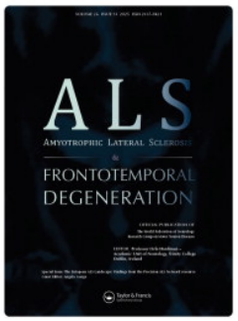

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RESEARCH ARTICLE

Examining changing working status and caregiver assistance in amyotrophic lateral sclerosis (ALS) using large-scale European databases as part of PRECISION-ALS

HARRY MCDONOUGH[1]*, ROBERT MCFARLANE[2]*, ALEJANDRO CARAVACA PUCHADES[3], ADRIANO CHIÒ[4], PHILIPPE CORCIA[5], MIRIAM GALVIN[2], MARK HEVERIN[2], FREDERIK HOBIN[6], OSKAR HOLMDAHL[7], CAROLINE INGRE[7], NIKITA LAMAIRE[6], ÉANNA MAC DOMHNAILL[2], UMBERTO MANERA[4], MOHAMMED MOUZOURI[5], FOUKE OMBELET[6], SARAH OPIE-MARTIN[8], MÓNICA POVEDANO PANADÉS[3], STEFAN SENNFÄLT[7], CRISTINA TERRAFETA PASTOR[3], JAN H. VELDINK[9], PHILIP VAN DAMME[6], LEONARD VAN DEN BERG[9], RUBEN P. A. VAN EIJK[9], ROSARIO VASTA[4], DAPHNE N. WEEMERING[9], AMMAR AL-CHALABI[8], PAMELA SHAW[1], CHRISTOPHER J. MCDERMOTT[1†] & ORLA HARDIMAN[2†]

[1]*Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK,* [2]*School of Medicine, Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College Dublin, The University of Dublin, Dublin, Ireland,* [3]*Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain,* [4]*"Rita Levi Montalcinì" Department of Neuroscience, University of Turin, Turin, Italy,* [5]*Centre de Reference Maladies Rares SLA, CHU Tours, Tours, France,* [6]*Neurology Department, University Hospitals Leuven and Neuroscience Department, Leuven Brain Institute, University of Leuven (KU Leuven), Leuven, Belgium,* [7]*Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden,* [8]*Department of Basic and Clinical Neuroscience, King's College London, Maurice Wohl Clinical Neuroscience Institute, London, UK, and* [9]*Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands*

Abstract

Objective: To examine the working status of people living with ALS (plwALS), the identity of their caregivers, the amount of informal care provided to them, and how these factors change over time. *Methods*: Data from nine specialist European ALS centers and previously funded projects, such as ALSCarE, were collated. The cohort was stratified into progression groups based on the calculated ΔFRS and compared longitudinally. *Results*: Twenty-one thousand eight hundred and twenty patients were identified at the time of data analysis. One thousand one hundred and eighty-four had working status data. Two hundred and thirty-seven patients in this group were followed in the form of semi-structured interviews. Within the 1184 patient group, 45% were identified as in "paid employment" prior to diagnosis, taking a median of 12 months to leave the workforce post-onset. Eighty-three percent of patients were no longer working 20 months post-diagnosis. Informal care hours increased over time, and were primarily provided by spouses and children. In those less than 12 months from symptom onset, the median number of care hours per week was 15.0 (IQR 63.8), rising to 60.0 (IQR 154.0) 48–96 months after onset. There was a significant relationship between ALSFRS-R total score and hours of care delivered ($r = -0.47$, $p < 0.001$). *Conclusion*: Up to 45% of plwALS are working prior to diagnosis and their working status changes rapidly, taking an average of 12 months to leave the workforce. Caregiver input increases over time, proportional to ALSFRS-R score. Caregivers are primarily spouses and children. Further work is needed to comprehensively capture this information and calculate its true socioeconomic impact.

Keywords: *working status, employment, caregiver, socio economic*

Correspondence: Harry McDonough, The University of Sheffield, Sheffield Institute for Translational Neuroscience, Sheffield S10 2TN, UK. E-mail: h.mcdonough@sheffield.ac.uk

*Joint first authors.

†Joint senior authors.

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Introduction

Amyotrophic lateral sclerosis is a neurodegenerative condition affecting motor function and cognition. Patients are generally affected in the 6th or 7th decade of life with progressive disability. Disease duration is however highly variable. While certain clear trends have been demonstrated in terms of variables such as site of onset or sex, significant variation persists (1).

