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Municipality-level incidence of clinically diagnosed amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease☆

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ABSTRACT

Background: The prevalences of Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), and Parkinson's Disease (PD) have been shown to covary which suggests that they may share common pathogenetic factors.
Objective: Investigate the contemporaneous incidence patterns of ALS, MS, and PD on a municipal level in easternmost Finland.
Methods: Previously published ALS (years 2010–2018) and MS (years 2012–2016) cohorts were leveraged and PD data (years 2010–2018) were obtained from the national drug reimbursement entitlement registry. Population data were collected from a governmental registry.
Results: There were no municipalities with high incidences of all three disorders in both sexes. An ALS hotspot was observed in southeastern municipality of Tohmajärvi, driven by men. PD incidence was lowest in the central municipalities, around the urban area. Age-adjusted ALS and PD incidence was high and MS incidence low in Nurmes. Analyses of ALS and PD incidences using population aged >45 as reference showed an area of low PD incidence in the westernmost municipalities but no clear ALS incidence pattern. No municipality showed a high incidence of both disorders but the ones with the highest incidences are neighboring municipalities (Tohmajärvi and Kitee) in the southern part of the province. There was no correlation between ALS and PD incidence ($p = 0.17$).
Conclusions: Contemporaneous incidences of ALS, MS, and PD showed no correlations. These results suggest that epidemiological research for their common pathogenic factors needs to employ very long study periods and birth cohorts in large populations. Neuropathological and/or biomarker validation of cases should also be included whenever possible.

1. Introduction

Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) are not leading causes of neurological disability globally but have all become more common during the recent decades [1]. Moreover, their combined burden is among the 10 most important causes of disability among diseases of the nervous system. This is relevant because their prevalences have been shown to covary significantly, suggesting that they may share common pathogenetic factors [2]. Indeed, the Guam Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex (ALS/PDC) demonstrates that it may be useful to study ALS and PD as interrelated neurodegenerative disorders [3]. Identifying shared causative factors could help to mitigate the combined burden of these disorders.

Defining appropriate geographic area of investigation is essential for identifying such factors. Previous Finnish data suggest that this may not always correspond to specific geographically definable areas since there are marked differences in the epidemiology of these disorders: MS is most prevalent in the western and southwestern areas of Finland whereas ALS displays a clear hotspot in southeastern part of the country and PD has a belt of both high incidence and prevalence extending from easternmost Finland across central Finland to the western coast [4–6].

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Prevalence is a function of disease incidence and survival whereas incidence is more directly linked to origins of a disease. Therefore, investigating contemporaneous incidence patterns on a municipal level might yield suggestions about where to focus the search for common causative factors.

2. Methods

2.1. Study setting

North Karelia (total area c.21,500 km^2 of which 18,790 km^2 is on land) is the easternmost province of Finland (Fig. 1A). Its population (c.166,000) is declining (−12,872 between 1998 and 2018) and aged (25.8 % over 65 years of age in 2018). Over half (50.5 %) of the population lived in rural areas in 2018. The study period included in total 1,218,970 person-years at risk (50.5 % women) of which 794,910 (51.9 % women) were of persons >45 years of age. The area is served by only one public secondary healthcare facility, North Karelia Central Hospital (NKCH), located in the city of Joensuu (Fig. 1B). It has a neurology clinic providing in- and outpatient services by nine general neurologists. All suspected and diagnosed ALS and MS cases and the majority of PD patients (some are initially treated in the private sector which offers very limited neurological services in the area and these patients often transfer to the hospital's patients after the initial disease stages) are investigated and treated here.

2.2. Patient data

The aggregated annual numbers (per year and sex) of individuals who were newly granted special reimbursement entitlement for prescription PD medication expenses (entitlement code 110) in North Karelia between 2010 and 2018 were acquired from the national Social Security Institution of Finland (SSIF). Medications for PD are available only by prescription in Finland, and patients receive reimbursement for these medications. Entitlement for PD and related dopamine-responsive movement disorders requires an appropriate diagnosis verified clinically by a neurologist, and all applications are reviewed by a medical specialist at SSIF. Virtually all patients with PD in Finland apply for and are granted the entitlement after the appropriate diagnosis is made, and a previous preliminary report suggested a specificity of 80 % for these data [7].

Municipality-level incidence patterns in North Karelian hospital cohorts of patients with MS (diagnosed in 2012–2016) and ALS (diagnosed in 2010–2018) that have been previously reported were analyzed [8,9]. Population data were extracted from Statistics Finland databases [10].

2.3. Analyses

Incidence rates were initially calculated for the entire population of each municipality. Considering the limited nature of the MS data available they were only included in the primary analyses in which total population was used as reference. Age-standardize incidence rates (SIRs) were calculated using the indirect method with age-specific figures for global PD incidence, ALS incidence in Denmark and MS incidence for the entire NK as the reference data for expected number of cases [8,11,12] Further analyses focused on ALS and PD, for which incidence rates were recalculated using municipal populations >45 years of age as the denominator. This cut-off was chosen because during the study period 1 % of ALS diagnoses had been made (mean age at symptom onset 62.9 years, mean age at diagnosis 65.1 years) and < 1 % of PD reimbursement

