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ORIGINAL COMMUNICATION

Changing epidemiology of motor neurone disease in Scotland

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Abstract

Objectives Scotland benefits from an integrated national healthcare team for motor neurone disease (MND) and a tradition of rich clinical data capture using the Scottish MND Register (launched in 1989; one of the first national registers). The Scottish register was re-launched in 2015 as **C**linical **A**udit **R**esearch and **E**valuation of MND (CARE-MND), an electronic platform for prospective, population-based research. We aimed to determine if incidence of MND is changing over time.

Methods Capture–recapture methods determined the incidence of MND in 2015–2016. Incidence rates for 2015–2016 and 1989–1998 were direct age and sex standardised to allow time-period comparison. Phenotypic characteristics and socioeconomic status of the cohort are described.

Results Coverage of the CARE-MND platform was 99%. Crude incidence in the 2015–2017 period was 3.83/100,000 person-years (95% CI 3.53–4.14). Direct age-standardised incidence in 2015 was 3.42/100,000 (95% CI 2.99–3.91); in 2016, it was 2.89/100,000 (95% CI 2.50–3.34). The 1989–1998 direct standardised annual incidence estimate was 2.32/100,000 (95% CI 2.26–2.37). 2015–2016 standardised incidence was 66.9% higher than Northern European estimates. Socioeconomic status was not associated with MND.

Conclusions Our data show a changing landscape of MND in Scotland, with a rise in incidence by 36.0% over a 25-year period. This is likely attributable to ascertainment in the context of improved neurological services in Scotland. Our data suggest that CARE-MND is a reliable national resource and findings can be extrapolated to the other Northern European populations.

Keywords Epidemiology · Motor neurone disease · Amyotrophic lateral sclerosis

Introduction

Motor neurone disease (MND) refers to a spectrum of neurodegenerative diseases for which there remains no cure. The most common manifestation is amyotrophic lateral sclerosis (ALS), which typically results in progressive involvement of upper and lower motor neurones. Recent discoveries support a multifactorial etiopathogenesis, with genetic and/or environmental risk factors [1, 2]. Regional variation in disease incidence could be expected, corresponding with population ancestral origin and environmental exposures [3]. However, a recent meta-analysis of global registry data of ALS and MND subtypes observed epidemiological homogeneity amongst populations of European origin [4].

Scotland benefits from a culture of longstanding MND data capture [5]. The Scottish Motor Neurone Disease Register (SMNDR) was established in 1989, aiming to collect

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data regarding incident patients [6]. Annual incidence of MND was 2.40 per 100,000 population [95% confidence interval (CI) 2.22–2.58] between 1989 and 1998, standardised to 1994 mid-year Scottish population estimates [7]. A two-source capture–recapture model demonstrated 97.8% national coverage [7]. SMNDR coverage declined between 1999 and 2014 [8]. However, in 2015, the SMNDR was relaunched and modernised as an integrative platform, Clinical Audit Research and Evaluation of Motor Neurone Disease (CARE-MND). The platform facilitates the electronic collection of prospective patient data. We aimed to use CARE-MND to describe the epidemiology of MND in Scotland in 2015–2017, in comparison to the 1989–1998 study period and in the context of recent European population statistics. Phenotypic characterisation and social deprivation mapping of the 2015–2016 cohort were studied.

Methods

Inclusion criteria

Inclusion criteria were: (i) diagnosed by a neurologist with possible, probable, or definite ALS according to El Escorial revised criteria or an MND subtype [primary lateral sclerosis (PLS), progressive bulbar palsy (PBP), and progressive muscular atrophy (PMA)] [9], (ii) diagnosed 2015–2017, (iii) ≥ 16 years old at diagnosis, and (iv) resident in Scotland at time of diagnosis.

Case ascertainment

CARE-MND retrieves population data from five sources (Fig. 1).

CARE-MND database

The CARE-MND platform is a prospective clinical tool and all cases are monitored by neurologists and nurse/allied health specialists. If a diagnosis is revised or revoked, the patient is removed from the database. CARE-MND notifications are, therefore, considered 'gold-standard'. Patients are referred to a local MND nurse/allied health specialist, who coordinates care. The CARE-MND electronic platform operates via a secure website hosted on an academic server. MND specialists enter information about incident patients following referral and until death. If a patient is diagnosed with MND shortly before, or after, death, the relevant care provider can refer for retrospective data entry.

Patients are invited to participate in the CARE-MND platform and can self-notify online. A member of the CARE-MND team contacts the patient's neurology consultant/clinical specialist to confirm diagnosis before entry onto the database.

ISD data

Information Services Division (ISD) Scotland data were extracted. Patients were sourced if they were assigned International Statistical Classification of Diseases v10 (2016) (ICD-10) codes for Motor Neurone Disease (G12.2) or Frontotemporal Dementia (G31.0 and/or F02.0) on hospital records or as primary or secondary cause of death during 2015 and 2016. Patients prescribed riluzole, a drug uniquely used for MND, were also included.