In Europe, decades-long capture of patient information has been possible through the use of population registers and targeted projects, providing information that has helped map this disease heterogeneity (2–4). Despite this, certain aspects remain poorly understood or incompletely captured, such as changes in working status and the role of caregivers.

Working status has been identified as a significant factor in health-related quality-of-life in conditions such as breast cancer (5), inflammatory bowel disease (6), and multiple sclerosis (7). From clinical experience, this changes rapidly following an ALS diagnosis (8–12). The rate with which these factors change has both personal and socioeconomic consequences. Understanding who is more likely to leave work and when, or who is more likely to become a full-time carer or not is difficult to predict with any certainty. Similarly, the availability of formal and informal caregivers varies both because of personal circumstances and available healthcare resources, likely playing a role on a personal and practical level.

Here, we have collated and harmonized international longitudinal data as part of the PRECISON-ALS project (13). Data were analyzed with the aim of describing working status of people diagnosed with ALS, the identity of their caregivers, the amount of care provided, and how these factors change over time, modeling a resource-intensive—and often overlooked—aspect of patient care.

Methods

Participants

Under GDPR compliant data sharing agreements, data from previously funded collaborations and large-scale genomics projects have been harmonized and collated for analysis. In brief, nine European specialized ALS centers, part of the TRICALS consortium, with active population-based registries were approached to participate. Data requests were sent to each site to provide patient-level, de-identified data on demographic and disease characteristics, both obtained at diagnosis and during longitudinal follow-up. All patients diagnosed with either possible, probable (±laboratory supported) or definite ALS according to the revised El Escorial criteria were eligible in PRECISION-ALS. Sites were asked to provide all consecutively diagnosed patients from the beginning of their registry until December 2022. Data were obtained by direct questioning, either by a clinician or trained interviewer and then verified with patient records. Follow-up was at each hospital/community follow-up visit. The sites included were Trinity College Dublin, The University of Sheffield, King's College London, UZ Leuven, Bellvitge University Hospital, University Hospital Tours, The Karolinska Institute, The University of Turin, and UMC Utrecht. The dates spanned by these registries are available in the supplementary materials.

These population and clinic-based register datasets were combined with other data from the ALSCarE study (A Programme for Amyotrophic Lateral Sclerosis Care in Europe). ALSCarE was a European, multi-center study investigating the wellbeing of people with ALS and primary informal caregivers throughout Europe. ALSCarE participants were included only if also available in their respective population registry. ALSCarE data were collected at 4-monthly intervals. Data were generated through semi-structured interviews that included demographic and socio-economic details, caregiver burden, psychological distress, and quality of life assessments. ALSCarE did not recruit formally paid caregivers, nor people aged less than 18 years. All free text responses (e.g. relationship of caregivers) were translated into English and standardized into categorical variables.

Progression calculation

The cohort was stratified into three progression groups based on the calculated ΔFRS. ΔFRS at baseline was calculated as previously published (14). "Slow" progressors comprised those below the 25th ΔFRS percentile, "intermediate" progressors were between the 25th and 75th percentiles, and "fast" progressors above the 75th ΔFRS percentile.

Statistical analysis

Data analysis was performed in both R (version 4.2.2) (15) and Python (version 3.9.13). Descriptive statistics summarized the socio-demographic and wellbeing measures of caregivers in Ireland, England, Italy, and the Netherlands. These are presented as frequency with percentage (%), mean with standard deviation (SD), or median with interquartile range (IQR), as appropriate. Data were plotted to visually represent relationships between variables, with simple linear regression models fitted and correlation assessed

using Pearson's or Spearman's rank correlation coefficients as appropriate. Non-normally distributed groups were compared for statistical significance using the Kruskal–Wallis test.

Results

Working status

Twenty-one thousand eight hundred and twenty patients were identified across all sites at time of data analysis. One thousand eight hundred and eleven had working status data for analysis. Additionally, 237 of the patients with working status data participated in ALSCarE semi-structured interviews. Background clinical information such as sex, site of onset, age of onset, age at diagnosis, and onset to death are included in the Supplementary Figures.

Of all patients with working status data, prior to diagnosis; 45% were identified as in "paid employment", 49% were "retired", 2.65% were "unemployed", 1.82% were "unable to work", 0.6% were "looking after home/family", and 0.2% were recorded as "other". Significantly more men were in employment (47.83%) than women (42.38%, $p = 0.027$), no other gender comparisons reached statistical significance.

