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Incidence, Prevalence and Geographical Clustering of Motor Neuron Disease in the Netherlands

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Abstract

Objective: To assess time trends in MND incidence, prevalence and mortality and investigate geographical clustering of MND cases in the Netherlands from 1998 to 2017, we analyzed data from the Netherlands Personal Records database, the Netherlands MND Center and the Netherlands Patient Association of Neuromuscular Diseases.

Methods: In this prospective cohort study, Poisson regression was used to assess time trends in MND risk. We calculated age- and sex-standardized, observed and expected cases for 1,694 areas. Bayesian smoothed risk mapping was used to investigate geographical MND risk.

Results: We identified 7,992 MND cases, reflecting an incidence of 2.64 (95% CI 2.62-2.67) per 100,000 person-years and a prevalence of 9.5 (95% CI 9.1-10.0) per 100,000 persons. Highest age-standardized prevalence and mortality rates occurred at a later age in men than in women (p<0.001). Unadjusted mortality rates increased by 53.2% from 2.57 in 1998 to 3.86 per 100,000 person-years in 2017. After adjustment for age and sex, an increase in MND mortality rate of 14.1% (95% CI 5.7%-23.2%, p<0.001) remained. MND relative risk ranged from 0.78 to 1.43 between geographical areas; multiple urban and rural high-risk areas were identified.

Conclusions: We found a significant national increase in MND mortality from 1998 through 2017, only partly explained by an ageing Dutch population, and also a geographic variability in MND risk, suggesting a role for environmental or demographic risk factors.

Introduction

Motor neuron disease (MND) is a fatal neurodegenerative disease caused by both genetic and environmental factors, many of which remain to be elucidated (1,2). Worldwide MND incidence and prevalence have been shown to increase in the last decades (3). Ageing of the world population is seen as its primary driver, but does not account entirely for the increasing incidence and prevalence (3,4). This indicates that important genetic or potentially preventable, environmental risk factors are currently driving the increase in MND risk. Urgent identification of these risk factors is paramount given the debilitating and care-intensive nature of MND, and its future impact on healthcare services (2,5).

Although assessing whether MND risk is increasing may aid planning of health services, it does not directly identify underlying risk factors. Geographical studies, on the other hand, can stimulate etiological research by identifying specific disease clusters. Examples are identification of patient clusters in Guam (6) and the Kii Peninsula (7) which were subsequently linked to neurotoxic plant consumption and the *C9orf72* repeat-expansion. Studies of time trends or clusters have, however, often been limited by methodological issues, such as incomplete case ascertainment or geographic risk assessment in a limited area (8).

We, therefore, use multiple, independent, national data sources in the Netherlands, including a nationwide population-based study operational since 2006, in order to 1) determine the change in MND incidence, prevalence, mortality rates and survival time in the Netherlands over the last two decades and; 2) investigate geographical clustering of MND cases.

Methods

Data sources

Three independent sources of prospectively collected data were used to estimate incidence, prevalence and mortality of adult-onset MND (i.e. amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS) and progressive muscular atrophy (PMA)) in the Netherlands. The first source was the Netherlands Personal Records (DPR) database covering the period 1998 to 2017. All Dutch residents are registered in the DPR database and Dutch law requires that all deaths in the Netherlands be registered by a physician according to the International Classification of Diseases, Tenth revision (ICD-10). MND (ICD-10 codes G12.21 through G12.24) is registered as the cause of death even if it was an underlying cause (e.g. in the case of death due to pneumonia). We also selected Alzheimer cases (ICD-10 code G30) to compare the effect of age on Alzheimer and MND mortality rates. As a second source, we used data from the population-based Netherlands MND Center registry, described in more detail elsewhere (9). In brief, patients diagnosed with MND, according to the revised El Escorial criteria (10), have been prospectively registered centrally by the Netherlands MND Center since 2006. Patients were identified via annual screening of large hospital registries, specialized MND rehabilitation clinic registries and by contacting neurologists individually (9). Survival times after date of diagnosis (date of death or date last known to be alive) were obtained for patients in the Netherlands MND registry by checking the online municipal register at 3-monthly intervals. Third, patients were identified within the register of a national patient advocacy organization, the Netherlands Patients Association for Neuromuscular Diseases (11).

Statistical analysis

Comprehensive MND health surveillance estimates were calculated as follows. Age- and gender-adjusted incidence and mortality rates were calculated by dividing the

number of observed cases by the person-years of observation. Cases were identified in the DPR database from 1998 through 2017 and in the Netherlands MND registry from 2006 through 2017. MND prevalence was the number of MND patients alive on 31 December 2017 expressed as a proportion of the total Dutch population. The number of unobserved cases in the MND registry was estimated via two methods. First, two source capture-recapture methodology was applied to each 5-year age and sex stratum, using data from the MND registry and the Netherlands Patients Association for Neuromuscular Diseases. Capture-recapture methodology aims to correct for under-ascertainment in health surveillance studies (12), and has been successfully applied in other neuromuscular epidemiological studies (13). Chapman's formulae were used to estimate the total number of prevalent MND patients and the proportion identified by the MND registry (12). As a sensitivity analysis, we also estimated incidence and prevalence based on the MND deaths per year recorded in the DPR database. Individual survival times were sampled from a Weibull distribution (14) and subtracted from the date of death to calculate date of diagnosis. Simulations were repeated 50,000 times to obtain empirical 95% confidence intervals for incidence and prevalence estimates.