Data extraction and statistical analysis

Related sources were collapsed, resulting in two independent sources for capture–recapture analysis (Fig. 1). Maximum-likelihood estimates determined database coverage and total incidence rates [7]. Prevalence was extracted directly from CARE-MND. Rates were calculated in reference to National Records of Scotland (NRS) mid-population estimates [10]. Incidence rates were standardised using the direct method to the US 2010 Census population [11]. This population has been used historically for Scottish and other population standardisation [4, 7]. The 2010 population was chosen to

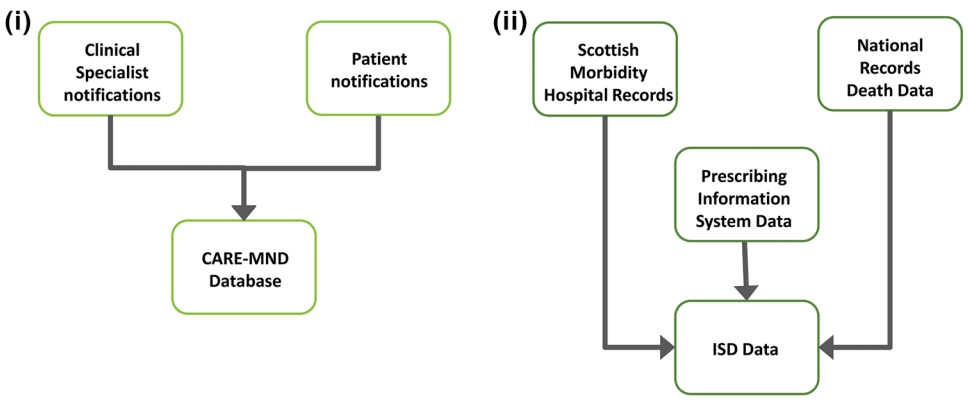

Fig. 1 Multiple source algorithm for accurate ascertainment of MND cases: (i) sources related to CARE-MND database; (ii) sources related to Information Services Division (ISD) Scottish Government data

allow direct comparison with the recent pooled incidence data [4]. Confidence intervals were calculated assuming a Poisson distribution.

The CARE-MND platform provides a standardised national proforma and phenotypic fields were extracted (Table 2). Individuals diagnosed in 2015–-2016 were followed up for at least 1 year; 6-month and 12-month survival from onset and diagnosis were examined. Patients were mapped to their corresponding Scottish Index of Multiple Deprivation (SIMD) 2016 data zone. The SIMD ranks 6976 small data zones according to the level of deprivation, accounting for employment, income, crime, housing, health, education, and access to medical care/transport. SIMD quintiles (1 most deprived; 5 least deprived) were analysed using Dunn's test of multiple comparisons using rank sums. R v3.4.3 was used for all statistical analyses [12].

Ethics

Ethical approvals were obtained for the SMNDR/CARE-MND (MREC/98/0/56 1989–2010, 10/MRE00/78 2011–2015, Scotland A Research Ethics Committee (15/SS/0216) 2015-present). Access to ISD data was approved by the Public Benefit and Privacy Panel for Health and Social Care, Scotland.

Results

Crude results

The CARE-MND database alone identified 406 true MND cases diagnosed in 2015–2016 (Table 1). There were 596 prevalent patients in 2015–2016 coded with the G12.2 code in ISD data sets. Of these, 342 were 'true' incident cases (also present in CARE-MND 2015–2016). Further 262 patients were coded with G12.2: 21 were incident MND cases unique to ISD and were included in our analyses (Table 1); eight had MND but were diagnosed before 2015 and were not included. Case notes of the remaining 233 patients were reviewed; none had MND. In summary, we identified 21/596 (3.5%) people with MND unique to ISD and 233/596 (39.1%) patients from ISD records who were coded with an ICD-10 MND code inaccurately. Forty-two percent (99/233) of these patients had progressive supranuclear palsy (PSP). Other diagnoses included pseudobulbar palsy secondary to cerebrovascular disease or dementia.

Table 1 CARE-MND platform case ascertainment and crude incidence 2015–2016

Year	2015	2016
CARE-MND notifications	221	185
Notifications unique to CARE-MND	19	45
Notifications unique to ISD	9	12
Notifications common to CARE-MND and ISD	202	140
Total notifications	230	197
Maximum-likelihood estimate	0.8465	3.8671
CARE-MND coverage (%)	99.6	98.1
Mid-year population estimate	5,373,000	5,404,700
Crude incidence (per 100,000 population)	4.28	3.64

Sensitivity of ISD code G12.2 for incident patients 2015–2016 was, therefore, 0.89 (95% CI 0.86–0.92) with a positive predictive value (PPV) of 0.61 (95% CI 0.57–0.65). The specificity and negative predictive values were 100% and 1 respectively, as MND is rare in the general population. Sensitivity and PPV for hospital records were 0.74 (95% CI 0.69–0.78) and 0.66 (95% CI 0.62–0.71), respectively; for death records, 0.42 (95% CI 0.37–0.47) and 0.55 (95% CI 0.49–0.61); for PIS records, 0.40 (95% CI 0.35–0.45) and 0.96 (95% CI 0.92–0.98).

Average case ascertainment/coverage of the CARE-MND database was 98.9% (Table 1).