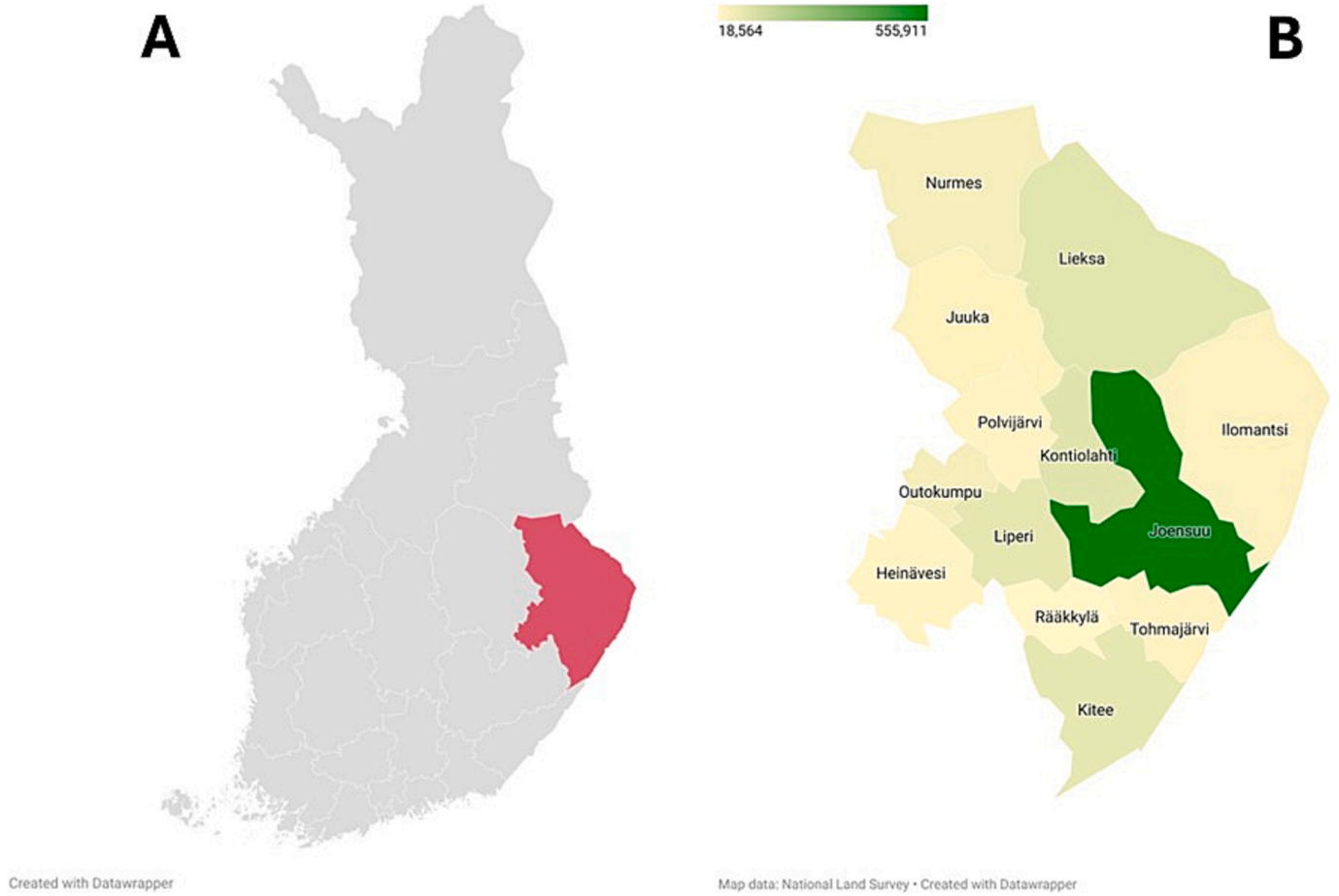

Fig. 1. A) The study area, North Karelia, within Finland; B) the municipalities of North Karelia with color coding of total person-years in 2010–2018.

entitlements had been given to persons <45 years of age in North Karelia [13].

The distribution of continuous data was assessed using the Shapiro-Wilk test and correlations were analyzed using linear regression with SPSS ver. 29 (IBM Corp.).

3. Results

3.1. Total population as reference

Crude incidence of ALS varied between 0 and 21.5 in men and 0–11.2 in women, that of PD between 60.2 and 210.6 in men and 40.6–104 in women and that of MS between 0 and 16.5 in men and 0–15.3 in women (Fig. 2A-F). In no municipality was the incidence of all three disorders high in both sexes. The northernmost municipality, Nurmes, exhibited high incidence of ALS in both sexes and PD in men but low MS incidence for both sexes. An ALS hotspot was observed in southestern municipality of Tohmajärvi, driven by very high incidence in men (in whom PD incidence was highest in the northernmost municipality of Nurmes and MS incidence in the easternmost municipality of Ilomantsi). PD incidence appeared to be lowest in the most central municipalities, around the city of Joensuu whereas there had been no single MS cases diagnosed in many small rural municipalities. There was no apparent pattern in the ALS incidences. In Nurmes and Tohmajärvi SIRs were high for ALS and PD and low for MS whereas SIRs were well above 1 (1.3–2.4) for all disorders in Ilomantsi (Fig. 3A-C). In Polvijärvi and Rääkkylä the SIRs were low (0–0.8) for ALS and MS and average (1.0–1.2) for PD.

3.2. Population > 45 years of age as reference (ALS and PD)

In these analyses PD incidence was clearly higher in the more peripheral municipalities and lower in the central ones and a particular cluster of low PD incidence (100.6–111.3) was apparent in the western municipalities of Outokumpu, Polvijärvi, Liperi and Kontiolahti (Fig. 4A). There was still no unambiguous pattern in ALS incidence (Fig. 4B). No municipality showed a high incidence of both disorders but the ones with the highest incidences (Kitee for PD and Tohmajärvi for ALS) are neighboring municipalities in the southern part of the province. Liperi (right next to the central city Joensuu) showed a high ALS incidence and a low PD incidence. There was no statistically significant correlation between ALS and PD incidence ($p = 0.17$; Fig. 5).

Ranking the incidence rates highlighted the patterns of increasing PD incidence towards the periphery (Fig. 6B) and showed a somewhat clearer opposite pattern of ALS incidence (Fig. 6A) than the crude incidence rates. Summing these ranks for each municipality clearly showed that there were no municipalities with high incidence rates of both and the municipalities with the highest summed ranks (Ilomantsi, Heinävesi, Nurmes, Tohmajärvi) were scattered across the province but it became apparent that the neighboring westernmost municipalities of Outokumpu, Polvijärvi and Juuka had quite low rates of both (Fig. 6C).

Both ALS and PD incidences were high in women in the municipality of Ilomantsi and ALS incidence was high in both sexes in the municipality of Liperi, but no other high incidence correlations were apparent when investigated by sex (Table 1). Both ALS and PD incidences were low in men in the municipality of Outokumpu and no new ALS cases were diagnosed for either sex in municipalities of Juuka and Rääkkylä during the study period.

4. Discussion

Municipal-level analyses revealed no unambiguous associations between the incidences of ALS, MS, and PD in North Karelia in the 2010s. If anything, there were suggestions of inverse associations between 1) the incidences of ALS and PD which, however, was not statistically significant; 2) the age-standardized peak and trough incidence of MS and those of ALS and PD. Incidences of PD were higher in peripheral parts of the province. There were no apparent hotspots of high incidence of both ALS and PD, although the municipalities with the highest incidence rates of each disorder are neighboring municipalities in the southern part of the province and the western part of the province showed a tendency of low incidences of both diseases.