Next, we assessed whether MND mortality rates changed between 1998 and 2017. We used a Poisson generalized linear model and data from the DPR database to estimate MND mortality rate per year. We incorporated age (quadratic), sex, their interaction and years since 1998 as covariates with the natural logarithm of population size as an offset. To test both whether the effect of age differs across sexes, and whether rates have increased since 1998, we tested each term using a likelihood ratio test. As a sensitivity analysis, we evaluated how loss of competing risks and longevity of a subpopulation susceptible to MND influence MND mortality rates as described elsewhere (15). We evaluated whether patient characteristics of the Netherlands MND

registry changed between early periods (2006 to 2009) and late periods (2014 to 2017). Cox regression was used to assess whether survival recorded by the Netherlands MND registry changed from 2006 through 2017. The hazard ratio for time in years since 2006 was adjusted for the patient's individual risk profile according to the European Network for the Cure of ALS (ENCALS) survival prediction model (16). The ENCALS risk profile is a relative measure and indicates whether a patient's survival time is shorter or longer relative to other patients. Five prognostic subgroups were defined based on the quintiles of the individual risk profiles (17). Missing values in baseline characteristics, necessary to determine the ENCALS risk profile, were accounted for by creating 100 imputed datasets as described earlier (17). Estimates were pooled across imputations using Rubin's rules (18).

Finally, we evaluated the geographical distribution of MND cases in the Netherlands. For the mapping of MND risk and to identify both high- and low-risk areas, data from the DPR database were used. As per 1 January 2018, the Netherlands comprises 13,305 geographical areas (i.e. neighborhoods). The DPR database contains detailed individual residential history data, dating from approximately 1990. The address where a case had resided the longest since 1990 was used to calculate the number of observed cases per geographical area. Nationwide mortality rates per 5-year age and sex group were applied to the mean population per time period to calculate the number of expected MND cases per geographical area. To obtain sufficient sample size in order to conduct spatial smoothing of MND risk, areas with an expected incidence lower than 3 cases (i.e. approximately 6,000 residents from 1998 through 2017) were merged iteratively with adjacent areas with the lowest expected incidence, until all areas had at least an expected incidence of 3. Next, crude standardized mortality ratios (SMRs) were calculated by dividing the observed by the expected

number of cases. SMRs were subsequently smoothed to estimate MND relative risk (RR) per area by using a Bayesian autoregression model with local random effects, as described elsewhere (18). As an example, a RR of 1.3 means that the observed MND rate in that area is estimated to be 30% higher than expected (i.e. the national rate of MND) (8). For each area, we determined the posterior probability that the local risk of MND would be either lower or higher than the national risk based on 10,000 draws from the posterior distribution (i.e. the posterior probability that RR < 1.0 or RR > 1.0, respectively). Bayesian analyses control for multiplicity by using a conservative prior which shrinks all estimates towards the null-hypothesis (i.e. a relative risk of 1.0). Therefore, it is not necessary to adjust the posterior probability for multiplicity. Additionally, the prior ensures that MND relative risk can be estimated even in rural areas when data are sparse. As an exploratory analysis, we assessed the weighted association between RR and the average age, percentage males and population density per area. Population density was analyzed as number of residents per square kilometer; the following definitions from Statistics Netherlands were used: <500 (very low), 500 – 1,000 (low), 1,000 – 1,500 (average), 1,500 – 2,500 (high) and >2,500 (very high).

Standard protocol approvals, registrations and patient consents

This study is reported according to the Standards of Reporting of Neurological Disorders (STROND) guideline (19). The medical ethics committee and institutional review board of the University Medical Center Utrecht approved this study.

Data Availability

All protocols, analyses and anonymized data will be shared on request from any qualified investigator. Access to data from the DPR database can be requested from Statistics Netherlands (CBS) via https://www.cbs.nl/en-gb/our-services/customised-services-microdata/microdata-conducting-your-own-research/microdata-catalogue.

Results

MND incidence, prevalence and mortality

From 1998 through 2017, there were, on average, 16.4 million residents and a total of 3.2 million deaths recorded in the Netherlands, of which 7,992 (0.25%) were MND-related. The total number of incident MND patients in this time period was estimated to be 8,676 (95% CI 8,585-8,767), resulting in an average annual incidence of 2.64 (95% CI 2.62-2.67) per 100,000 person-years. Since the start of the MND registry in 2006, the number of incident patients was 5,764, 4,152 (72.0%) of whom were identified by the MND registry. **Table 1** presents their patient characteristics; patients identified via the MND registry were, on average, younger (67.7 versus 69.7 years) and more likely to be male (58.4% versus 54.8%) compared to patients in the DPR database.