Case notes of the 21 patients identified through ISD alone were examined. Sixteen (76.2%) patients were diagnosed shortly before death {median 3.5 days [interquartile range (IQR) 1.8–9.5]}, in which case contact with an MND specialist might not have been made or pursued. Site of onset for these patients varied: bulbar ($n=6$, 37.5%), limb ($n=6$, 37.5%), respiratory ($n=3$, 18.8%), and weight loss ($n=1$, 6.3%). Two patients were diagnosed posthumously: one from electromyography and one on post-mortem. The remaining three patients were: a nursing home resident, unknown to specialist teams; a patient with FTD-predominant disease receiving care from other specialists; a patient with PLS who declined specialist input.

Due to the excellent coverage of CARE-MND, incidence for 2017 was estimated using CARE-MND values alone: 192 new diagnoses, giving a crude incidence of 3.55/100,000 (3.07–4.09) (using 2016 mid-year population estimate as 2017 not yet available). Crude incidence over the 3-year period was 3.83/100,000 person-years (3.53–4.14). On 31st December 2015, 409 people were living with MND in Scotland according to CARE-MND/ISD figures [crude prevalence 7.61 per 100,000 (6.89–8.39)]. Similarly, the prevalence rates in 2016 and 2017 were 413 [7.64/100,000 (6.92–8.42)] and 422 [7.81/100,000 (7.08–8.59)].

Direct standardisation

Incidence rates for 2015 and 2016 were age and sex standardised to the US Census Population 2010 (Supplementary Table 1). Age-standardised incidence for 2015 was 3.42/100,000 (2.99–3.91). Age-standardised incidence

for males was 2.00/100,000 (1.68–2.39) and for females 2.64/100,000 (2.12–3.27); age-adjusted male-to-female relative risk (RR) 0.76:1. Age-standardised incidence for 2016 was 2.89/100,000 (2.50–3.34) overall; for males, 3.51/100,000 (2.90–4.24), and for females, 2.26/100,000 (1.78–2.86) with an RR of 1.55:1. In both years, peak age-group incidence for males was 65–69 years. In 2015, female peak incidence was in the 75–79 age group, but in the 60–64 age range in 2016 (Fig. 2). Incidence rates for 1989–1998 were age-standardised to allow time-period comparison (Fig. 3). Overall, age-standardised incidence for this period was 2.32/100,000 (2.26–2.37).

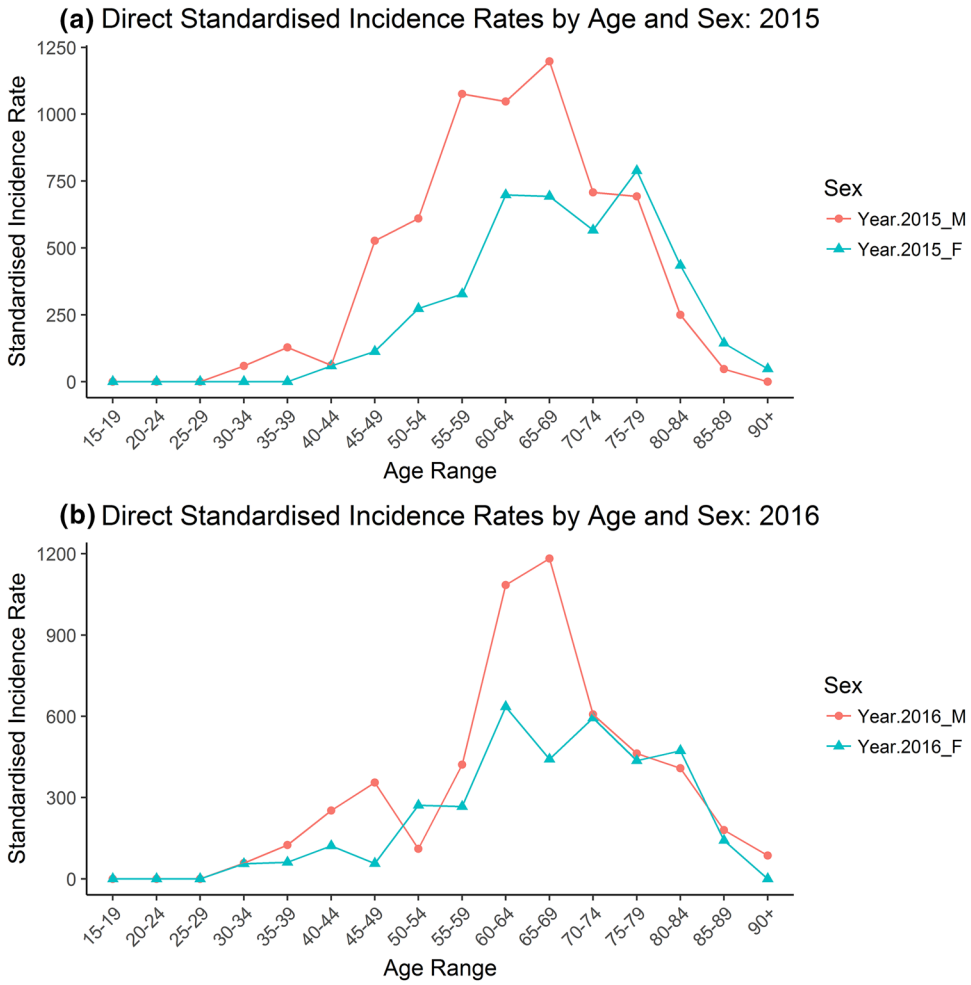

Fig. 2 Age and sex rates direct standardised to the 2010 US Census population for **a** 2015 and **b** 2016 cohorts