As expected, the ages of the groups showed significant variation, with the "retired" group (70.5 years, IQR 9.80) being significantly older than the "unemployed" (55.7 years, IQR 9.6, $p < 0.00001$) or "paid employment" groups (55.1 years, IQR 12.7, $p < 0.00001$). Ages were not significantly different between the "unable to work" (58.2 years, IQR 9.6), "looking after home/family" (68 years, IQR 6.49) and "other" (59.2 years, IQR 10.1) groups.

Those with longitudinal information collected as part of ALSCarE ($n = 237$) were examined for how their employment status changed over time. The proportion of patients in paid employment changed over time and was compared to status at diagnosis. At 20 months post-diagnosis, only 15% of patients continued paid employment ($p = 0.002$) and the proportion of patients who reported that they were unable to work due to permanent sickness or disability increased to 45% at 20 months post-diagnosis ($p = 0.001$). Overall, the proportion of patients not working 20 months post-diagnosis was 83.51% ($p = 0.0001$).

Those who were identified as in employment prior to diagnosis were then analyzed to calculate the time it took them to leave paid employment (Figure 1). It took a median of 12 months (IQR 10.3) for patients to leave employment post-onset; women remained in work for longer post-onset, with a median of 12 months (IQR 2.83) as opposed to men with a median of 11 months (IQR 10.5, $p = 0.001$). There was a small negative correlation coefficient between the time taken to give up work and the number of years of education (-0.021, $p = 0.8$).

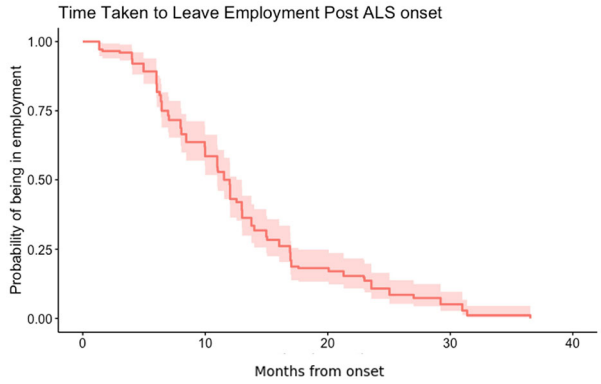

Figure 1. Where a patient was recorded as employed at the time of onset, they were longitudinally followed and the date at which they left full-time employment was recorded; this probability graph shows the rate at which this change occurs in our cohort in months.

Caregiver identities

Data from 172 patient/caregiver dyads were available. Informal caregivers were primarily immediate family members, either the patient's spouse/partner (45.0%) or children (26.4%). However, friends (7.2%), siblings (6.2%), extended family (4.6%), in-laws (3.9%), parents (3.6%), and care services (3.3%) were also identified. The identity of these caregivers remained consistent across the 20 months of follow-up. At the time of baseline data capture, patients received care from a mean of 1.75 people (SD 0.88, range 1–5). 32.5% of caregivers were male and 49.7% female, with the sex of the caregiver unknown in 17.8% of cases.

Caregiver hours

There was evidence of increasing informal care hours over time. In those less than 12 months from symptom onset, the median number of care hours per week was 15.0 (IQR 63.8), rising to 32.0 (IQR 81.0) 12–24 months after onset, 35.5 (IQR 154.0) 24–48 months after onset, and 60.0 (IQR 154.0) 48–96 months after onset. Median hours provided fell in those >96 months after onset to 36.5 (IQR 158.0) (Table 1).

A weakly positive correlation was observed between hours of care provided and time since onset of symptoms ($r = 0.11$, $p = 0.02$, Figure 2). This correlation was consistently positive across the three progression groups: slow ($r = 0.22$, $p = 0.08$), intermediate ($r = 0.23$, $p = 0.001$), and fast ($r = 0.26$, $p = 0.06$, Figure 3). Of note, a cluster at 168 hours of care per week was observed, likely to represent individuals requiring 24-h care; for individuals with one carer, this would be the maximum care hours that could be received per week.

Table 1. Descriptive longitudinal data showing an increase in median informal care hours per week.