On 31 December 2017, we identified 1,215 prevalent patients in the MND registry (source 1) and the Netherlands Patient Association for Neuromuscular Diseases (source 2). A total of 953 patients were unique to source 1, 83 were unique to source 2 and 179 patients were identified by both sources. The total number of prevalent patients with MND was estimated at 1,654, resulting in a prevalence of 9.6 (95% CI 9.5-9.8) per 100,000 persons (Supplementary Table 1). The simulation-based sensitivity analysis based on data from the DPR database resulted in a similar prevalence estimate (N = 1,639 patients, 9.5 per 100,000 persons).

Overall MND incidence and mortality rates were highest in the 70-74 and 75-79 age groups, respectively (**Figure 1**). Incidence and prevalence data are available in Dryad (Figure 1). There was a differential effect of age for men and women (i.e. different shape of the age-standardized rates graphs in **Figure 1**) on incidence ($p < 0.01$ for interaction term), prevalence and mortality (both $p < 0.001$). For example, highest MND prevalence and mortality rates occurred at later ages for men compared to

women (80-84 years versus 75-79 years, respectively). In contrast, highest Alzheimer mortality rates occurred in the oldest age group (>95 years) for both men and women **(Figure 1D)**.

Time trends

In 2017, 0.31% of all recorded deaths in the Netherlands were MND-related, resulting in a lifetime risk of 1 in 323. The absolute number of MND deaths increased from 299 in 1998 to 466 in 2017 with an average annual increase of 2.7% (95% CI 2.4%-3.1%) (**Figure 2A**). Unadjusted estimated mortality rates increased by 53.2% (95% CI 42.0%-65.4%, $p < 0.001$) from 2.57 in 1998 to 3.86 per 100,000 person-years in 2017 (**Figure 2B**).

Overall, we found no evidence that the increase in MND mortality rates differed among age groups ($p = 0.57$ for interaction term). The observed increase did, however, seem largely to be driven by younger age groups, as mortality rates increased by 60.3% (95% CI 40.8%-82.6%) in people under 70 years and by 15.6% (95% CI 4.1%-28.4%) in age groups older than 70 years. After adjustment for age and sex, MND mortality rates increased by 14.1% (95% CI 5.7%-23.2%, $p < 0.001$) in this time period; this increase was similar for men and women ($p = 0.62$ for interaction term) (**Figure 2C**). Consequently, the average male:female ratio among MND cases did not increase significantly over time ($p = 0.09$) and was, on average, 1.19 (95% CI 1.14-1.25), (**Figure 2D**). Similarly, the mean age at death due to MND in the DPR database was on average 69.7 years and did not significantly change during the study period (change in age was 0.62 years (95% CI -0.23 to 1.47, $p = 0.15$).

In contrast to the observed increase in MND mortality rates, age- and sex-adjusted mortality rates from competing (i.e. non-MND) causes of death decreased by 1.98% (95% CI 1.96%-2.00%) per year. This annual decrease was larger for men than for women ($p < 0.001$ for interaction term): 2.48% (95% CI 2.41% to 2.54%) and 1.51% (95% CI 1.48% to 1.54%) for men and women, respectively. As a sensitivity analysis, we used the Gompertz model (15) to evaluate whether longevity of a subpopulation

susceptible to MND, as a result of loss of competing risks, may be driving increase in MND mortality rates. We estimated that the susceptible subpopulation decreased by -253 men per 100,000 (95% CI -529 to 23, $p = 0.05$) and by -210 women per 100,000 (95% CI -356 to -56, $p = 0.006$).

Figure 3A shows the annual distribution of the five prognostic subgroups defined by the ENCALS personalized prediction model of patients enrolled in the Netherlands MND registry since 2006. According to the ENCALS prediction model, the average risk profile at time of diagnosis has worsened since 2006 ($p < 0.001$), meaning that in recent years more patients have been diagnosed with a relatively poor risk profile. This finding is in line with Table 1 which shows that, even though diagnostic delay had not significantly changed since 2006 (-0.76 months 95% CI -4.4 to 2.9, $p = 0.31$), the average age of MND patients had increased and more patients had been diagnosed with concomitant frontotemporal dementia since 2006. This suggests the Netherlands MND registry has become more population-based by improving recruitment strategies to ascertain incident patients instead of a mixture of incident and prevalent (i.e. long-surviving) patients in earlier register years. **Figure 3B** shows the adjusted annual probability of survival in the Netherlands. The adjusted risk of death during follow-up decreased by 16.2% during the time period 2006-2017 (hazard ratio per five years 0.93, 95% CI 0.88–0.98, $p = 0.006$). This resulted in an adjusted median survival time that increased from 19.6 months (95% CI 18.7-20.9) to 22.4 months (95% CI 21.1-23.7) for patients diagnosed in 2006 and 2017, respectively.

