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 relaunched in 2015 as Clinical Audit Research and Evaluation 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 incidence of MND in 2015-16. Incidence rates for 2015-16 and 1989-98 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 2015-17 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, 2.89/100,000 (95% CI 2.50-3.34). The 1989-98 direct standardised annual incidence estimate was 2.32/100,000 (95% CI 2.26-2.37). 2015-16 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 other Northern European populations.
Response to Reviewers:	Dear Editors, Re: Changing epidemiology of motor neurone disease in Scotland. Leighton et al. ID: JOON-D-18-01432 Thank you for your detailed review of our manuscript. Please find our responses to your helpful comments below. We have highlighted changes made in our revised manuscript in red. Responses to reviewers: Reviewer #1: This is an interesting study of the national register of people with ALS in Scotland describing a change in the incidence of ALS, comparing the results with their previous data published in Journal of Neurology in 2007 .It is a well written paper and the results are properly discussed . I have only one minor point. In the discussion section, when authors examine possible hypotheses for their results, the chapter iii) Genetics (pages 12-13) is not clear. Do authors think that the increase of incidence is related in a change of the genetic landscape of ALS in Scotland? How the known presence of the SOD1 variant p.I114T could influence the incidence. How genetics can explain the increase of incidence of ALS in other countries (Italy for example). Please rewrite this paragraph. Response: We agree that our message was not clear in this paragraph. We had amended this paragraph to reflect two points: 1) identification of genetic MND, particularly patients with the C9orf72 repeat expansion, may have contributed to better awareness of the extended phenotype of MND and 2) presence of the Scottish SOD1 I114T mutation may suggest other founder mutations in this population, which is relatively ethnically homogenous and we hope to do further work in the future to elucidate this. Reviewer #2: This paper reports the first of the renewed Scottish MND register. Comparing to the old register (1989-1998) the authors found rise in incidence by 36.0% over a 25-year period. Data were collected using several concurrent sources. The paper used an excellent methodology and demonstrates a very good cover of the MND population. I have some comments: 1. The comparison between the two periods may have some faults. The original Scottish data were collected before revised El Escorial diagnostic criteria were published (Brooks et al, 2000). This caveat should be considered and discussed. Response: We have made this clearer in the text. 2. About 7% of the whole population in the 2015-2016 cohort is represented by 'MND with Frontotemporal Dementia'. It is likely that these cases would not have been included in the original Scottish register, since awareness of co-morbid dementia in MND is more recent (again, the first publication date back to 2000). Response: We agree that this is a potential factor in change in incidence. We have expanded on this observation as better recognition of this phenotype is likely secondary to development of effective screening tools for ALS-associated cognitive impairment. 3. Prevalence is much lower than that published in Italy (reference 13). This paper

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Editors
Journal of Neurology

19th December 2019

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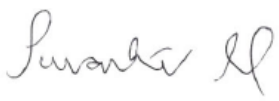

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Changing epidemiology of motor neurone disease in Scotland

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Epidemiology; motor neurone disease; amyotrophic lateral sclerosis

CONFLICTS OF INTEREREST

The authors declare that they have no conflicts of interest.

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DL receives doctoral funding from the Chief Scientist Office for Scotland, MND Scotland, and the MND Association (grant CAF/MND/15/01).

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 relaunched 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 incidence of MND in 2015-16. Incidence rates for 2015-16 and 1989-98 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 2015-17 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, 2.89/100,000 (95% CI 2.50-3.34). The 1989-98 direct standardised annual incidence estimate was 2.32/100,000 (95% CI 2.26-2.37). 2015-16 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 other Northern European populations.

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 aetiopathogenesis, 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 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 1989-1998, 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 re-launched and modernised as an integrative platform, Clinical Audit Research and Evaluation of Motor Neurone Disease (CARE-MND). The platform facilitates 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 2015-16 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), progressive muscular atrophy (PMA))[9], ii) diagnosed 2015-2017, iii) ≥16 years old at diagnosis, iv) resident in Scotland at time of diagnosis.