The peripheral municipalities with the highest PD incidences (Kitee, Lieksa, Ilomantsi, Rääkkylä, Heinävesi, Juuka) are all entirely rural. This aligns with previous national data showing higher PD rates in rural regions [14]. This is probably explained by the fact that the environmental factors most robustly linked with PD risk are pesticides, especially paraquat (97.6 tons sold in Finland before banned in 1987) [15]. In North Karelia, agriculture and forestry have always been a more important source of employment than in the rest of the country [16]. Correspondingly, in 2020–2019 North Karelia displayed the highest (although declining) age-specific incidence of PD in Finland [17].

In contrast, there are no apparent similarities between the municipalities with the highest ALS incidences (Tohmäjärvi, Liperi, Nurmes, Kontiolahti, Heinävesi, Ilomantsi). Previous Finnish data also showed no difference in the urban/rural distribution of ALS [14,18]. Interestingly, the southernmost municipalities of the study (Kitee, Tohmajärvi, Rääkkylä, Liperi, Heinävesi and the southernmost parts of Joensuu) belong to the previously reported ALS cluster in southwestern Finland [4], but they are only partially included in the highest incidences list which also includes municipalities clearly outside the cluster (especially Nurmes). Post-World War II evacuations from the ALS cluster region (Ruskeala, Pälkjärvi, Värtsilä, and Impilahti) to Tohmajärvi, Liperi, Joensuu, and Kontiolahti may partly account for this contribution [19,20]. Moreover, the distribution of the strongest genetic ALS risk factor, *C9orf72* hexanucleotide expansion, probably explains a considerable proportion of the cluster which clearly centered in South Savonia [4,21,22]. There are also many environmental factors with strong ALS associations: β-*N*-methylamino-L-alanine (BMAA), formaldehyde, manganese, mercury, and zinc [23]. BMAA is produced by algae and can be found not only in water but also seafood, and fruits and vegetables irrigated algae-containing water [24]. Exposure to the factors may therefore vary non-geographically.

Neurodegenerative disorders share common pathophysiological hallmarks, multiple concurrent pathologies are common and pathology-phenotype correlations are not absolute [25–27]. Therefore, it is not surprising that their prevalences have been observed to covary [2]. However, key pathological hallmarks differ substantially across these disorders and that the patterns of combined pathologies differ between phenotypes [25,26]. Thus, it is possible that any similarities in pathogenetic factors might be limited in many ways. Most clinical ALS cases are associated with pure TDP-43 pathology whereas only a third of patients with clinical Lewy body disease (LBD, including PD) have pure Lewy body pathology [25]. TDP-43 pathology is rarely observed in clinical LBD cases and LBD pathology in similarly rare in ALS [25]. These disease-specific differences support the credibility of our observed lack of correlation between ALS and PD incidences observed in the current study is credible. Furthermore, recent studies show diverging incidence trends of ALS and MS in France and ALS and PD in North Karelia [9,17,28,29].

The current findings do not rule out common pathogenic or living-area related environmental factors underlying ALS, MS and PD but suggest that focusing on geographically tightly defined microenvironmental factors is perhaps not crucial to discovering them. ALS and PD are both strongly influenced by environmental factors and appear to develop through multiple steps, making it important to continue searching for factors associated with this process [30–34]. Considering that people often move beyond their immediate living environment due to factors such as work, hobbies and social connections, it seems possible that any common underlying factors may be shared culturally or across regions larger or differently defined than municipalities (e.g. by coastal areas of rivers) [35]. Furthermore, since neurodegenerative disorders develop slowly over years or even decades before the onset of clinical