Finally, the probability that local MND risk is higher than expected (i.e. the national MND risk) per geographical area is shown in **Figure 4**. The DPR database contained one patient with a missing address (0.01%). After merging areas to obtain sufficient sample sizes, there were 1,694 areas with a median population size of 9,507 residents and 4.0 observed MND cases per area. We found geographic variation in MND risk with RRs ranging from 0.78 to 1.43 with the highest risk near Ten Boer in the province of Groningen and the lowest risk near Wijk bij Duurstede in the province of Utrecht. The table in **Figure 4** presents areas that have a probability of at least 0.90 that local MND risk is either higher or lower than national MND risk (i.e. RR > 1.0 or RR < 1.0). We identified 10 areas, both urban and rural, with a greater than 0.90 probability of either high or low MND risk scattered across the Netherlands. As an exploratory analysis, we assessed whether population density, mean age and proportion males per area were related to MND risk. Median population density was 2,591 residents/km^2 (range: 82 - 14,452) and was not significantly related to MND risk: RR changed by -0.015% (95% CI -0.006 – 0.003) for every doubling in population density (p = 0.49). Similarly, mean age and proportion males were also unrelated. The change in RR for a 10-year increase in mean age and an absolute increase of 10% in proportion males was 0.003 (95% CI -0.024 – 0.0295, p = 0.85) and -0.79 (95% CI -5.94 – 4.35, p = 0.76), respectively.

Discussion

In this study, we used multiple independent data sources to provide comprehensive health surveillance estimates of MND in the Netherlands from 1998 to 2017, resulting in an average estimated incidence of 2.64 per 100,000 person-years, prevalence of 9.5 per 100,000 persons and a lifetime MND risk of 1 in 323. Mean diagnostic delay did not significantly change while median survival time improved by three months from 2006 through 2017, possibly as a result of improved multidisciplinary care. This observed increase in median survival time could imply that the increase in MND incidence may be larger than the observed increase in MND mortality rates since 1998. After age and sex adjustment, MND mortality rates increased by 14.1% over the last two decades in both men and women. The 53.2% increase in unadjusted MND mortality rates could have significant consequences for planning of future healthcare services as it may indicate a doubling of MND prevalence by the year 2050. Our results suggest that either genetic or potentially preventable environmental risk factors are driving MND risk and urgent identification is needed, which may be aided by detailed geographical studies of MND risk.

We found a different effect of age when comparing MND and Alzheimer risk. The decline of MND risk in the oldest age groups contrasts with Alzheimer and suggests that there is a time period of maximal susceptibility and that MND is not only a result of ageing. Short survival in cases of MND compared to Alzheimer may also play a role. MND may be exclusive to a small susceptible subpopulation, the majority of whom are deceased by 70-80 years of age, either from MND or other unrelated causes. There is evidence that loss of competing risks and longevity of this susceptible subpopulation could also be driving the increase in MND mortality rates (15). Indeed, we found that the risk of death due to causes other than MND decreased during the study period. Our findings of a reduction of the size of a susceptible subpopulation

and larger increase of MND mortality rates among younger age groups, however, contrast with this hypothesis. Nevertheless, we cannot rule out that longevity of a susceptible subpopulation might had an impact on increase of MND mortality rates.

Ageing of the general population is an important driver of the increasing incidence of neurodegenerative diseases (20). An earlier study found no statistically significant change in MND incidence in Minnesota in the United States in the period 1925 to 1998 (21). In contrast, there have been several studies that indicate that MND incidence has increased in the last two decades (3,4,22). For example, in an epidemiological study in Northern Italy, MND incidence increased by 14% in the time period 1995-2014, mostly in women (4). A possible explanation for the larger increase in MND incidence in more recent years may be that those born during the baby boom after World War II reached ages with highest incidence in the period 2005 to 2017. Most studies were based on registry data only while using capture-recapture methodology to correct for under-ascertainment, which can under- or overestimate the total number of cases when data sources are not independent (23). In our study, we have, therefore, performed both capture-recapture and simulation-based sensitivity analyses with three independent data sources, including unselected data from a national compulsory health database. In absolute terms, the number of cases per year increased from 298 in 1998 to 466 in 2017. If this increase continues, the lifetime risk of MND would increase to 1 in 205 by 2050. Importantly, this observed increase is not solely driven by ageing of the general population, as it could only explain about 75% of the increase. Increased awareness and more timely referral of patients suspected of MND since the start of the Netherlands MND Center in 2003 may play a role, although several environmental risk factors that have been linked to MND could be involved, such as exposure to organic dust, agricultural pesticides, air pollution and other occupational hazards (24-27).