Case ascertainment

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

i) 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.

ii) 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 (Figure 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 allow direct comparison with 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 2015-16 were followed up for at least one 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 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 2015-16 (Table 1). There were 596 prevalent patients in 2015-2016 coded with the G12.2 code in ISD datasets. Of these, 342 were 'true' incident cases (also present in CARE-MND 2015-16). A 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.

Sensitivity of ISD code G12.2 for incident patients 2015-16 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 value 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).

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	5373000	5404700
Crude incidence (per 100,000 population)	4.28	3.64

Table 1: CARE-MND Platform Case Ascertainment and Crude Incidence 2015-16

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 a 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%), weight loss (n=1 (6.3%). Two patients were diagnosed posthumously: one from electromyography, 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 three-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, 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 a 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 (Figure 2). Incidence rates for 1989-98 were age-standardised to allow time period comparison (Figure 3). Overall, age-standardised incidence for this period was 2.32/100,000 (2.26-2.37). In 2015-16, incidence was greater than 1989-98 across most age groups, but particularly in the 55-74 year cohort. Finally, age *and* sex time period comparison was plotted (Figure 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 2015-16 versus 1989-98.

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 ($p<0.0016$).

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 (%)					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**	100	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 (bibrachial/flail limb)**		1.6	2.7	0.0	Z-test proportion	0.077
Site of Onset					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**	98.8	20.6	26.2	12.0	Z-test proportion	0.00072*
- **Mixed (upper limb, lower limb, 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 (%)					Chi square	0.71
- **White Scottish**	90.6	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	3.27x10-5*
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

Table 2: Patient characteristics and sex comparison of the 2015-2016 cohort. 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

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 1989-98 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].

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 six 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 2015-17 ranged from 7.61-7.81/100,000 population. This is comparable with recently published cohorts in Italy, Cyprus and the Faroe Islands[19–21]. However, it is lower than prevalence reported in 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 other European populations will be of particular interest.

Direct standardised incidence in 2015-16 (average 3.16/100,000) has increased by 36.0% compared with the 1989-98 period, mirroring 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 2015-16 is 66.9% higher than pooled Northern European standardised rates[4]. Possible hypotheses for these observations include:

i) 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 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 better awareness of the extended phenotype of MND. In comparison to 1989-98, MND-FTD is a new addition (6.8% of 2015-16 cohort). Such patients were previously classified as having a "MND plus" disorder[8,15,27]. 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].

ii) Environmental

The rise in incidence is dominated by males age 65-69, contradicting studies suggesting 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 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 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].

iii) 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 six 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 1989-98 and 2015-17 cohorts, there were key differences in diagnostic inclusion criteria: the historical dataset 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 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 aetiological factors.

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

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) 1989-98, ii) 2015 and iii) 2016 direct age standardised to the 2010 US Census population

Fig.4 Time period comparison of incidence rates for i) 1989-98, ii) 2015 and iii) 2016 direct age and sex standardised to the US Census population 2010 (a) Males, b) Females)

REFERENCES

1. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. Nat Rev Neurol. 2013 Oct 15;9(11):617–28.

2. Al-Chalabi A, Calvo A, Chio A, Colville S, Ellis CM, Hardiman O, et al. Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. Lancet Neurol. 2014 Nov;13(11):1108–13.

3. Marin B, Logroscino G, Boumédiene F, Labrunie A, Couratier P, Babron MC, et al. Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. Vol. 31, European Journal of Epidemiology. Springer Netherlands; 2016. p. 229–45.

4. Marin B, Boumédiene F, Logroscino G, Couratier P, Babron M-C, Leutenegger AL, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. Int J Epidemiol. 2016 May 16;46(1):57–74.