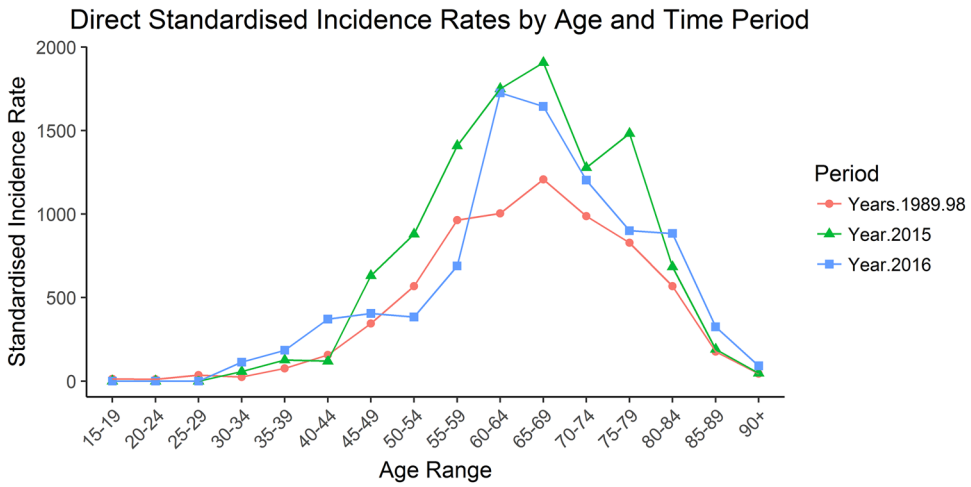

Fig. 3 Time-period comparison of incidence rates for (i) 1989–1998, (ii) 2015, and (iii) 2016 direct age standardised to the 2010 US Census population

In 2015–2016, incidence was greater than 1989–1998 across most age groups, but particularly in the 55–74 year cohort. Finally, age and sex time-period comparison was plotted (Fig. 4), highlighting that the clearest change is among males age 60–69. There was a 79–81% increase in incidence of males' age 65–69 years in 2015–2016 vs 1989–1998.

Patient characteristics

Phenotypic characteristics were evaluated from the 2015 and 2016 cohorts (Table 2). Statistical comparisons were made between males and females. Females were significantly older at onset and diagnosis ($p < 0.0016$). Significantly fewer females had onset of disease in the upper limbs ($p < 0.0016$). Although there was no sex difference for respiratory-onset disease, significantly fewer females received NIV ($p < 0.0001$). Six-month survival from onset was significantly worse in females than males ($p < 0.0016$).

Scottish index of multiple deprivation (SIMD) mapping

Patients for whom postcodes were recorded on the database ($n = 382$) were assigned their corresponding SIMD rank. Ranks ranged from 24 (most deprived) to 6953 (least deprived) (median 3512; IQR 1964–5210). There was an equal spread across deprivation quintiles (Dunn's test of multiple comparisons using rank sums $p = 0.41$).

Discussion

Capture–recapture

We report an up-to-date, standardised epidemiological analysis of the Scottish MND population. Case ascertainment methods were similar to those in the 1989–1998 Scottish analysis and capture–recapture coverage has improved. Case ascertainment is high for a national study and comparable with other small country/regional epidemiological MND studies [13–15].

