authors report no conflicts of interest in this work.

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University (SV).

## ETHICS APPROVAL

The study was approved by the Danish Data Protection Agency (record number 1-16-02-18-12). Ethics committee review is

not required for register data studies in Denmark.

**DATA SHARING STATEMENT**

Additional data are available on request by emailing vaeth@dadlnet.dk

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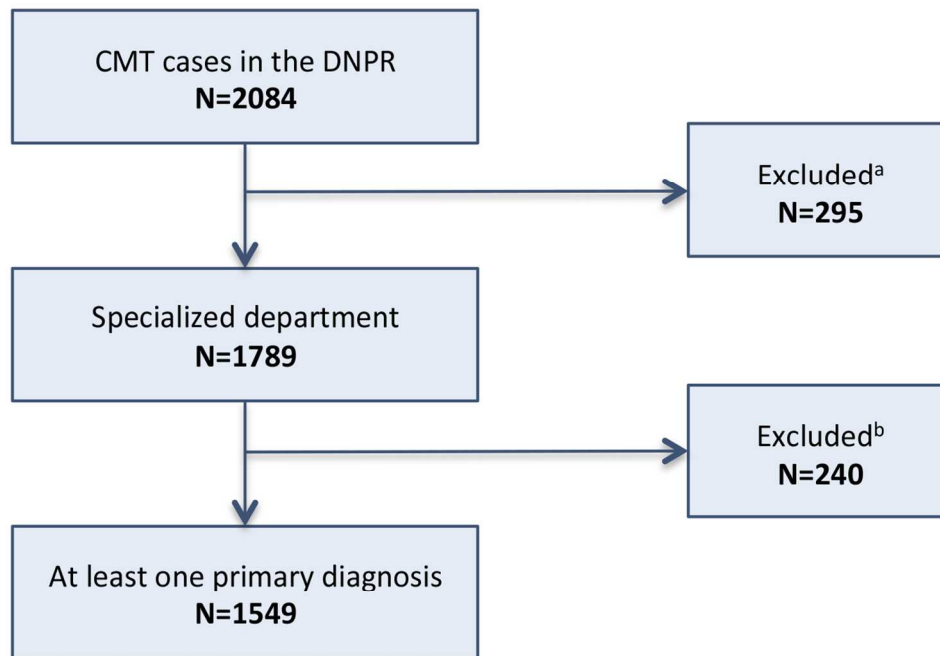
**FIGURE LEGENDS**

**Figure 1:** Flowchart of study population selection.

Notes: CMT case = Diagnosed with ICD8 33009 or ICD10 DG60.0. Specialized department = At least one diagnosis (ICD8 33009 or ICD10 DG60.0) given at a neurological, neurophysiological, pediatric or clinical genetic department. Excluded[a] = Cases not diagnosed at a specialized department. Excluded[b] = Cases only registered with a secondary CMT diagnoses.

Abbreviations: CMT, Charcot Marie Tooth; DNPR, Danish National Patients Registry.

**Figure 2:** Distribution of first CMT diagnoses per year in the DNPR from 1977 to 2012 in males and females.
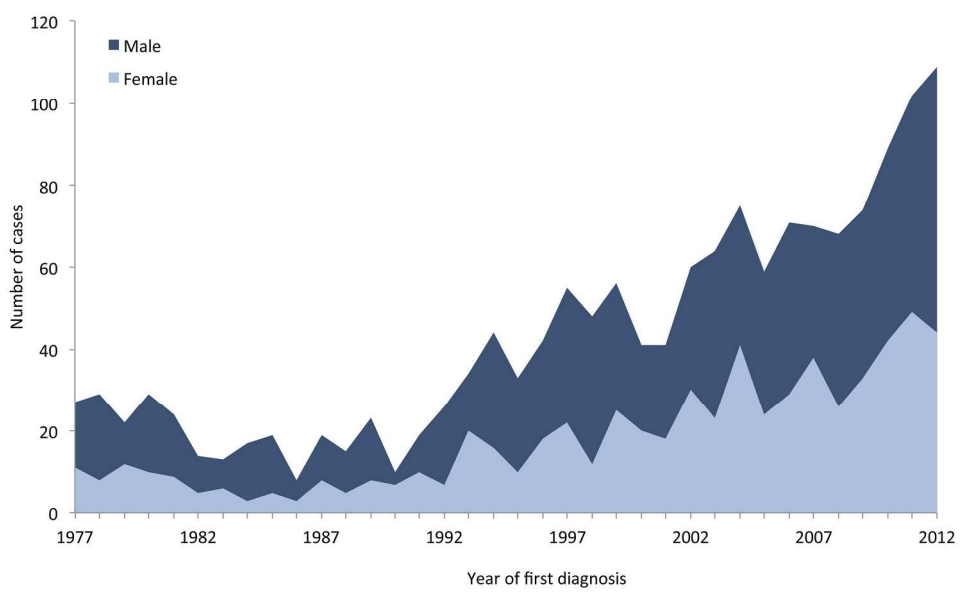
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┌─────────────────────────┐
│   CMT cases in the DNPR │
│         N=2084          │
└─────────────────────────┘
            │          ┌──────────────┐
            │─────────▶│  Excludedᵃ   │
            ▼          │    N=295     │
┌─────────────────────────┐ └──────────────┘
│  Specialized department │
│         N=1789          │
└─────────────────────────┘
            │          ┌──────────────┐
            │─────────▶│  Excludedᵇ   │
            ▼          │    N=240     │
┌─────────────────────────┐ └──────────────┘
│ At least one primary    │
│      diagnosis          │
│         N=1549          │
└─────────────────────────┘
```

Flowchart of study population selection.

120x86mm (300 x 300 DPI)

Distribution of first CMT diagnoses per year in the DNPR from 1977 to 2012 in males and females.

199x122mm (300 x 300 DPI)