		Hours of informal care/week		
Months from symptom onset	*n* (patients)	Mean (SD)	Median (IQR)	Range
<12	22	46.3 (65.3)	15.0 (63.8)	1–216
12–24	67	65.5 (78.2)	32.0 (81.0)	1–336
24–48	94	71.4 (71.6)	35.5 (154.0)	1–338
48–96	27	79.9 (75.5)	60.0 (154.0)	0.7–336
>96	10	68.9 (70.6)	36.5 (158.0)	2–172

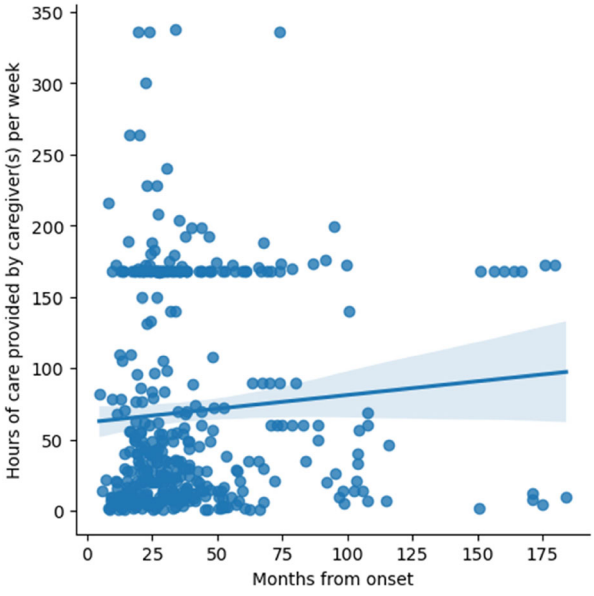

Figure 2. Scatterplot with simple linear regression representing positive relationship between time since symptom onset and hours of informal care provided per week ($r = 0.11$, $p = 0.02$).

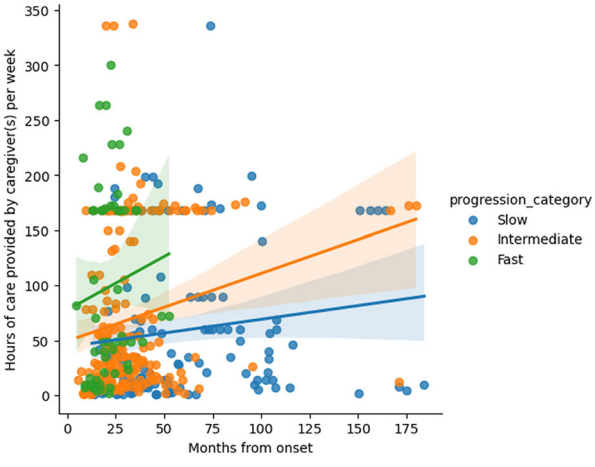

Figure 3. Scatterplot with simple linear regression representing positive relationship between time since symptom onset and hours of informal care provided per week across slow- ($r = 0.22$, $p = 0.08$), intermediate- ($r = 0.23$, $p = 0.001$), and fast-progressors ($r = 0.26$, $p = 0.06$).

Significant differences in care hours provided were seen between the three progression groups ($H = 12.8$, $p = 0.002$). Stepwise analysis showed fast progressing individuals received significantly more informal care hours per week than slow ($p < 0.001$) or intermediate ($p = 0.02$) progressing individuals (Table 2).

At a group-level, there was no statistically significant difference in care hours provided to male and female patients ($p = 0.42$). However, when stratifying by progression group, as above, slow progressing males did receive significantly more care hours than slow progressing females ($p < 0.001$), though this difference was not observed in intermediate ($p = 0.09$) or fast ($p = 0.10$) progressors. There was also no statistically significant difference between the care hours provided by male or female carers ($p = 0.25$) at a group-level (Table 3).

We observed a significant relationship between functional impairment, as measured by the ALSFRS-R total score, and hours of care delivered per week. Broadly, those with increased functional impairment received more care per week ($r = -0.47$, $p < 0.001$, Figure 4).

Tasks performed by caregivers

As part of the semi-structured interviews, data were collected on the specific tasks with which patients were helped. Categories were as follows: "personal care", "housework", "transport", "shopping", and more broadly "general support". Across all time points, general support was provided most frequently (81%), followed by support with housework (75%), shopping (65%), personal care (59%), and transport (55%), represented in Figure 5.

Comparing patients less than 12 months from symptom onset and those greater than 96 months since onset, there was a 32% rise in those assisted with personal care, a 9.9% rise for assistance with housework, 11.0% rise for assistance with transport, 41.5% rise for assistance with shopping, and 15.4% rise in general support (Figure 5).