5. Holloway SM, Emery AEH. The epidemiology of motor neuron disease in Scotland. Muscle Nerve. 1982 Feb 1;5(2):131–3.

6. Chancellor AM, Slattery JM, Fraser H, Swingler RJ, Holloway SM, Warlow CP. The prognosis of adult-onset motor neuron disease: a prospective study based on the Scottish Motor Neuron Disease Register. J Neurol. 1993 Jun;240(6):339–46.

7. Forbes RB, Colville S, Parratt J, Swingler RJ. The incidence of motor nueron disease in Scotland. J Neurol. 2007 Jul;254(7):866–9.

8. Hardiman O, Al-Chalabi A, Brayne C, Beghi E, Van Den Berg LH, Chio A, et al. The changing picture of amyotrophic lateral sclerosis: Lessons from European registers. Vol. 88, Journal of Neurology, Neurosurgery and Psychiatry. BMJ Publishing Group; 2017. p. 557–63.

9. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000 Dec;1(5):293–9.

10. National Records of Scotland. Statistics and Data: Mid-Year Population Estimates [Internet]. National Records of Scotland. National Records of Scotland; 2017 [cited 2018 Feb 28]. Available from: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates

11. United States Census Bureau 2010. 2010 Census Data Products: United States [Internet]. United States Census Bureau. 2010. Available from: https://www.census.gov/population/www/cen2010/glance/

12. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienne, Austria: R Foundation for Statistical Computing, Vienna, Austria; 2017.

13. Chiò A, Mora G, Moglia C, Manera U, Canosa A, Cammarosano S, et al. Secular trends of amyotrophic lateral sclerosis: The Piemonte and Valle d'Aosta register. JAMA Neurol. 2017 Sep 1;74(9):1097–104.

14. Donaghy C, Clarke J, Patterson C, Kee F, Hardiman O, Patterson V. The epidemiology of motor neuron disease in Northern Ireland using capture-recapture methodology. Amyotroph Lateral Scler. 2010 Aug 16;11(4):374–8.

15. Rosenbohm A, Peter RS, Erhardt S, Lulé D, Rothenbacher D, Ludolph AC, et al. Epidemiology of amyotrophic lateral sclerosis in Southern Germany. J Neurol. 2017 Apr 20;264(4):749–57.

16. Horrocks S, Wilkinson T, Schnier C, Ly A, Woodfield R, Rannikmäe K, et al. Accuracy of routinely-collected healthcare data for identifying motor neurone disease cases: A systematic review. Le W, editor. PLoS One. 2017 Feb 28;12(2):e0172639.

17. Doyle P, Brown A, Beral V, Reeves G, Green J. Incidence of and risk factors for motor neurone disease in UK women: a prospective study. BMC Neurol. 2012 May 6;12:25.

18. Maxwell R, Wells C, Verne J. Under-reporting of progressive supranuclear palsy. Lancet (London, England). 2010 Dec 18;376(9758):2072.

19. Scialò C, Novi G, Bandettini di Poggio M, Canosa A, Sormani MP, Mandich P, et al. Clinical epidemiology of amyotrophic lateral sclerosis in Liguria, Italy: An update of LIGALS register. Amyotroph Lateral Scler Front Degener. 2016 Jul 11;17(7–8):535–42.

20. Demetriou CA, Hadjivasiliou PM, Kleopa KA, Christou YP, Leonidou E, Kyriakides T, et al. Epidemiology of Amyotrophic Lateral Sclerosis in the Republic of Cyprus: A 25-Year Retrospective Study. Neuroepidemiology. 2017;48(1–2):79–85.

21. Joensen P. Incidence of amyotrophic lateral sclerosis in the Faroe Islands. Acta Neurol Scand. 2012 Jul;126(1):62–6.

22. Georgoulopoulou E, Vinceti M, Bonvicini F, Sola P, Goldoni CA, Girolamo G De, et al. Changing

incidence and subtypes of ALS in Modena, Italy: A 10-years prospective study. Amyotroph Lateral Scler. 2011 Nov 6;12(6):451–7.