To help develop hypotheses as to which risk factors are currently driving MND risk, we mapped geographic MND risk from 1998 through 2017 in order to identify high risk areas. The use of national data is particularly advantageous, as assessing geographic risk in a limited area is an approach known to exaggerate the likelihood of identifying high-risk areas (8). There was considerable spatial variation in MND risk, which indicates that it may be worthwhile associating spatial risk with characteristics of that particular area (i.e. identify factors that explain spatial variation in risk). For example, by quantifying risk factors such as lifestyle, physical activity levels and environmental exposures in well-defined geographical areas (27-29), we may be able to efficiently identify risk factors. We have illustrated its potential use by associating MND risk with population density, which may act as a proxy for other risk factors (30). Though we found no direct correlation of population density with MND risk, its simplicity could stimulate etiological research in MND. For example, air pollution could be more severe in cities; by combining spatial risk estimates with exposure levels, both on an individual and geographical level, one may increase power to find potential associations. A similar approach may hold true for exposure to agricultural pesticides, which are more common in rural areas. An illustrative example of the latter is the increased risk of Parkinson's disease in the Netherlands associated with living in the vicinity of agricultural fields where pesticides are used (31).

Furthermore, genetic risk factors may also cause geographic variability in MND risk (7). Previously, studies found that rare genetic variants appear to be important drivers of MND risk (32), and that genetic variation can be localized geographically, meaning there is relatively little migration in the Netherlands (33). As a result, local MND incidence may increase via a genetic founder effect when new genetic variations occur. We hypothesize that both environmental risk factors, unique to each area, and local genetic admixture may thus explain geographic variation in MND risk.

Quantification of a broad spectrum of risk factors, both on an individual level as per geographical area, remains paramount.

Due to privacy regulations, our study was limited as we could not confirm a clinical diagnosis in the DPR database for individual cases. Therefore, we cannot rule out some misclassification in the DPR database. Nevertheless, we considered the DPR database to be of a high standard for several reasons. As registration is mandatory, the DPR database includes all Dutch residents. Furthermore, it is likely that patients with MND will visit a neurologist at least once, as the Dutch public healthcare system ensures there are no financial or physical hurdles to receiving healthcare. As a result, it is probable that if a patient receives a MND diagnosis, this will also be communicated to their general practitioner or nursing home physician. Dutch law requires that a physician (usually the general practitioner or nursing home physician) lists all possible contributing causes of death on the death certificate. Additionally, we found that both age at death and male to female ratio were stable, suggesting that case ascertainment has not changed during the study period. Moreover, the incidence and prevalence estimates which we found are in line with estimates found in other North-European countries with compulsory national health databases. In Denmark, Norway and Sweden, incidence and prevalence estimates ranged from 2.47 to 3.54 per 100,000 person-years and 8.0 to 8.7 per 100,000 persons, respectively (34-40). Lastly, we found similar prevalence estimates using capture-recapture methodology and a simulation-based approach using data from independent sources, thus further confirming the accurate case ascertainment of the data sources used.

Using the national DPR database enabled us to assess that 72.0% of all Dutch MND patients were identified by the Netherlands MND registry. This coverage rate is comparable to or higher than other large population-based registries (41-43). Interestingly, the higher mean age of patients and higher proportion of female patients

in the DPR database suggests that older female patients may be underrepresented in the Dutch population-based MND registry. This unintended selection of younger male patients, with, on average, longer survival, was also observed when trial participants were compared to the eligible MND population (17). It is important to recognize this unintended selection of patients, as it can lead to biased effect sizes in population-based studies when investigating etiological risk factors or genes (29,44). In order to resolve unintended selection in population-based studies, future studies, that investigate reasons for non-participation in observational studies, are needed to identify these yet unknown patient factors.

In conclusion, we found a national 53.2% increase in MND mortality rates from 1998 through 2017 in both men and women. This large increase in the last two decades underlines the impact the care for MND will have on health services in the future. There was geographic variation in MND risk, which could be related to local genetic admixture or complex environmental risk factors. Associating spatial risk, with possible MND risk factors, could stimulate etiological research in MND.

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Appendix I: Authors

Name	Location	Contribution
Adriaan de Jongh, MD	University Medical Center Utrecht, Netherlands	Design and conceptualization of study. Acquired and analyzed data, drafted manuscript
Ruben van Eijk, MD, PhD	University Medical Center Utrecht, Netherlands	Analyzed data and drafted manuscript
Susan Peters, PhD	Utrecht University, Netherlands	Design and conceptualization of study. Drafted manuscript
Michael van Es, MD, PhD	University Medical Center Utrecht, Netherlands	Acquired data and revised the manuscript for intellectual content
Anja Horemans, PhD	National Patient Organization for Neuromuscular Diseases, Baarn, Netherlands	Acquired data and revised the manuscript for intellectual content
Anneke van der Kooi, MD, PhD	University Medical Center, Amsterdam, Netherlands	Acquired data and revised the manuscript for intellectual content
Nicol Voermans, MD, PhD	Radboud University Medical Center, Nijmegen, Netherlands	Acquired data and revised the manuscript for intellectual content
Roel Vermeulen, PhD	Utrecht University, Utrecht, Netherlands	Design and conceptualization of study. Revised manuscript for intellectual content.
Jan Veldink, MD, PhD	University Medical Center, Amsterdam, Netherlands	Acquired data and revised the manuscript for intellectual content
Leonard van den Berg, MD, PhD	University Medical Center, Amsterdam, Netherlands	Design and conceptualization of study. Acquired data and revised the manuscript for intellectual content