Discussion

Maintaining independence for people living with ALS (plwALS) is an important aspect of their clinical care. Here, we have examined working status and caregiver assistance as a proxy measure of this independence. Understanding the factors that influence the decision to leave the workforce and the rate at which informal caregivers become more

Table 2. Group-level comparison of informal care hours provided to slow-, intermediate-, and fast-progressors.

		Hours of informal care/week			
Progression rate	*n* (patients)	Mean (SD)	Median (IQR)	Range	Kruskal–Wallis (*H*, *p* value)
Slow	56	58.4 (67.5)	29.5 (81.8)	0.7–336	12.8, 0.002
Intermediate	72	70.1 (73.0)	35.0 (136.0)	1–338	
Fast	21	98.8 (85.7)	62.2 (146.4)	2–300	

Table 3. Group-level comparison of informal care hours provided to those with differing levels of functional impairment.

		Hours of informal care/week			
ALSFRS-R total score	*n* (patients)	Mean (SD)	Median (IQR)	Range	Kruskal–Wallis (*H*, *p* value)
37–48	137	39.9 (46.1)	24.5 (47.0)	0.7–168	61.8, <0.001
25–36	155	78.9 (70.8)	49.0 (148.0)	2–336	
13–24	58	117.7 (77.9)	154.0 (118.0)	6–264	
1–12	11	93.5 (46.6)	90.0 (55.0)	10–168	

Those that have more significant functional impairment broadly receive more informal care.

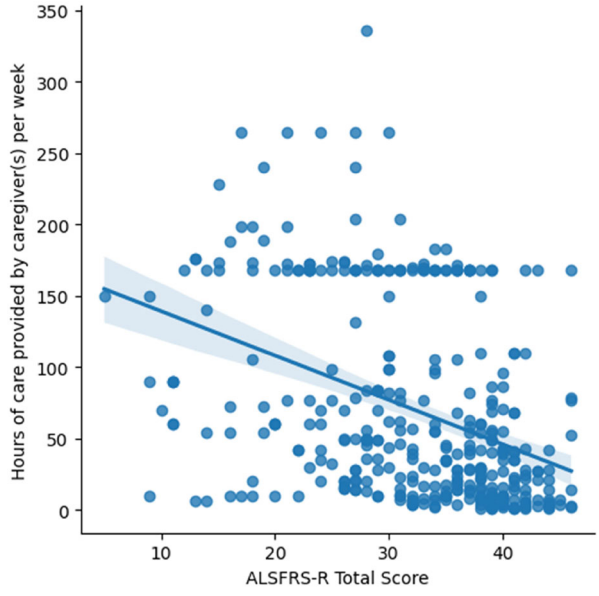

Figure 4. Scatterplot with simple linear regression representing strong relationship between functional impairment and hours of informal care provided per week ($r = -0.47$, $p < 0.001$).

involved is crucial, as it impacts both plwALS and their communities.

Working status

From clinical experience, working status changes quickly following an ALS diagnosis. A considerable proportion of people are retired at the time of diagnosis, however—as we have demonstrated here—45% were in paid employment. As populations work for longer and retirement ages increase across Europe, this proportion of individuals is likely to become more important. We have also shown here that men are more commonly employed at the time of diagnosis and are more likely to exit the workforce at an earlier timepoint than women.

Continued employment is often associated with better quality of life (5,7). Due to the nature of disease progression in ALS, sustained participation in the workforce is likely representative of a more slowly progressive disease course. Clearly, leaving the workforce early has a socioeconomic impact. However, from a clinical trial perspective in ALS, if an intervention could be shown to delay the need to leave the workforce, that would be a meaningful outcome.

Informal caregivers

Caregivers have a central but challenging role within the multi-disciplinary management of ALS. The commitment of informal caregivers enables plwALS to stay in their own home for longer, where much of ALS care delivered, focusing on symptom control and quality of life (9,11,16). As has been previously reported (17,18), informal caregivers in this study were most likely to be partners or close relatives. This undoubtedly alters the dynamics of close inter-personal relationships, as loved ones adopt a new care role. This period of adjustment accompanies a new diagnosis of a universally fatal disease, understandably resulting in caregivers often struggling with their new reality and increased responsibility (19–23).