23. Huisman MHB, de Jong SW, van Doormaal PTC, Weinreich SS, Schelhaas HJ, van der Kooi AJ, et al. Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. J Neurol Neurosurg Psychiatry. 2011 Oct 1;82(10):1165–70.

24. Arthur KC, Calvo A, Price TR, Geiger JT, Chiò A, Traynor BJ. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. Nat Commun. 2016;7(12408).

25. Marin B, Fontana A, Arcuti S, Copetti M, Boumédiene F, Couratier P, et al. Age-specific ALS incidence: a dose–response meta-analysis. Eur J Epidemiol. 2018 Jul 23;33(7):621–34.

26. Information Services Division (ISD) S. Annual Trends in Consultant-led Outpatient Activity [Internet]. ISD Scotland. 2017 [cited 2018 May 16]. Available from: http://www.isdscotland.org/Health-Topics/Hospital-Care/Outpatient-Activity/

27. Davenport RJ, Swingler RJ, Chancellor AM, Warlow CP. Avoiding false positive diagnoses of motor neuron disease: lessons from the Scottish Motor Neuron Disease Register. J Neurol Neurosurg Psychiatry. 1996 Feb;60(2):147–51.

28. Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2014 Mar;15(1–2):9–14.

29. Beghi E, Logroscino G, Chiò A, Hardiman O, Mitchell D, Swingler R, et al. The epidemiology of ALS and the role of population-based registries on behalf of the EURALS Consortium. 2006;

30. Forbes RB, Colville S, Swingler RJ, Scottish ALS/MND Register. The epidemiology of amyotrophic lateral sclerosis (ALS/MND) in people aged 80 or over. Age Ageing. 2004 Mar;33(2):131–4.

31. Rooney JPK, Tobin K, Crampsie A, Vajda A, Heverin M, Mclaughlin R, et al. Social deprivation and population density are not associated with small area risk of amyotrophic lateral sclerosis. Environ Res. 2015;142:141–7.

32. Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MG. Race/ethnicity, socioeconomic status, and ALS mortality in the United States. Neurology. 2016 Nov 29;87(22):2300–8.

33. Information Services Division (ISD) S. Scottish Heart Disease Statistics [Internet]. 2017 [cited 2018 Jun 25]. Available from: http://www.isdscotland.org/Health-Topics/Heart-

Disease/Publications/2017-02-21/2017-02-21-Heart-Disease-Report.pdf

34. Rohrer JD, Isaacs AM, Mizlienska S, Mead S, Lashley T, Wray S, et al. C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis. Lancet Neurol. 2015 Jan 28;

35. Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011 Oct 20;72(2):257–68.

36. Black HA, Leighton DJ, Cleary EM, Rose E, Stephenson L, Colville S, et al. Genetic epidemiology of motor neuron disease-associated variants in the Scottish population. Neurobiol Aging. 2017 Mar;51:178.e11-178.e20.

37. Cleary EM, Pal S, Azam T, Moore DJ, Swingler R, Gorrie G, et al. Improved PCR based methods for detecting C9orf72 hexanucleotide repeat expansions. Mol Cell Probes. 2016 Aug;30(4):218–24.

38. Hayward C, Swingler RJ, Simpson SA, Brock DJ. A specific superoxide dismutase mutation is on the same genetic background in sporadic and familial cases of amyotrophic lateral sclerosis. Am J Hum Genet. 1996 Nov;59(5):1165–7.

39. Lohmueller KE, Indap AR, Schmidt S, Boyko AR, Hernandez RD, Hubisz MJ, et al. Proportionally more deleterious genetic variation in European than in African populations. Nature. 2008 Feb 21;451:994.