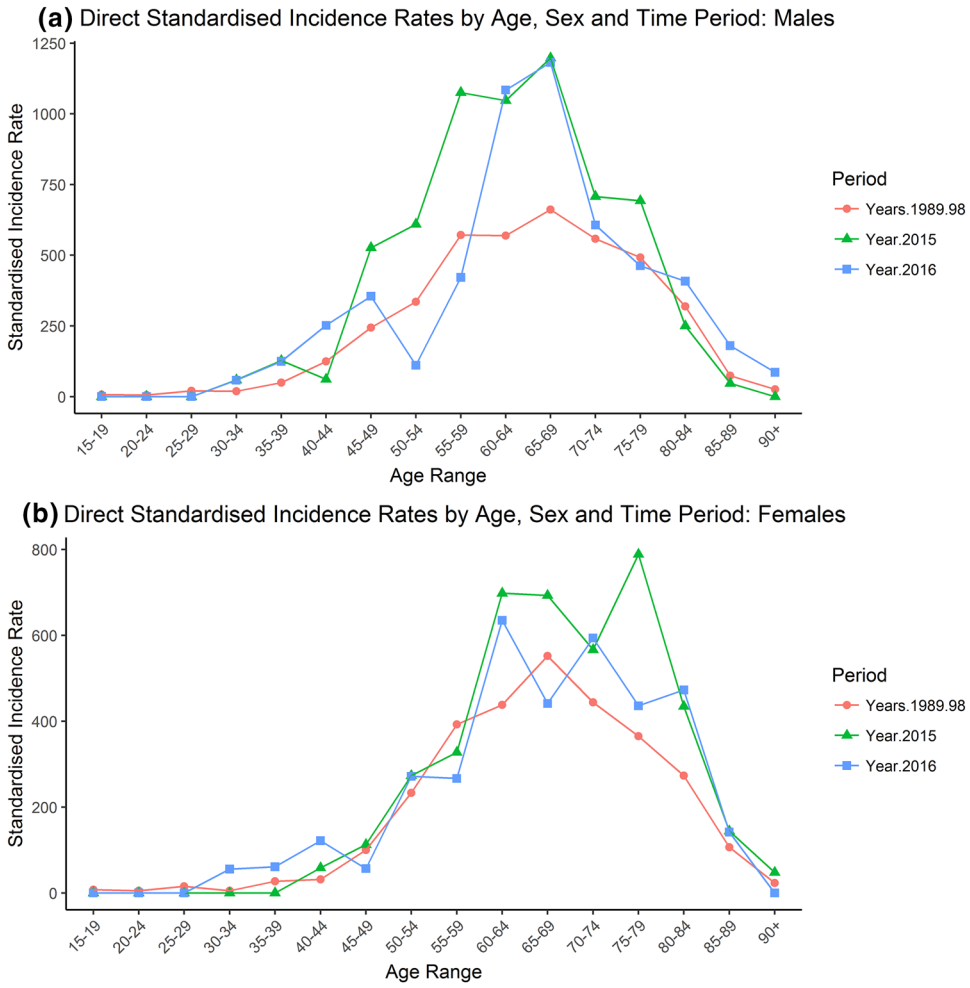

Fig. 4 Time-period comparison of incidence rates for (i) 1989–1998, (ii) 2015, and (iii) 2016 direct age and sex standardised to the US Census population 2010 **a** males and **b** females

Table 2 Patient characteristics and sex comparison of the 2015–2016 cohort

Patient characteristic ($n=427$)	% Complete data	Total	Males ($n=258$)	Females ($n=169$)	Significance test	p value
Male-to-female relative risk	100	1.53:1				
Mean age of onset (SD), years	97.7	65.3 (11.6)	63.7 (11.3)	67.6 (11.7)	t-test	0.00086*
Mean age of diagnosis (SD), years	100	66.8 (11.2)	65.4 (11.0)	69.0 (11.1)	t-test	0.00099*
Median time to diagnosis (IQR), months	97.7	11.0 (7.0–21.0)	11.0 (7.0–20.0)	11.0 (7.0–23.0)	Wilcoxon-rank sum test	0.92
Classification (%)	100				Chi-square	0.039
Amyotrophic lateral sclerosis		79.4	80.6	77.5	Z test proportion	0.51
MND with frontotemporal dementia		6.8	6.2	7.7	Z test proportion	0.69
Progressive bulbar palsy		4.9	2.7	8.2	Z test proportion	0.018
Progressive muscular atrophy		4.0	4.3	3.6	Z test proportion	0.91
Primary lateral sclerosis		3.3	3.5	3.0	Z test proportion	0.98
Other (brachial/flail limb)		1.6	2.7	0.0	Z test proportion	0.077
Site of onset	98.8				Chi-square	0.0048
Bulbar		28.2	22.7	36.7	Z test proportion	0.0024
Lower limb		28.4	28.1	28.9	Z test proportion	0.16
Upper limb		20.6	26.2	12.0	Z test proportion	0.00072*
Mixed (upper limb, lower limb, and bulbar)		17.1	16.0	18.7	Z test proportion	0.56
Cognitive change		2.1	3.1	0.6	Z test proportion	0.16
Respiratory		1.7	1.6	1.8	Z test proportion	1
Other (weight loss, camptocormia)		1.9	2.3	1.2	Z test proportion	0.64
Ethnicity (%)	90.6				Chi-square	0.71
White Scottish		75.2	75.1	75.3	Z test proportion	1
White British/Irish/not specified		23.3	23.2	23.3	Z test proportion	1
Ethnic minority		1.3	0.9	1.3	Z test proportion	1
Family history (%)						
MND	96	8.5	5.6	12.8	Chi-square	0.013
Dementia	80	27.7	26.5	29.7	Chi-square	0.22
Riluzole medication prescription (%)	98.1	37.9	37.6	38.4	Chi-square	0.4
Gastrostomy insertion (%)	99.5	31.5	32.0	30.8	Chi-square	0.71
Non-invasive ventilation (%)	95.3	33.9	41.6	21.7	Chi-square	$3.27\times10-5$*
6-Month survival (%)						
From onset	97.6	94.2	95.3	92.1	Z test proportion	0.00039*
From diagnosis	100	70.0	74.4	62.7	Z test proportion	0.092
12-Month survival (%)						
From onset	97.6	70.0	85.0	80.0	Z test proportion	0.0033
From diagnosis	100	51.3	55.8	44.4	Z test proportion	0.0032

Censorship date for survival = 31st December 2017. Definition of family history = first, second, or third degree relative with disease of interest

*Bonferroni correct p value < 0.0016

Validation of ISD coding

With reference to the CARE-MND database, ISD records had relatively low PPVs for MND. Death records were likely under-representative due to the relatively short follow-up time for this incident cohort (median 6 months; maximum 18 months). The high predictive power of prescribing records is expected as riluzole is unique to the disease. One of the main problems with coding was inaccurate coding of patients with PSP. While individuals with this condition can develop a bulbar palsy similar to that seen in MND, their disease course and pathology is distinct. This error has been observed previously and has implications for both national MND and PSP statistics [16–18].