Caregiver burden is a term that encompasses the emotional, physical, social, and financial effects that stem from adopting a caregiving role (10). Previous longitudinal study has shown ALS caregivers experience increasing levels of physical and emotional distress, or caregiver burden, over time (10,19,22,24). Our study showed an increase in informal care hours over time, both as the disease duration lengthens and as the level of functional disability worsens. This is in line with previous findings and complements study into caregiver burden, which has demonstrated that the level of

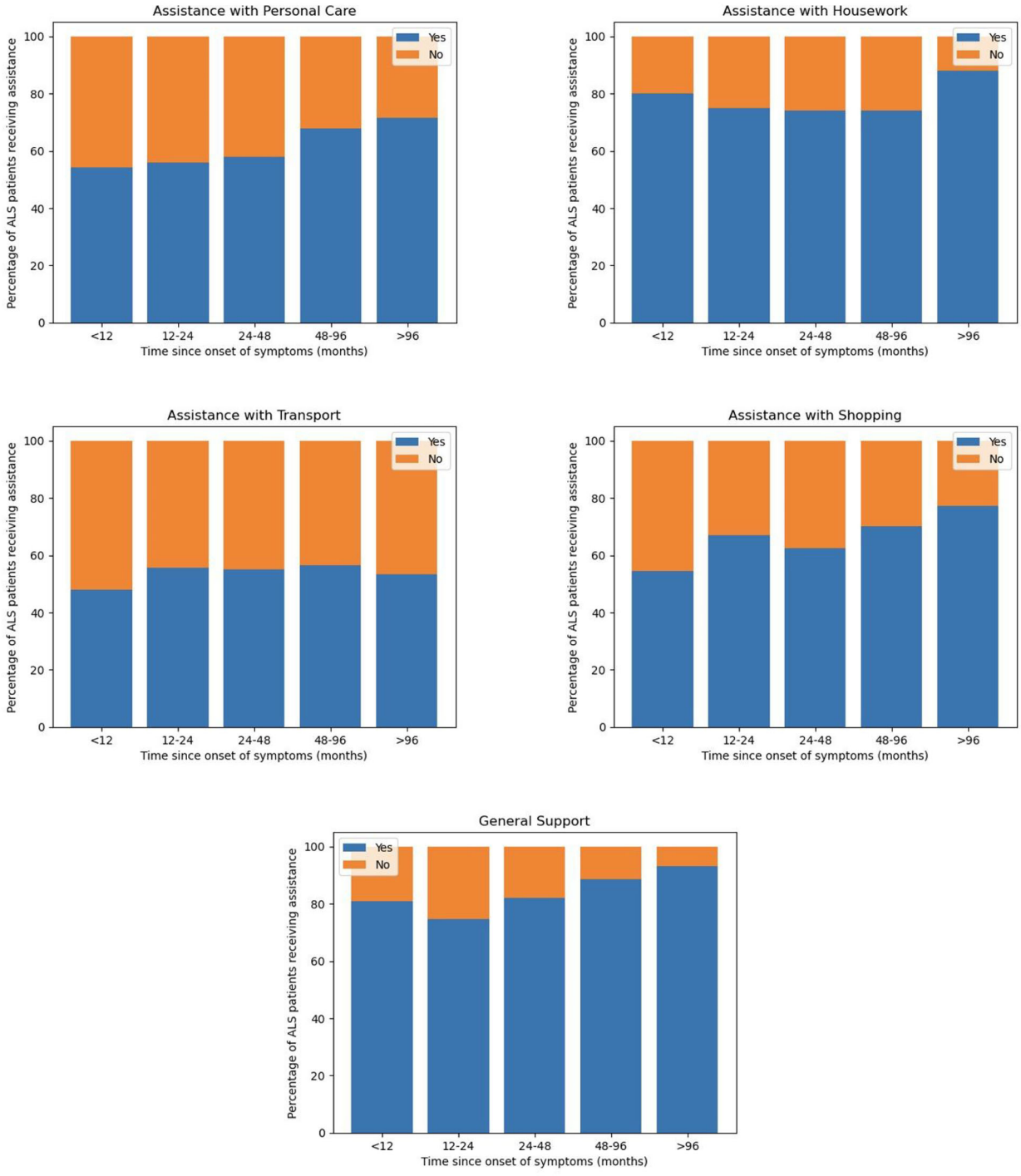

Figure 5. Series of bar plots representing specific tasks with which patients were helped by their informal caregivers. We observe broadly an increase in the proportion of pwALS assisted as time passes from onset of symptoms.

disability experienced by a plwALS is strongly correlated to caregiver burden (25). In addition, we did not identify significant differences in hours of provided care between male and female carers, consistent with previous study that has reported the sex of the caregiver not to be a significant factor in the degree of caregiver burden (26).