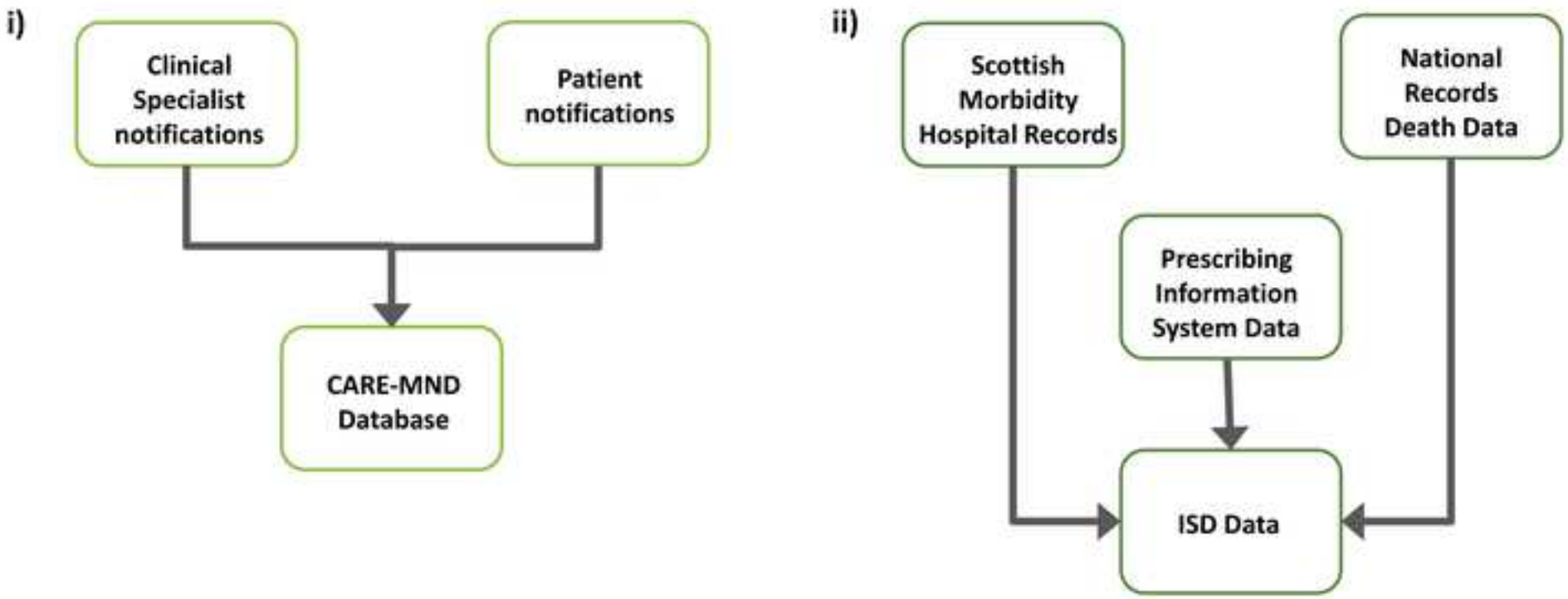
40. FALCONER DS. The inheritance of liability to certain diseases, estimated from the incidence among relatives. Ann Hum Genet. 1965 Aug 1;29(1):51–76.

41. Hern JEC, Dundee RK, Davidson D, Forster A, Roberts R, Swingler RJ, et al. 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. 1992;55:536–41.

42. Brooks BR. 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. 1994 Jul;124 Suppl:96–107.

43. Tobin K, Gilthorpe MS, Rooney J, Heverin M, Vajda A, Staines A, et al. Age-period-cohort analysis of trends in amyotrophic lateral sclerosis incidence. J Neurol. 2016 Oct 2;263(10):1919–26.