Table 1. Baseline characteristics of the Netherlands MND registry and Netherlands Personal Records database

Patient characteristic	**MND registry** *2006 - 2009* (N = 1,190)	**MND registry** *2014 - 2017* (N = 1,573)	**MND registry** *2006 - 2017* (N = 4,152)	**Personal Records database** *1998 - 2017* (N = 7,992)
Age at diagnosis, years	63.7 (63.1-64.4)	66.0 (65.5-66.5)	65.0 (64.7-65.4)	-
Age at death, years	66.6 (65.9-67.2)	68.7 (68.2-69.3)	67.7 (67.4-68.1)	69.7 (69.4-70.0)
Male sex	59.0% (702)	58.2% (915)	58.4% (2424)	54.8% (4380)
MND subtype				
ALS	79.4% (944)	74.9% (1179)	80.2% (3329)	-
PMA	13.7% (163)	17.3% (271)	13.3% (554)	-
PLS	7.0% (83)	7.8% (123)	6.5% (269)	-
Spinal onset	70.2% (835)	73.2% (1152)	71.5% (2967)	-
Diagnostic delay, months[a]	11.4 (9.9-12.9)	11.0 (9.7-12.4)	11.0 (10.7-11.3)	-
ALSFRS-R total score at	39.0 (38.7-39.4)	38.7 (38.5-39.0)	39.0 (38.8-39.1)	-

diagnosis				
ΔFRS[a]	0.56 (0.54-0.58)	0.51 (0.50-0.53)	0.54 (0.53-0.55)	-
Vital capacity, % of predicted value at diagnosis	86.9 (85.3-88.5)	87.6 (86.4-88.8)	87.7 (86.9-88.6)	-
C9orf72 carrier	7.2% (86)	6.7% (106)	7.0% (289)	-
Frontotemporal dementia	5.2% (62)	11.3% (1395)	7.5% (310)	-
Family history of MND	6.7% (80)	8.4% (1395)	7.1% (294)	-
ENCALS risk profile[b]				
Very short survival	12.7% (120)	18.1% (213)	15.5% (517)	-
Short survival	22.4% (212)	22.2% (261)	22.3% (744)	-
Intermediate survival	16.8% (159)	19.0% (224)	18.4% (611)	-
Long survival	20.6% (195)	20.3% (239)	20.5% (682)	-
Very long survival	27.5% (260)	20.5% (242)	23.3% (775)	-

MND=motor neuron disease; ALS=amyotrophic lateral sclerosis; PMA=progressive muscular atrophy; PLS=primary lateral sclerosis; ALSFRS-R=revised ALS functional rating scale; ΔFRS = (48 – ALSFRS-R total score) / diagnostic delay in months. Data are mean (95% confidence interval) or percent (n). a) Medians are presented for diagnostic delay and ΔFRS, because of skewed distributions. b) Patient's individual risk profile according to the European Network for the Cure of ALS (ENCALS) survival prediction model (16). The ENCALS risk profile is a relative measure and indicates whether a patient's survival time is shorter or longer relative to other patients. The Netherlands Personal Records database contains data on all Dutch residents including date and cause of death. MND cases in the Netherlands Personal Records database were defined as deaths with MND (ICD code G12.2) as a contributing cause of death. Due to privacy regulations and as clinical data are not collected, limited data were available for these patients.

Figure 1. Age- and gender-adjusted MND incidence (A), prevalence (B), mortality (C) and Alzheimer mortality (D)

Figure 1 legend. This panel plot shows MND incidence (A), prevalence (B), mortality (C) and Alzheimer mortality (D) in the Netherlands from 1998 through 2017 determined via Poisson regression. Dashed lines indicate the age group with maximum rates. There was a differential effect of age for men and women on incidence ($p < 0.01$ for interaction term), prevalence and mortality (both $p < 0.001$). For example, highest MND prevalence and mortality rates occurred at later ages for men than for women. In contrast, highest Alzheimer mortality rates occurred in the oldest age group (>95 years) for both men and women. This suggests that MND risk is not merely a result of ageing. Age- and sex-stratified MND incidence was determined on the basis of data from the Netherlands MND registry. MND prevalence was determined by capture-recapture methodology using data from the Netherlands MND registry and Netherlands Patient Association for Neuromuscular Diseases. MND and Alzheimer mortality were determined based on mortality records in the Netherlands Personal Records database.