The impact on ALS caregivers is broad-reaching, with caregiver burden restricting the ability of carers to work full-time, thus affecting financial income and stability, as well as impacting physical and mental health, leading to a reduction in health-related quality of life and quality of life more broadly (27,28). Using the median hourly wage of €16.09 for a carer across the localities included in this study (29), the annual caregiving costs per plwALS, were they not to be cared for informally, would range from €20,499 for pwALS with mild disability to €128,849 for pwALS with severe disability. With an estimated ALS prevalence in Europe of 6.22/100,000 (30), the total annual cost of ALS caregiving in Europe could be crudely estimated at €1.28 billion (supplementary file).

Looking forward, there is increasing recognition of the need to address caregiver burden within the holistic management of ALS (11). Clinicians are encouraged to be aware of and screen for depression and anxiety within caregivers, thus enabling early intervention (25). It has also been suggested that supportive measures may lean on factors that have been found to mitigate caregiver burden, such as spirituality and existential wellbeing (31), social support (32), and mindfulness (33). The positive aspects of caregiving, such as a sense of personal satisfaction, a meaning in life, and a sense of hope, have also been highlighted as potential sources for future design and implementation of supportive interventions for caregivers and pwALS (11).

Limitations

This study analyzes data from plwALS attending European clinics, which should be considered when generalizing these results. It should also be considered that, when looking at the longitudinal data, those who participate in the semi-structured interviews are likely to be overrepresented, compared with those presented in the population registries.

In this study of over 21,000 ALS patients, there was variable data capture regarding working status and caregiver information. Indeed, only 1184 of these patients had working status recorded and therefore the bias inherent in this smaller group analysis should also be considered. Despite this variable data capture, there is clear change captured in this analysis, which has implications for care planning, disease trajectory delineation, and therefore event prediction. These findings could, however, be refined further with more comprehensive data capture moving forward.

Conclusion

Working status and the amount of care provided by caregivers change over the disease course. Up to 45% of people are in paid employment at the time of diagnosis and their rapid change in employment status post-diagnosis is likely to have a socioeconomic impact. This problem is likely to worsen as demographic changes take place with time. Spouses and children are often principal caregivers and the care they provide rapidly increases in proportion to disease progression. Men are more likely to be in full time employment at the time of diagnosis and exit the workforce more quickly than women post-diagnosis.

Caregiver input and working status information are not captured comprehensively across the cohorts examined. Further work is needed to harmonize data collection across Europe so that these variables can be interrogated for socioeconomic planning and disease stratification. Collecting such granular data as part of PRECISION-ALS will help inform future investigation into the hidden costs of ALS via frameworks such as Health Technology Assessments.

Acknowledgements

We would like to thank the people with MND who provided their data for this study by consenting to their inclusion.

Ethics statement

All procedures and methodologies were in accordance with the ethical guidelines and standards of the institutional and national ethics committees of each of the sites involved. Ethical approvals were obtained from the local Institutional Review Board (IRB) at each participating site for use of the data in this study and for the central storage required to facilitate the cleaning and harmonization of the data. Personal data were transferred and stored securely to ensure that the privacy of these data was maintained, and relevant steps were taken to minimize any potential harm to participants.

Consent form

Informed consent was obtained from all participants, ensuring their autonomy and understanding of the study's objectives.

Declaration of interest

Alejandro Caravaca Puchades reports no competing interests to declare. Cristina Terrafeta Pastor reports no competing interests to declare. Mónica Povedano Panadés reports consultancies/advisory boards for Amylyx Pharmaceuticals, Biogen, Ferrer, Grifols, Italfarmaco, Mitsubishi Tanabe Pharma, and Roche. Stefan Sennfält reports no competing interests to declare. Oskar Holmdahl reports no competing interests to declare. Nikita Lamaire reports no competing interests to declare. Caroline Ingre has consulted for Cytokinetics, Pfizer, BioArctic, Novartis, Tikomed, Ferrer, Amylyx, Prilenia, and Mitsubishi. She is also a board member of Tobii Dynavox; all outside the submitted work. Sarah Opie-Martin reports no competing interests to declare. Ammar Al-Chalabi reports consultancies or advisory boards for Amylyx, Apellis, Biogen, Brainstorm, Clene Therapeutics, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, QurAlis, Sano, Sanofi, and Wave Pharmaceuticals. Frederik Hobin reports no competing interests to declare. Fouke