Incidence and prevalence

Prevalence in 2015–2017 ranged from 7.61 to 7.81/100,000 population. This is comparable with the recently published cohorts in Italy, Cyprus, and the Faroe Islands [19–21]. However, it is lower than prevalence reported in the other Italian and Dutch studies (approximately 10 per 100,000 of the population) [13, 22, 23], perhaps, suggesting poorer survival in Scotland. Future work comparing survival in the Scottish population with the other European populations will be of particular interest.

Direct standardised incidence in 2015–2016 (average 3.16/100,000) has increased by 36.0% compared with the 1989–1998 period, mirroring the recent analyses of disease burden [24]. The age-standardised incidences of MND in Scotland for both 2015 and 2016 are the highest reported in the literature. Combined incidence for 2015–2016 is 66.9% higher than pooled Northern European standardised rates [4]. Possible hypotheses for these observations include the following.

Ascertainment

Patient ascertainment may contribute to our high incidence rates. The data suggest that no age groups are overlooked; older age groups are well represented (11.9% ≥ 80 years at diagnosis). This challenges recent discourse, suggesting that MND is underdiagnosed in older populations [25]. Awareness of MND amongst health professionals and the public has heightened in recent years. In 2015, Scottish MND funding and care services were boosted through substantial government investment. 2016 marked a doubling of MND nurse/allied health specialists, with a specialist-to-prevalent-patient ratio of 1:26. Each nurse acquires approximately 12 new patients annually, compared with 31 patients annually 1989–1998. Similarly, in 1989, there was one neurologist for approximately 231,500 people in Scotland but 1:63,500 in 2016. New patient referrals to neurology rose by 50% from 2007 to 2016, suggesting a better access to and more timely referral for tertiary review [26]. Indeed, median diagnostic delay in this study was slightly better than pooled European delays (11.0 months vs 12.0 months) [3].

Concomitant with an increase in neurology service provision is a better awareness of the extended phenotype of MND. In comparison to 1989–1998, MND-FTD is a new addition (6.8% of 2015–2016 cohort). Such patients were previously classified as having an "MND plus" disorder [8, 15, 27]. A better recognition of the cognitive phenotype, using tools such as the Edinburgh Cognitive and Behaviour ALS Screen, may explain some of the change in incidence over time [28].

Environmental

The rise in incidence is dominated by males' age 65–69, contradicting studies, suggesting that older women drive increased incidence in aging populations [13, 29]. In a Scottish analysis of patients > 80 years, standardised incidence was greater in men suggesting a possible localised geographical effect [30]. We found no association between MND incidence and social deprivation (SIMD), in agreement with the recent publications [31, 32]. SIMD is a marker of residence, rather than individual exogenous variables; the latter requires separate evaluation.

The change in incidence might be consequent on the improved survival from competitive diseases (such as cardiovascular disease), allowing for increased manifestation of MND (a Gompertizian model) [29]. Age- and sex-adjusted mortality from heart disease has decreased by 37.6% in Scotland over the last 10 years [33].

Genetics

Since the identification of 'genetic' MND, in particular *SOD1* mutations and the *C9orf72* hexanucleotide repeat expansion, people with MND are increasingly undergoing genetic testing as part of their diagnostic work-up. Clinicians are more aware of the phenotypic spectrum of disease of these mutations; for example, *C9orf72* carriers can present with a pure FTD phenotype but have subsequent sequential motor involvement [34]. The *C9orf72* expansion was first associated with MND in 2011, and so, it is possible that these patients were missed from historical epidemiological cohorts [35]. The *C9orf72* expansion is present in 11% of patients with MND in Scotland (familial or sporadic) [36, 37].

In this Scottish population, a previously published *SOD1* genetic founder variant (p.I114T) is found in 4% of all (familial and apparently sporadic) cases of MND [36, 38]. We do not anticipate that the frequency of this mutation has changed over time, but the identification of a founder mutation in this population may suggest the presence of other Scottish haplotypes which are driving disease. The relative ethnic homogeneity of Scotland may support this hypothesis. Genetic admixture seen in African American populations is thought to be protective against disease, whereas people of European origin are more likely to harbour homozygous and "probably damaging" genetic alleles [39]. Further comprehensive genetic characterisation of the Scottish population in future studies will help to answer this question.

Phenotypic characteristics

In this cohort, the male-to-female ratio and mean ages of onset/diagnosis are typical [5, 7, 19, 36]. The majority of

patients (79.4%) had ALS; the remainder MND subtypes. Family history of MND was higher in females than males, although this did not reach statistical significance. In our previous genetic analyses, we observed that female sex was significantly associated with having genetic MND [36]. This is in keeping with a liability threshold genetic model which dictates that, in a male-dominated disease such as MND, females require more disease risk factors to pass the threshold for disease onset [40].

Rates of gastrostomy insertion are similar to the LIGALS population, although NIV use is lower (33.9 vs 55.7%) [19], perhaps, reflective of the relatively short follow-up period. We observe significantly poorer survival of females at 6 months. More females than males have bulbar-onset disease which might explain the drop in survival shortly after onset. Interestingly, significantly fewer females than males used NIV.