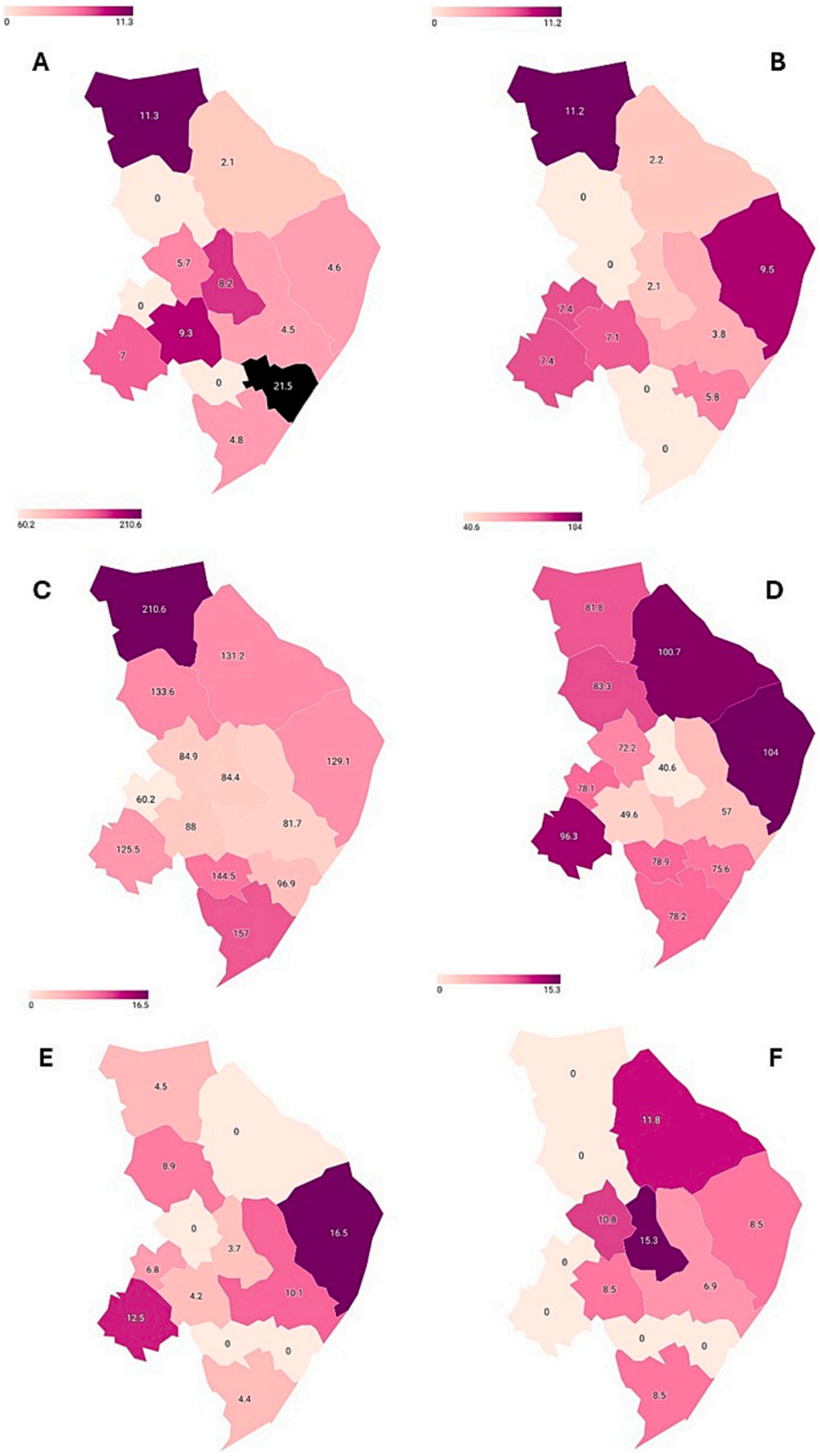

Fig. 2. Incidence results with the total population as the reference. A) ALS incidence in men 2010–2018; B) ALS incidence in women 2010–2018; C) PD incidence in men 2010–2018; D) PD incidence in women 2010–2018; E) MS incidence in men 2012–2016; F) MS incidence in women 2012–2016.

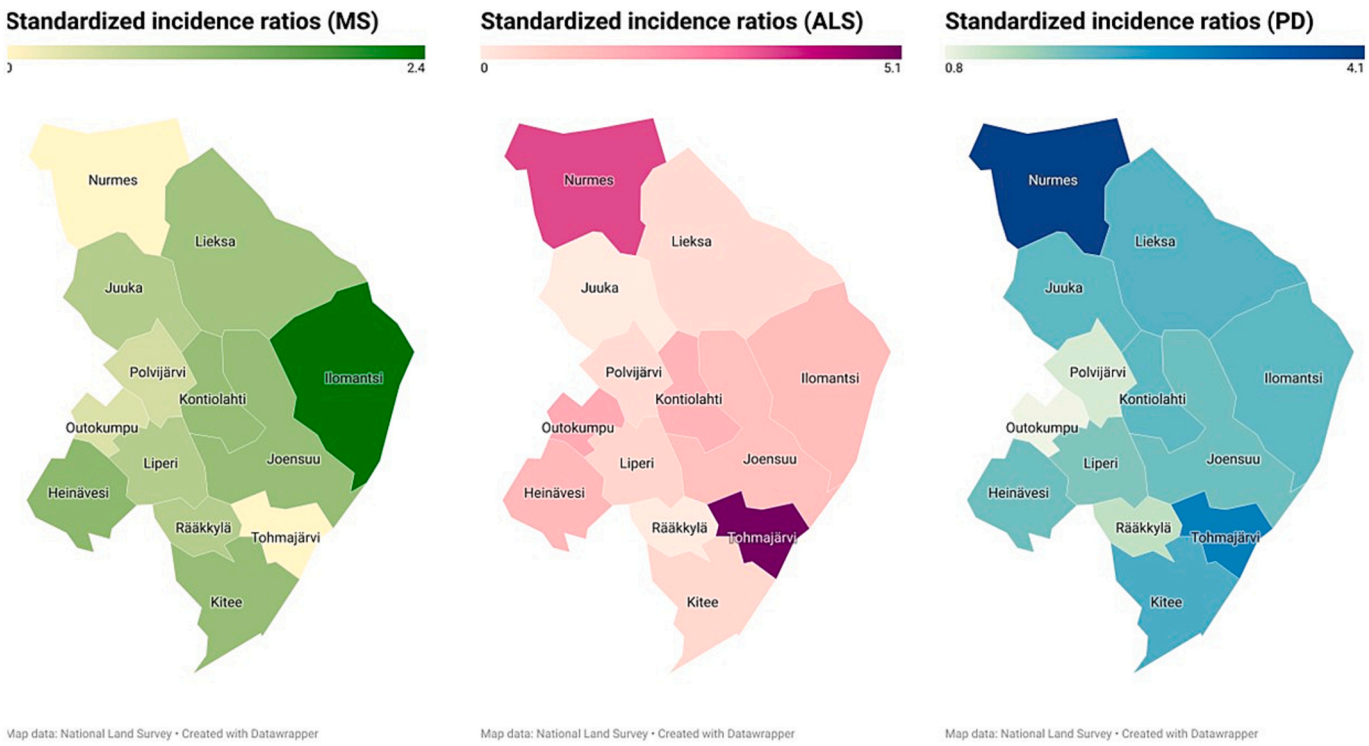

Fig. 3. Age-adjusted standardized incidence rates (SIRs) of Multiple sclerosis (MS, 2012–2016), Amyotrophic lateral sclerosis (ALS, 2010–2018) and Parkinson's disease (PD, 2010–2018) by municipality.