Ombelet reports no competing interests to declare. Philip Van Damme reports advisory boards for Biogen, CSL Behring, Alexion Pharmaceuticals, Ferrer, QurAlis, Cytokinetics, Argenx, UCB, Muna Therapeutics, Alector, Augustine Therapeutics, VectorY, Zambon, Amylyx (paid to institution). He has received speaker fees from Biogen, Zambon and Amylyx (paid to institution). He is supported by the E. von Behring Chair for Neuromuscular and Neurodegenerative Disorders (from CSL Behring, paid to institution). Harry McDonough reports no competing interests to declare. Christopher J. McDermott reports consultancies or advisory boards for Amylyx, Ferrer, Novartis, PTC Therapeutics, and Verge Therapeutics. Pamela J. Shaw reports consultancies or advisory boards for Biogen, Aclipse Therapeutics, Quell Therapeutics, BenevolentAI, QurAlis, Astex, GeniUS, Lilly, Novartis, Samsara, Eikinoklastes, Maat Pharma and AL-S Pharma and collaborates with and has received research funding from Quell Therapeutics, Aclipse Therapeutics, Pfizer SwanBio, and Takeda. Mohammed Mouzouri reports no competing interests to declare. Philippe Corcia reports consultancies or advisory boards for Amylyx, Biogen, Coave Therapeutics, Cytokinetics, Ferrer, Mitsubishi Tanabe, QurAlis, Vectory, and Zambon. He is a member of the Board of the Journal Amyotrophic Lateral Sclerosis and the Frontotemporal Dementias and of the Revue Neurologique. Robert McFarlane reports no competing interests to declare. Miriam Galvin reports no competing interests to declare. Mark Heverin reports no competing interests to declare. Éanna Mac Domhnaill reports no competing interests to declare. Orla Hardiman reports consultancies/advisory boards for Biogen, Takeda, Ferrer, Novartis, Alchemab, and Medici Nova. She is Editor in Chief of the Journal Amyotrophic Lateral Sclerosis and the Frontotemporal Dementias. Rosario Vasta reports no competing interests to declare. Umberto Manera reports no competing interests to declare. Adriano Chiò serves on the editorial advisory board of Amyotrophic Lateral Sclerosis and Neurological Sciences. Adriano Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Biogen, Roche, Denali Pharma, Cytokinetics, Lilly, Ferrer, Zambon Biotech, and Amylyx Pharmaceuticals, has received a research grant from Biogen and serve on Drug Safety Monitoring Board for AB Science, Corcept, and Eli Lilly. He has received research support from the Italian Ministry of Health (Ricerca Finalizzata), Regione Piemonte (Ricerca Finalizzata), Italian Ministry of University and Research (PRIN Projects), University of Turin, and the European Commission (Health Seventh Framework Programme, Horizon 2020 and Horizon Europe). Ruben P. A. van Eijk reports no competing interests to declare. Daphne N. Weemering reports no competing interests to declare. Jan H. Veldink reports no competing interests to declare. Leonard van den Berg reports no competing interests to declare.

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ORCID

Robert McFarlane http://orcid.org/0000-0001-7380-4219
Adriano Chiò http://orcid.org/0000-0001-9579-5341
Miriam Galvin http://orcid.org/0000-0002-8232-8020
Caroline Ingre http://orcid.org/0000-0001-5327-7204
Umberto Manera http://orcid.org/0000-0002-9995-8133
Sarah Opie-Martin http://orcid.org/0000-0003-0951-8589
Philip van Damme http://orcid.org/0000-0002-4010-2357
Ruben P. A. van Eijk http://orcid.org/0000-0002-7132-5967
Ammar Al-Chalabi http://orcid.org/0000-0002-4924-7712
Christopher J. McDermott http://orcid.org/0000-0002-1269-9053
Orla Hardiman http://orcid.org/0000-0003-2610-1291

Data availability statement

The data set used for the analysis in this paper was provided by PRECISION ALS. These data are stored, and access is governed by the PRECISION ALS Consortium. Requests to access these data can be made through the Scientific Board of the PRECISION ALS Consortium.

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