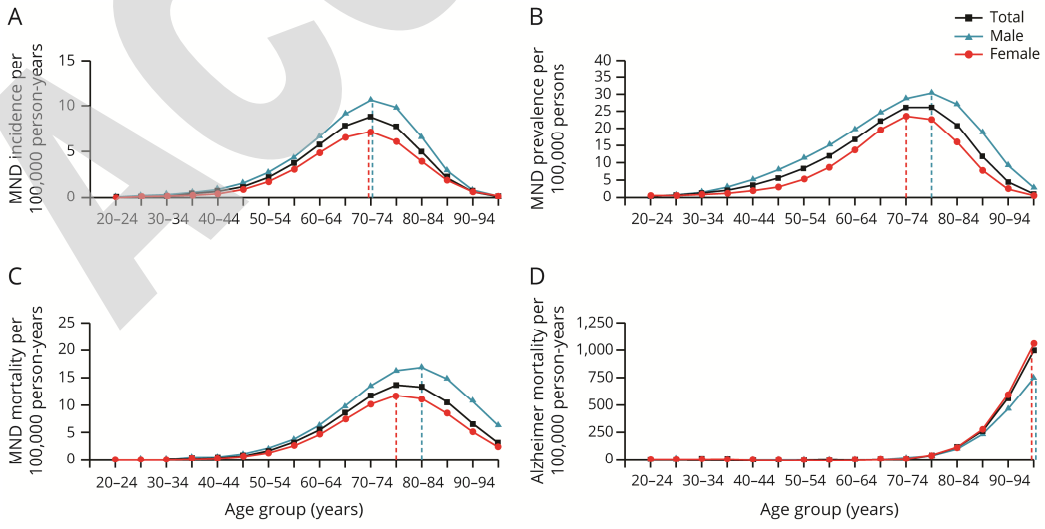


Figure 2. Time trends in MND mortality and sex ratios in the Netherlands from 1998 through 2017

Figure 2 legend. (**A**) The number of MND deaths observed in the Netherlands between 1998 and 2017. The absolute number of MND deaths increased from 299 in 1998 to 466 in 2017 with an average annual increase of 2.6%. (**B**) Adjusted for population size, mortality rates increased by 53.2% or by 14.1% after additional age and sex adjustment (both $p < 0.001$) in the time period 1998-2017, dashed lines indicate regression lines; (**C**) MND mortality rates are provided separately for males (*blue*) and females (*red*), the annual increase in MND mortality rates was not different for males and females ($p = 0.62$ for interaction term). (**D**) Similar to *panel C*, we provide the annual male to female ratio revealing a stable sex ratio of 1.19 (*dashed* line) over time ($p = 0.09$ for time trend).

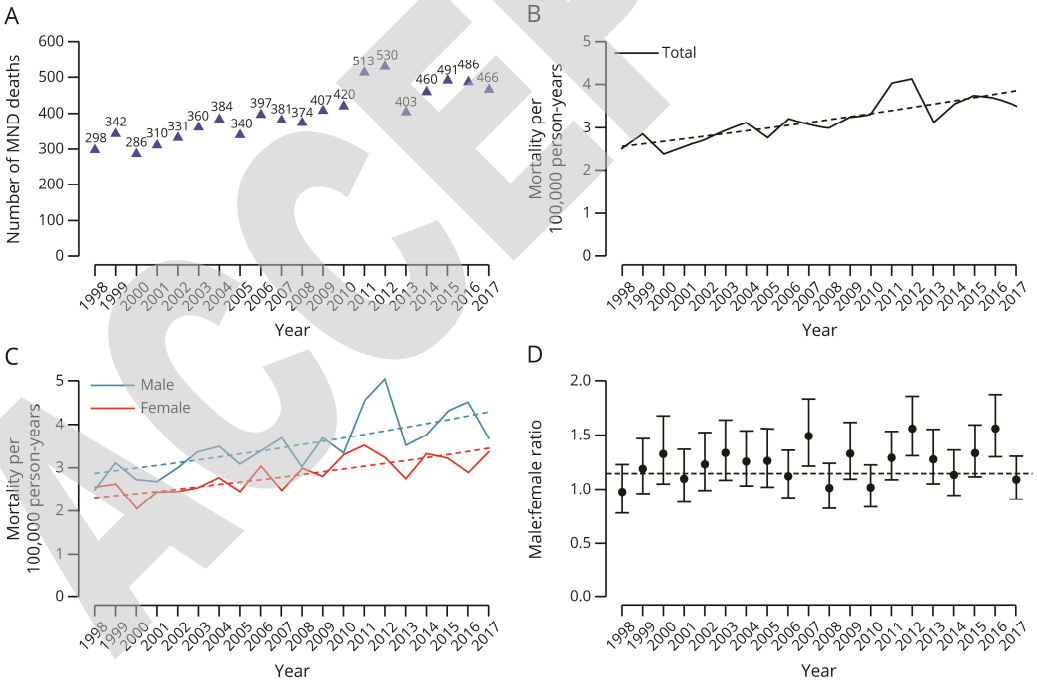


Figure 3. ENCALS risk profiles and adjusted survival trends in the Netherlands from 2006 through 2017