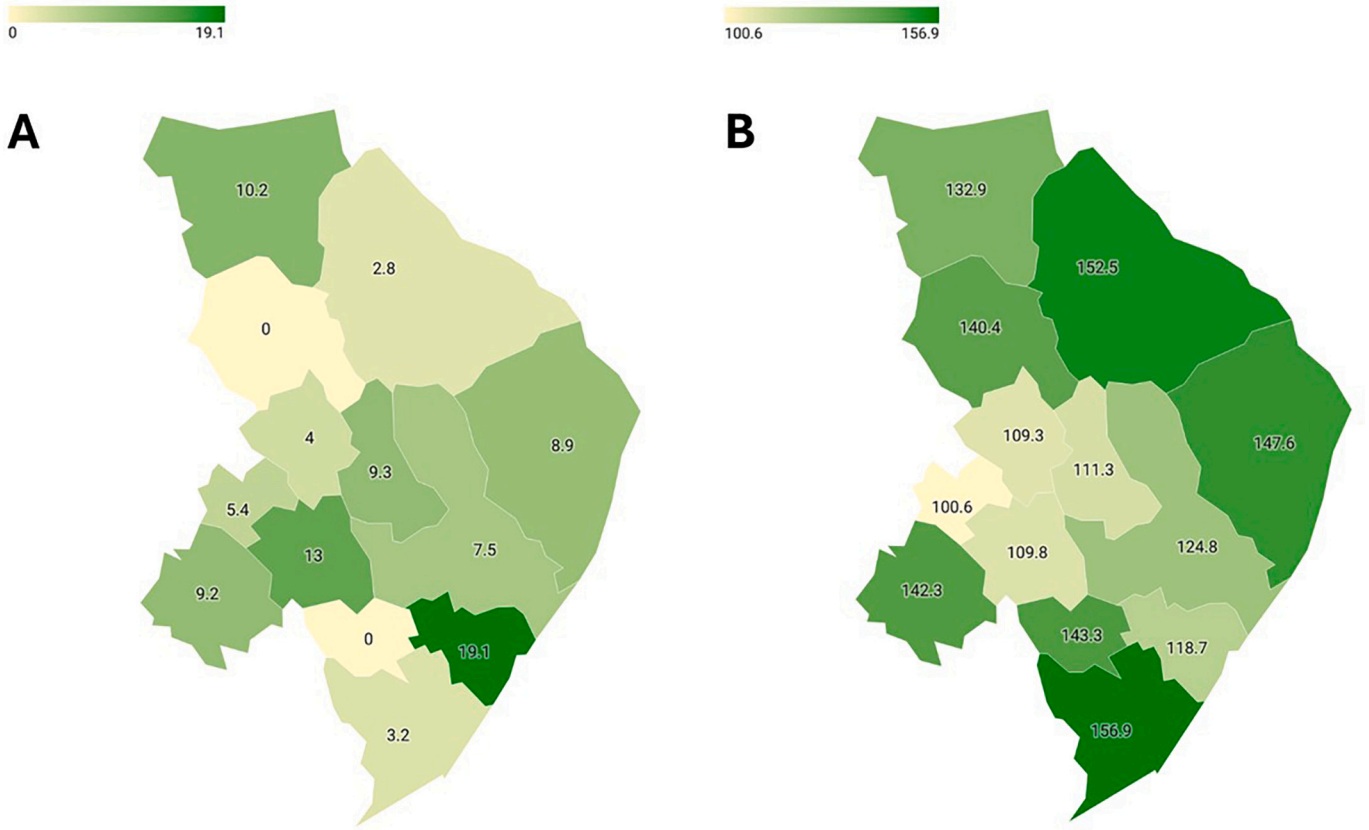

Fig. 4. Incidence results with the population > 45 years of age as the reference. A) ALS; B) PD.

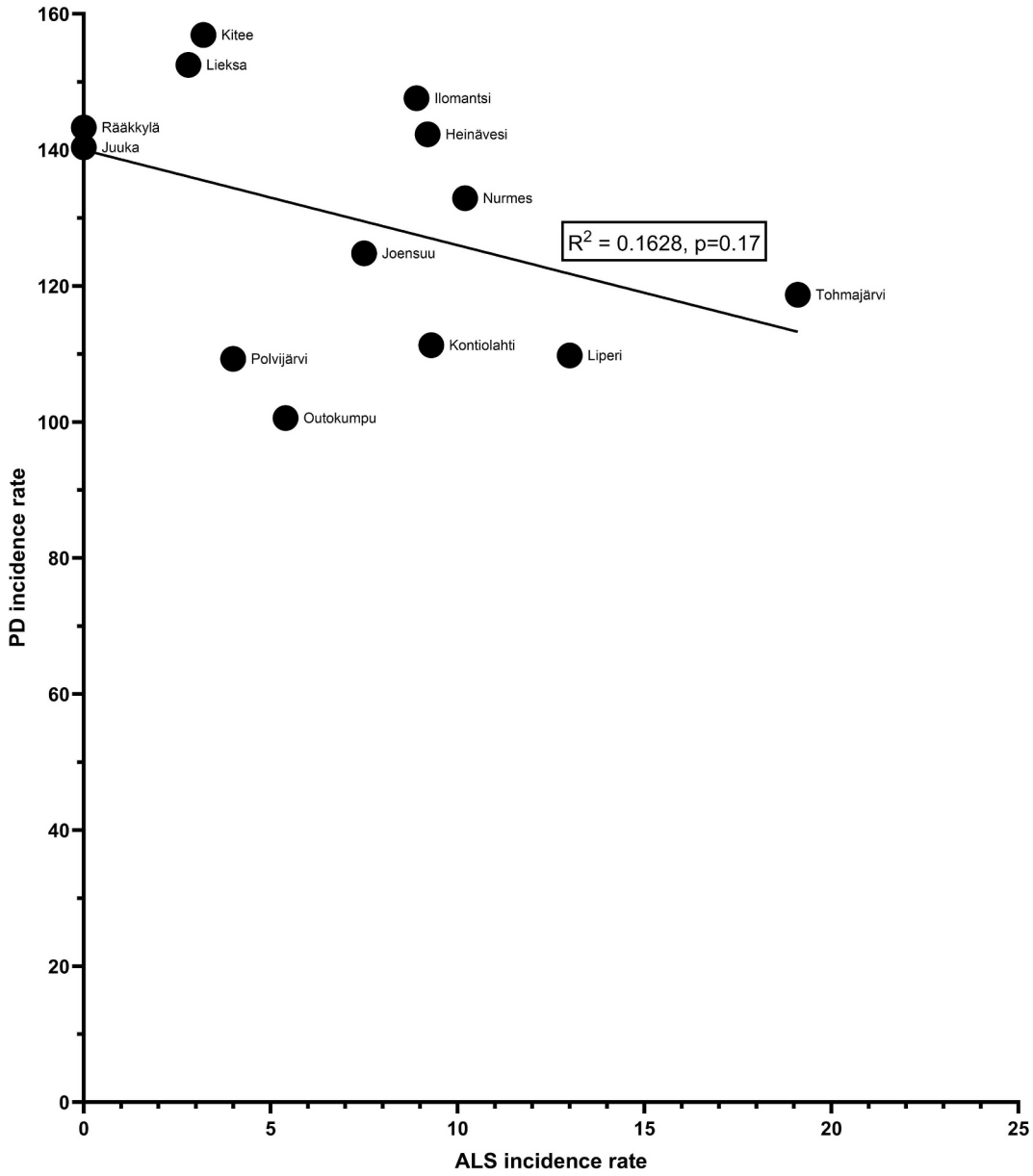

Fig. 5. Correlation analysis of ALS and PD incidence results.

symptoms, the type and timing of an exposure, the resulting phenotype and the age at its onset all should be considered together [36]. An example of all of these themes converging is the Guam ALS/PDC, caused by exposure to genotoxic cycad seeds and exhibiting a dose-response effect with larger and earlier exposure leading to ALS at an earlier age and more modest exposure to parkinsonism and/or dementia at a later age [3]. The pattern of slightly diverging ALS and PD incidences in our data with the fact that the mean age of ALS onset in North Karelia was 62.9 years in the current data and in 2010–2019 the mean age of PD onset in the province was 70.5 years (dr. Ayla Mehdiyeva, personal communication) suggest that a similar environmental exposure pattern cannot be ruled out for North Karelia.