Limitations

While data capture methods are similar between the 1989–1998 and 2015–2017 cohorts, there were key differences in diagnostic inclusion criteria: the historical data set was obtained before publication of revised El Escorial criteria, instead relying on modified World Federation of Neurology diagnostic criteria for half of the cohort, and original El Escorial criteria for the remainder [41, 42]. Unfortunately, this is a limitation for many longitudinal MND population studies.

Data collection was less comprehensive between 1999 and 2014, and our study does not allow for age-period-cohort (APC) analysis. Nevertheless, it gives an accurate representation of the current climate of MND in Scotland. APC analysis highlights historical rather than the existing potential environmental aetiology only. Recent APC analysis from Ireland, a population in geographical proximity to Scotland, showed no birth cohort effect [43].

Although the genetic epidemiology of the historical cohort has been studied [36], the frequency of rare MND-associated variants in this incident population is unknown. Detailed genetic characterisation of this cohort may highlight variants that are enriched in the homogenous Scottish population.

Conclusions

Our study shows an increasing incidence of MND in Scotland, with the highest and most up-to-date standardised incidence rates reported in the literature. We have re-established the Scottish MND Register (now CARE-MND platform) and can achieve 99% capture of patients. The high ascertainment rates obtained from a national prospective, multi-source register imply that findings can be generalised to other Northern European populations. This work and future CARE-MND analyses will help model demand for clinical MND services and potential etiological factors.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical standard statement The authors confirm that this article complies with ethical standards.

References

1. Al-Chalabi A, Hardiman O (2013) The epidemiology of ALS: a conspiracy of genes, environment and time. Nat Rev Neurol 9(11):617–628
2. Al-Chalabi A, Calvo A, Chio A, Colville S, Ellis CM, Hardiman O et al (2014) Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. Lancet Neurol 13(11):1108–1113
3. Marin B, Logroscino G, Boumédiene F, Labrunie A, Couratier P, Babron MC et al (2016) Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. Eur J Epidemiol 31:229–245 (Springer Netherlands)
4. Marin B, Boumédiene F, Logroscino G, Couratier P, Babron M-C, Leutenegger AL et al (2016) Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. Int J Epidemiol 46(1):57–74
5. Holloway SM, Emery AEH (1982) The epidemiology of motor neuron disease in Scotland. Muscle Nerve 5(2):131–133
6. Chancellor AM, Slattery JM, Fraser H, Swingler RJ, Holloway SM, Warlow CP (1993) The prognosis of adult-onset motor neuron disease: a prospective study based on the Scottish Motor Neuron Disease Register. J Neurol 240(6):339–346
7. Forbes RB, Colville S, Parratt J, Swingler RJ (2007) The incidence of motor nueron disease in Scotland. J Neurol 254(7):866–869
8. Hardiman O, Al-Chalabi A, Brayne C, Beghi E, Van Den Berg LH, Chio A et al (2017) The changing picture of amyotrophic lateral sclerosis: lessons from European registers. J Neurol Neurosurg Psychiatry 88:557–563 (BMJ Publishing Group)
9. Brooks BR, Miller RG, Swash M, Munsat TL (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1(5):293–299