Figure 3 legend. (A) The annual distribution of the five prognostic subgroups defined by the ENCALS personalized prediction model. Ideally, each prognostic subgroup should have a prevalence of approximately 20% per year. As can be seen, in 2006 the Netherlands MND registry enrolled relatively more very long- and long-surviving patients, indicating that the registry recruited mainly prevalent cases. Fortunately, as recruitment strategies improved to register also short and very short-surviving subgroups, the Netherlands MND registry has become more population-based. (**B**) The effect of year of diagnosis on survival time was modelled using a Cox proportional hazards model adjusted for the ENCALS risk prediction. The risk of death during follow-up decreased by 16.2% between 2006 and 2017 (hazard ratio per five years 0.93 95% CI 0.88-0.98, p = 0.006). The adjusted median survival increased from 19.6 months (95% CI 18.7-20.9) in 2006 to 22.4 months (95% CI 21.1-23.7) in 2017.

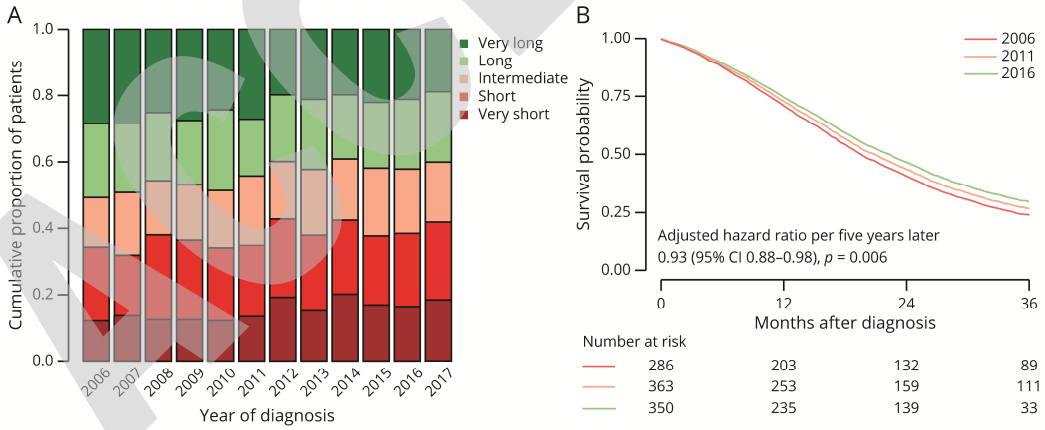
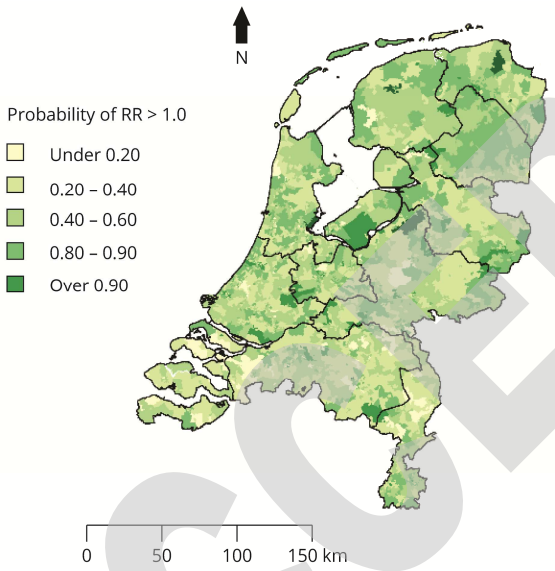


Figure 4. Probability of elevated MND risk in the Netherlands by geographical area

Figure 4 legend. MND relative risk for 1,694 areas was calculated and subsequently smoothed based on data from the Dutch Personal Records database from 1998 to 2017. This map shows the probability that MND relative risk per area is greater than expected based on the national rate of MND (i.e. the probability of relative risk > 1.0 based on 10,000 draws from the posterior distribution). Population density was estimated as number of residents per square kilometer; the following definitions from Statistics Netherlands were used: <500 (very low), 500 – 1,000 (low), 1,000 – 1,500 (average), 1,500 – 2,500 (high) and >2,500 (very high).



Nearby city	RR	Prob.	Pop.	Pop. density
Amsterdam	1.42	0.96	11,700	Very low
Ten Boer	1.43	0.95	7,500	Very low
Hilversum	1.42	0.95	7,400	Very low
Heumen	1.39	0.94	6,500	High
Waadhoeke	1.34	0.93	11,200	Very low
Veendam	1.37	0.93	6,200	Average
Epe	1.31	0.92	15,400	Very low
Best	1.31	0.91	11,300	High
Wijk bij D.	0.78	0.09	16,500	Very low
Tilburg	0.78	0.09	15,600	High

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