In the current data, MS incidence in women mostly centered around the urban area in the middle of the province whereas that of men diverged more. This is in line with previous data [37]. There were no similarities between the general incidence pattern of MS and those of ALS and PD but the municipalities with the highest SIRs for ALS and PD had the lowest SIRs of MS. These observation are in line with previous reports that show the highest national-level incidence areas of ALS, MS and PD to be in different parts of Finland [4–6]. However, the current results should be approached cautiously since the MS data in the current study were more limited than the data on ALS and PD. In addition, there is a considerable difference in the age of onset of MS and the other two, suggesting that contemporaneous data concerning short study periods might even be potentially misleading if the disease drivers are dependent on age of exposure [36]. This is particularly relevant given that there is sometimes a gap of even decades before the onset of MS symptoms and the diagnosis. On the other hand, any prevalence data as an alternative may be confounded by survival trajectories that may change and diverge over time [38,39].

Epidemiological studies of neurodegenerative disorders may be skewed by the use of data of suboptimal validity [25,27,40,41]. The ALS and MS data in the current study were fully validated using retrospective patient chart review while the SSIH PD data validity should be similar to clinical PD diagnoses [7]. Coverage should also be complete as all ALS and MS diagnoses in the region are made at single secondary hospital and PD medication reimbursement entitlements are always sought in Finland. Nevertheless, it is always possible that some cases have gone

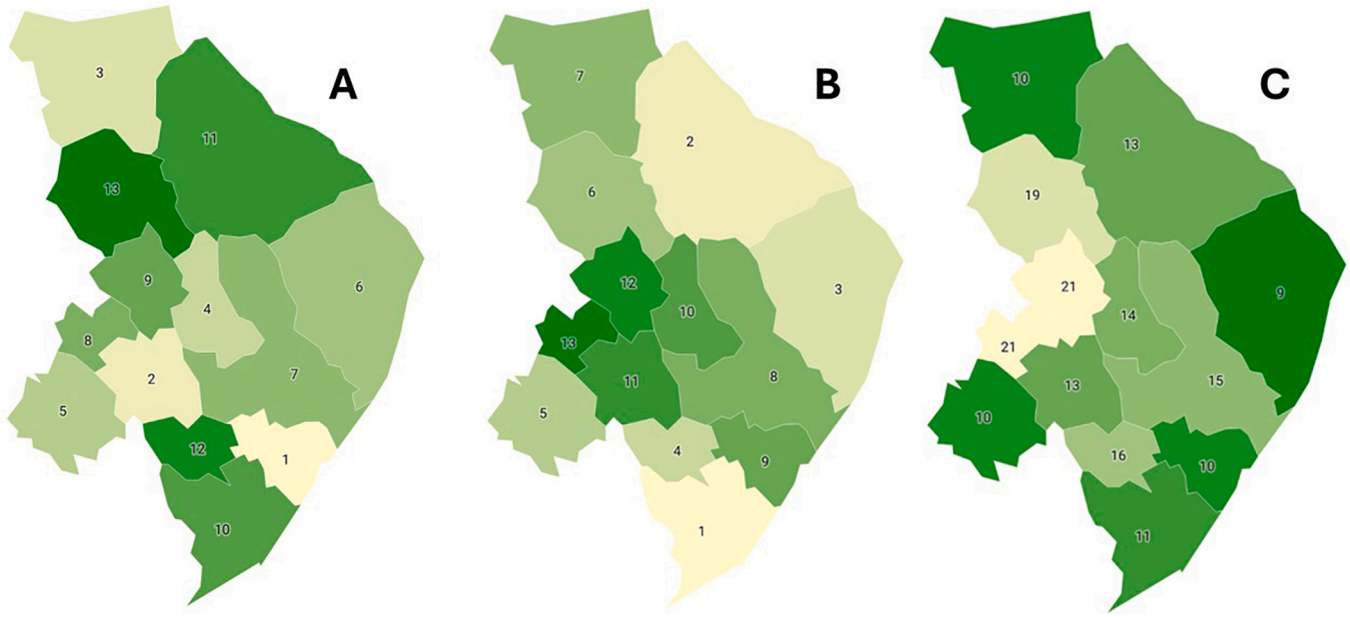

Fig. 6. Incidence results ranked (1 = highest incidence, 13 = lowest) and summed. A) ALS incidence results ranked; B) PD incidence results ranked; C) ALS + PD ranks sums.

Table 1
Incidence rates of ALS and PD and person-years (people >45 years of age) at risk during the study period by municipality. ALS, Amyotrophic Lateral Sclerosis; F, female; M, male; PD, Parkinson's disease.

	ALS		PD		Person-years	
	M	F	M	F	M	F
Heinävesi	9.1	9.2	164.3	120.0	10,953	10,833
Ilomantsi	5.9	11.8	166.0	129.3	16,865	17,014
Joensuu	8.5	6.6	156.0	96.5	140,414	166,413
Juuka	0	0	174.1	105.7	15,505	15,131
Kitee	6.6	0	215.7	102.1	30,138	32,311
Kontiolahti	14.6	3.8	149.9	71.6	27,348	26,543
Lieksa	2.9	2.8	177.5	128.2	32,925	35,876
Liperi	15.0	11.1	142.2	77.8	26,716	26,994
Nurmes	10.5	10.0	196.0	73.1	28,570	30,103
Outokumpu	0	10.5	90.7	109.7	17,642	19,137
Polvijärvi	8.1	0	121.9	96.8	12,309	12,400
Rääkkylä	0	0	183.9	99.5	7613	7038
Tohmajärvi	29.8	7.9	134.1	102.4	13,419	12,700

undiagnosed and consequently not ascertained here. Probably the greatest weakness of the current study is the modest population size of the province of North Karelia which, combined with a limited ascertainment period, leaves the results somewhat vulnerable to normal periodic fluctuations in disease occurrence. Differences in disease onset ages also means that the limited study period may not be optimal for observing possible correlations requiring longer period of time. Longer study periods and birth cohort studies with larger populations are hence needed. However, it should be noted that the limited correlation between phenotype and neuropathology naturally limits our ability to infer conclusions on pathophysiological clues from clinical epidemiological data meaning that neuropathological data validation would be preferable but unfortunately unrealistic in large scale studies. Advances in disease biomarkers may, however, mitigate this problem. Of course, many poorly studied, or yet unidentified factors may also contribute to these epidemiological patterns.