10. National Records of Scotland (2017) Statistics and Data: Mid-Year Population Estimates [Internet]. National Records of Scotland. National Records of Scotland. https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates. Accessed 28 Feb 2018
11. United States Census Bureau (2010) 2010 Census Data Products: United States [Internet]. United States Census Bureau. 2010. https://www.census.gov/population/www/cen2010/glance/. Accessed 28 Feb 2018
12. R Core Team (2017) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienne
13. Chiò A, Mora G, Moglia C, Manera U, Canosa A, Cammarosano S et al (2017) Secular trends of amyotrophic lateral sclerosis: the Piemonte and Valle d'Aosta register. JAMA Neurol 74(9):1097–1104
14. Donaghy C, Clarke J, Patterson C, Kee F, Hardiman O, Patterson V (2010) The epidemiology of motor neuron disease in Northern Ireland using capture-recapture methodology. Amyotroph Lateral Scler 11(4):374–378
15. Rosenbohm A, Peter RS, Erhardt S, Lulé D, Rothenbacher D, Ludolph AC et al (2017) Epidemiology of amyotrophic lateral sclerosis in Southern Germany. J Neurol 264(4):749–757
16. Horrocks S, Wilkinson T, Schnier C, Ly A, Woodfield R, Rannikmäe K et al (2017) Accuracy of routinely-collected healthcare data for identifying motor neurone disease cases: a systematic review. Le W, editor. PLoS One 12(2):e0172639
17. Doyle P, Brown A, Beral V, Reeves G, Green J (2012) Incidence of and risk factors for motor neurone disease in UK women: a prospective study. BMC Neurol 12:25
18. Maxwell R, Wells C, Verne J (2010) Under-reporting of progressive supranuclear palsy. Lancet (London, England) 376(9758):2072
19. Scialò C, Novi G, Bandettini di Poggio M, Canosa A, Sormani MP, Mandich P et al (2016) Clinical epidemiology of amyotrophic lateral sclerosis in Liguria, Italy: an update of LIGALS register. Amyotroph Lateral Scler Front Degener 17(7–8):535–542
20. Demetriou CA, Hadjivasiliou PM, Kleopa KA, Christou YP, Leonidou E, Kyriakides T et al (2017) Epidemiology of amyotrophic lateral sclerosis in the Republic of Cyprus: A 25-Year Retrospective Study. Neuroepidemiology 48(1–2):79–85
21. Joensen P (2012 Jul) Incidence of amyotrophic lateral sclerosis in the Faroe Islands. Acta Neurol Scand 126(1):62–66
22. Georgoulopoulou E, Vinceti M, Bonvicini F, Sola P, Goldoni CA, Girolamo G, De et al (2011 Nov) Changing incidence and subtypes of ALS in Modena, Italy: a 10-years prospective study. Amyotroph Lateral Scler 12(6):451–457
23. Huisman MHB, de Jong SW, van Doormaal PTC, Weinreich SS, Schelhaas HJ, van der Kooi AJ et al (2011) Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. J Neurol Neurosurg Psychiatry 82(10):1165–1170
24. Arthur KC, Calvo A, Price TR, Geiger JT, Chiò A, Traynor BJ (2016) Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. Nat Commun 7:12408
25. Marin B, Fontana A, Arcuti S, Copetti M, Boumédiene F, Couratier P et al (2018 Jul) Age-specific ALS incidence: a dose–response meta-analysis. Eur J Epidemiol 33(7):621–634
26. Information Services Division (ISD) S (2017) Annual Trends in Consultant-led Outpatient Activity [Internet]. ISD Scotland. http://www.isdscotland.org/Health-Topics/Hospital-Care/Outpatient-Activity/. Accessed 16 May 2018
27. Davenport RJ, Swingler RJ, Chancellor AM, Warlow CP (1996) Avoiding false positive diagnoses of motor neuron disease: lessons from the Scottish Motor Neuron Disease Register. J Neurol Neurosurg Psychiatry 60(2):147–151
28. Abrahams S, Newton J, Niven E, Foley J, Bak TH (2014) Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener 15(1–2):9–14
29. Beghi E, Logroscino G, Chiò A, Hardiman O, Mitchell D, Swingler R et al (2006) The epidemiology of ALS and the role of population-based registries. Biochim Biophys Acta 1762:1150–1157
30. Forbes RB, Colville S, Swingler RJ, Scottish ALS/MND, Register (2004) The epidemiology of amyotrophic lateral sclerosis (ALS/MND) in people aged 80 or over. Age Ageing 33(2):131–134
31. Rooney JPK, Tobin K, Crampsie A, Vajda A, Heverin M, Mclaughlin R et al (2015) Social deprivation and population density are not associated with small area risk of amyotrophic lateral sclerosis. Environ Res 142:141–147
32. Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MG (2016) Race/ethnicity, socioeconomic status, and ALS mortality in the United States. Neurology 87(22):2300–2308
33. Information Services Division (ISD) S (2017) Scottish Heart Disease Statistics [Internet]. http://www.isdscotland.org/Health-Topics/Heart-Disease/Publications/2017-02-21/2017-02-21-Heart-Disease-Report.pdf. Accessed 25 Jun 2018
34. Rohrer JD, Isaacs AM, Mizlienska S, Mead S, Lashley T, Wray S et al (2015) C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis. Lancet Neurol 14(3):291–301
35. Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR et al (2011) A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 72(2):257–268
36. Black HA, Leighton DJ, Cleary EM, Rose E, Stephenson L, Colville S et al (2017) Genetic epidemiology of motor neuron disease-associated variants in the Scottish population. Neurobiol Aging 51:178.e11–178.e20
37. Cleary EM, Pal S, Azam T, Moore DJ, Swingler R, Gorrie G et al (2016) Improved PCR based methods for detecting C9orf72 hexanucleotide repeat expansions. Mol Cell Probes 30(4):218–224
38. Hayward C, Swingler RJ, Simpson SA, Brock DJ (1996) A specific superoxide dismutase mutation is on the same genetic background in sporadic and familial cases of amyotrophic lateral sclerosis. Am J Hum Genet 59(5):1165–1167
39. Lohmueller KE, Indap AR, Schmidt S, Boyko AR, Hernandez RD, Hubisz MJ et al (2008) Proportionally more deleterious genetic variation in European than in African populations. Nature 451:994
40. Falconer DS (1965) The inheritance of liability to certain diseases, estimated from the incidence among relatives. Ann Hum Genet 29(1):51–76
41. Hern JEC, Dundee RK, Davidson D, Forster A, Roberts R, Swingler RJ et al (1992) The Scottish motor neuron disease register: a prospective study of adult onset motor neuron disease in Scotland. Methodology, demography and clinical features of incident cases in 1989. J Neurol Neurosurg Psychiatry 55:536–541
42. Brooks BR (1994) El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and th. J Neurol Sci 124 Suppl:96–107
43. Tobin K, Gilthorpe MS, Rooney J, Heverin M, Vajda A, Staines A et al (2016) Age-period-cohort analysis of trends in amyotrophic lateral sclerosis incidence. J Neurol 263(10):1919–1926