Figure



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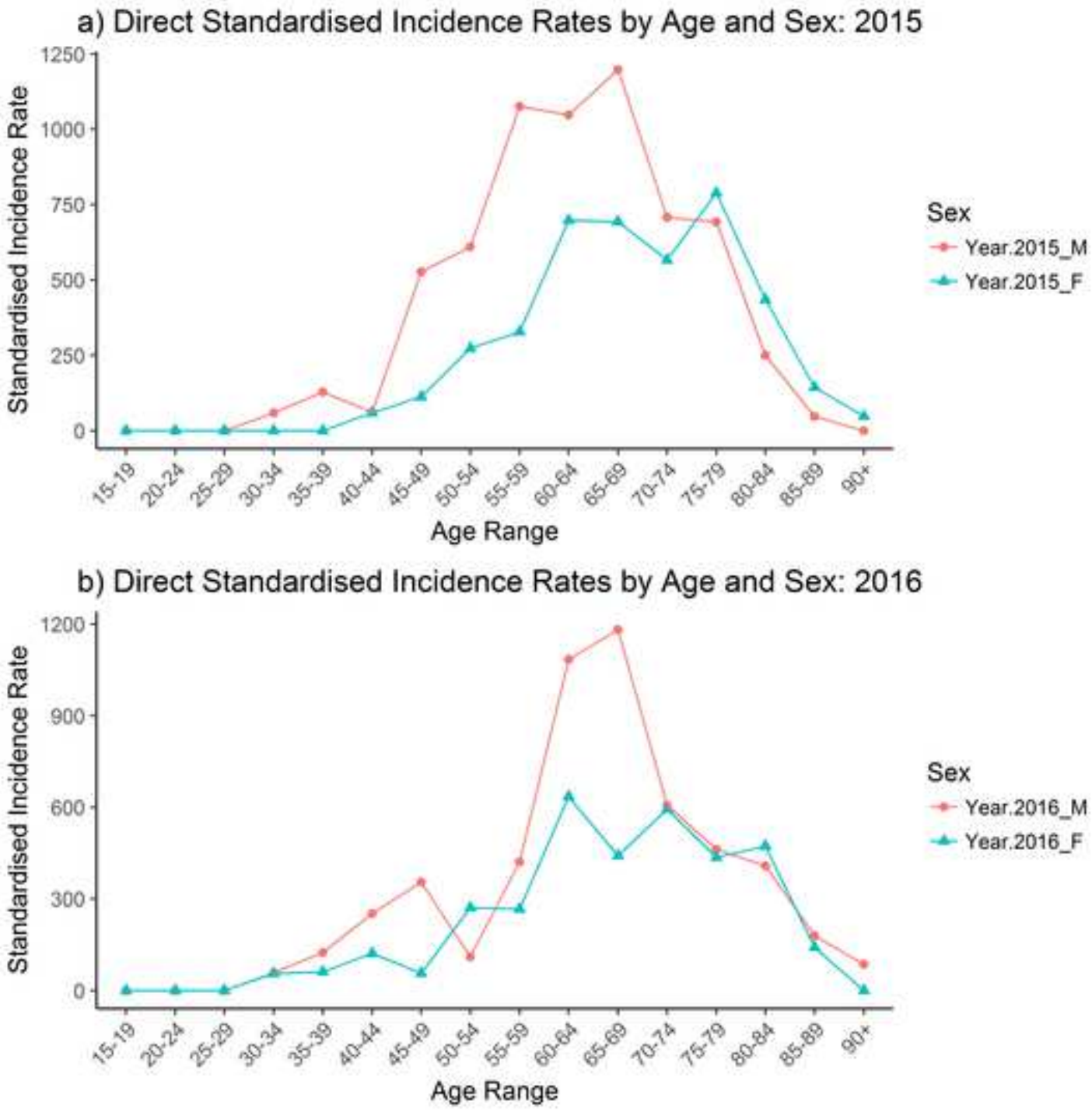