In conclusion, there were no unambiguous associations between the incidences of ALS, MS and PD in the province of North Karelia. Nevertheless, these and previous data suggest that the hunt for shared pathogenic factors of these disorders should be continued.

Ethical compliance statement

The ethical approval or informed consent were not required for this work according the laws of Finland. The authors affirm compliance with ethical publication standards.

Financial disclosure concerning the research related to the manuscript

Nothing to disclose.

CRediT authorship contribution statement

J. Sipilä: Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **M. Jokela:** Writing – review & editing, Formal analysis. **E. Solje:** Writing – review & editing, Investigation, Formal analysis.

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Conflicts of interest

J. Sipilä has as an advisory board member for Mertz, Boehringer-Ingelheim and Sandoz, received an honorarium from Novartis, received travel support from Lundbeck and owns shares of Orion corp.

M. Jokela has served as an advisory board member and as a consult for Roche and received travel support from CSL Behring and Roche.

E. Solje has served on the advisory board of Novartis, EISAI, Lilly and Roche, served as a consult for Novo Nordisk, BioaArctic and Roche and received honoraria from for lectures from Lundbeck, BioaArctic and Roche and travel support from Lilly.

References

[1] GBD 2021 Nervous System Disorders Collaborators, Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis

for the Global Burden of Disease Study 2021, Lancet Neurol. 23 (4) (2024) 344–381, https://doi.org/10.1016/S1474-4422(24)00038-3.
[2] L.M. James, A.P. Georgopoulos, High correlations among worldwide Prevalences of dementias, Parkinson's disease, multiple sclerosis, and motor neuron diseases indicate common causative factors, Neurosci Insights. 17 (2022), https://doi.org/10.1177/26331055221117598, 26331055221117598.
[3] P.S. Spencer, S.G. Berntsson, A. Buguet, et al., Brain health: pathway to primary prevention of neurodegenerative disorders of environmental origin, J. Neurol. Sci. 468 (2025) 123340, https://doi.org/10.1016/j.jns.2024.123340.
[4] C.E. Sabel, P.J. Boyle, M. Löytönen, et al., Spatial clustering of amyotrophic lateral sclerosis in Finland at place of birth and place of death, Am. J. Epidemiol. 157 (10) (2003) 898–905, https://doi.org/10.1093/aje/kwg090.
[5] A.S. Havulinna, P.J. Tienari, R.J. Marttila, et al., Geographical variation of medicated parkinsonism in Finland during 1995 to 2000, Mov. Disord. 23 (7) (2008) 1024–1031, https://doi.org/10.1002/mds.22024.
[6] A.L. Pirttisalo, M. Soilu-Hänninen, M.L. Sumelahti, et al., Changes in multiple sclerosis epidemiology in Finland over five decades, Acta Neurol. Scand. 142 (3) (2020) 200–209, https://doi.org/10.1111/ane.13295.
[7] P. Knekt, A. Kilkkinen, H. Rissanen, et al., Serum vitamin D and the risk of Parkinson's disease, Arch. Neurol. 67 (2010) 808–811, https://doi.org/10.1001/archneurol.2010.120.
[8] A.L. Pirttisalo, M. Soilu-Hänninen, J.O.T. Sipilä, Multiple sclerosis epidemiology in Finland: regional differences and high incidence, Acta Neurol. Scand. 139 (4) (2019) 353–359, https://doi.org/10.1111/ane.13057.
[9] M. Hanhisuanto, E. Solje, M. Jokela, J.O.T. Sipilä, Amyotrophic lateral sclerosis in southwestern and eastern Finland, Neuroepidemiology 57 (4) (2023) 238–245, https://doi.org/10.1159/000531238.
[10] Statistics Finland's free-of-charge statistical databases, 2025. https://statfin.stat.fi/PxWeb/pxweb/fi/StatFin/. accessed April 7, 2025.
[11] L.S. Levison, J.U. Blicher, H. Andersen, Incidence and mortality of ALS: a 42-year population-based nationwide study, J. Neurol. 272 (1) (2024) 44.
[12] M. Li, X. Ye, Z. Huang, L. Ye, C. Chen, Global burden of Parkinson's disease from 1990 to 2021: a population-based study, BMJ Open 15 (4) (2025) e095610.
[13] Kansaneläkelaitos, Statistics on reimbursement entitlements in respect of medicines (OFS), 2025. https://tietotarjotin.fi/en/statistic/2855926/statistics-on-reimbursement-entitlements-in-respect-of-medicines. accessed April 11, 2025.
[14] J. Isotalo, T. Vahlberg, V. Kaasinen, Unchanged long-term rural-to-urban incidence ratio of Parkinson's disease, Mov. Disord. 32 (3) (2017) 474–475, https://doi.org/10.1002/mds.26862.
[15] K. Atterling Brolin, E. Schaeffer, A. Kuri, et al., Environmental risk factors for Parkinson's disease: a critical review and policy implications, Mov. Disord. 40 (2) (2025) 204–221, https://doi.org/10.1002/mds.30067.
[16] E. Kinnunen, Väestö ja elinkeinorakenne, Elinkeinojen rakennemuutos, in: I. Björn (Ed.), Rajan maakunta — Pohjois-Karjalan historia 1939–2014, SKS Kirjat, Helsinki, Finland, 2014, pp. 113–115.
[17] J.O.T. Sipilä, V. Kaasinen, Parkinsonin taudin epidemiologia ja genetiikka Suomessa, Duodecim 138 (16) (2022) 1377–1384.
[18] M. Jokelainen, The epidemiology of amyotrophic lateral sclerosis in Finland: a study based on the death certificates of 421 patients, J. Neurol. Sci. 29 (1) (1976) 55–63, https://doi.org/10.1016/0022-510x(76)90080-0.
[19] E. Kinnunen, Väestö ja elinkeinorakenne, Elinkeinojen rakennemuutos, in: I. Björn (Ed.), Rajan maakunta — Pohjois-Karjalan historia 1939–2014, SKS Kirjat, Helsinki, Finland, 2014, pp. 92–112.
[20] M. Jokelainen, J. Wikström, J. Palo, Effect of birthplace on the development of amyotrophic lateral sclerosis and multiple sclerosis. A study among Finnish war evacuees, Acta Neurol. Scand. 60 (5) (1979) 283–288, https://doi.org/10.1111/j.1600-0404.1979.tb02983.x.
[21] H. Rostalski, V. Korhonen, T. Kuulasmaa, et al., A novel genetic marker for the C9orf72 repeat expansion in the Finnish population, J Alzheimer's Dis 83 (3) (2021) 1325–1332, https://doi.org/10.3233/JAD-210599.
[22] M. Jokelainen, J. Palo, J. Wikström, The distribution of amyotrophic lateral sclerosis in Finland, J. Neurol. Sci. 25 (4) (1975) 473–479.
[23] M.E. Newell, S. Adhikari, R.U. Halden, Systematic and state-of the science review of the role of environmental factors in amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease, Sci. Total Environ. 817 (2022) 152504, https://doi.org/10.1016/j.scitotenv.2021.152504.
[24] Z.A. Mohamed, R.O. Elnour, S. Alamri, et al., Occurrence of β-N-methylamino-L-alanine (BMAA) toxin in irrigation water and field vegetable plants and assessing its potential risk to human health, Water Air Soil Pollut. 235 (2024) 72, https://doi.org/10.1007/s11270-023-06861-0.
[25] J.L. Robinson, S.X. Xie, D.R. Baer, et al., Pathological combinations in neurodegenerative disease are heterogeneous and disease-associated, Brain 146 (6) (2023) 2557–2569, https://doi.org/10.1093/brain/awad059.
[26] D.M. Wilson 3rd, M.R. Cookson, L. Van Den Bosch, et al., Hallmarks of neurodegenerative diseases, Cell 186 (4) (2023) 693–714, https://doi.org/10.1016/j.cell.2022.12.032.
[27] P.W. Cullinane, S. Wrigley, J. Bezerra Parmera, et al., Pathology of neurodegenerative disease for the general neurologist, Pract. Neurol. 24 (3) (2024) 188–199, https://doi.org/10.1136/pn-2023-003988.
[28] O. Guinebretiere, C. Pierret, Q. Calonge, et al., Updated multiple sclerosis incidence in France, 2011–2021, Neurology 104 (9) (2025) e213586, https://doi.org/10.1212/WNL.0000000000213586.
[29] O. Guinebretiere, Q. Calonge, G. Bruneteau, et al., Time trends in incidence of motor neuron diseases in France: a comprehensive 14-year Nationwide study (2010−2023), Eur. J. Neurol. 32 (4) (2025) e70156, https://doi.org/10.1111/ene.70156.
[30] S.A. Goutman, M.G. Savelieff, D.G. Jang, et al., The amyotrophic lateral sclerosis exposome: recent advances and future directions, Nat. Rev. Neurol. 19 (10) (2023) 617–634.
[31] S. Bandres-Ciga, M. Diez-Fairen, J.J. Kim, A.B. Singleton, Genetics of Parkinson's disease: an introspection of its journey towards precision medicine, Neurobiol. Dis. 137 (2020) 104782.
[32] A. Al-Chalabi, A. Calvo, A. Chio, et al., Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study, Lancet Neurol. 13 (11) (2014) 1108–1113, https://doi.org/10.1016/S1474-4422(14)70219-4.
[33] C. Le Heron, M. MacAskill, D. Mason, et al., A multi-step model of Parkinson's disease pathogenesis, Mov. Disord. 36 (11) (2021) 2530–2538, https://doi.org/10.1002/mds.28719.
[34] D. Gerovska, M.J. Araúzo-Bravo, The common incidence-age multistep model of neurodegenerative diseases revisited: wider general age range of incidence corresponds to fewer disease steps, Cell Biosci. 12 (1) (2022) 11, https://doi.org/10.1186/s13578-021-00737-8.
[35] J. Wikström, Studies on the clustering of multiple sclerosis in Finland II: microepidemiology in one high-risk county with special reference to familial cases, Acta Neurol. Scand. 51 (3) (1975) 173–183, https://doi.org/10.1111/j.1600-404.1975.tb07598.x.
[36] J. de Pedro-Cuesta, P. Martínez-Martín, A. Rábano, et al., Drivers: a biologically contextualized, cross-inferential view of the epidemiology of neurodegenerative disorders, J Alzheimer's Dis 51 (4) (2016) 1003–1022, https://doi.org/10.3233/JAD-150884.
[37] D. Kotzamani, T. Panou, V. Mastorodemos, et al., Rising incidence of multiple sclerosis in females associated with urbanization, Neurology 78 (22) (2012) 1728–1735, https://doi.org/10.1212/WNL.0b013e31825830a9.
[38] M.L. Sumelahti, A. Verkko, V. Kytö, J.O.T. Sipilä, Stable excess mortality in a multiple sclerosis cohort diagnosed 1970-2010, Eur. J. Neurol. 31 (12) (2024) e16480, https://doi.org/10.1111/ene.16480.
[39] J.O.T. Sipilä, V. Kaasinen, P. Rautava, V. Kytö, Case-fatality rate in Parkinson's disease: a Nationwide registry study, Mov Disord Clin Pract. 11 (2) (2024) 152–158, https://doi.org/10.1002/mdc3.13948.
[40] S.M. Goldman, F.M. Weaver, L. Cao, et al., Validation of Parkinson's disease ascertainment in the veterans administration electronic medical record, Mov. Disord. 40 (2) (2025) 245–253, https://doi.org/10.1002/mds.30075.
[41] A. Mehdiyeva, V. Kaasinen, E. Heervä, J.O.T. Sipilä, Impact of Parkinson's disease diagnosis validity on the association with cancer: a systematic review and meta-analysis, Parkinsonism Relat. Disord. 135 (2025) 107846, https://doi.org/10.1016/j.parkreldis.2025.107846.