Figure

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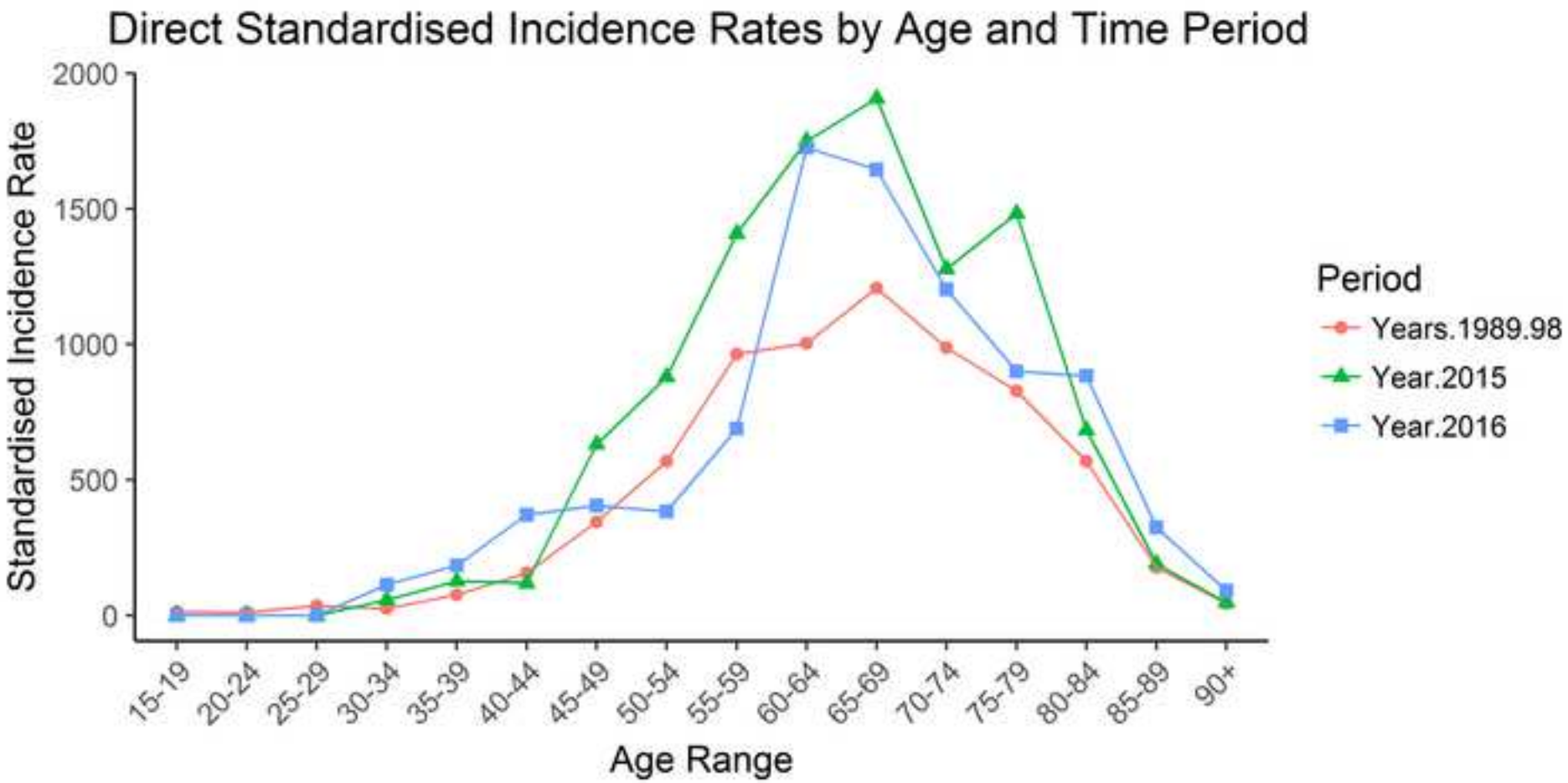

Figure

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