



HAL
open science

Amyotrophic lateral sclerosis : mortality and predictors of survival

Paul H. Gordon

► **To cite this version:**

Paul H. Gordon. Amyotrophic lateral sclerosis : mortality and predictors of survival. Santé publique et épidémiologie. Université Pierre et Marie Curie - Paris VI, 2012. English. NNT : 2012PAO66398 . tel-00829569

HAL Id: tel-00829569

<https://theses.hal.science/tel-00829569>

Submitted on 3 Jun 2013

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

UNIVERSITÉ PIERRE ET MARIE CURIE PARIS VI

Année 2012

N° attribué par la bibliothèque

□□□□□□□□□□□□□□□□

THÈSE

pour obtenir le grade de

DOCTEUR DE L'UNIVERSITÉ PARIS VI

Champ disciplinaire : ÉPIDÉMIOLOGIE ET SCIENCES DE
L'INFORMATION BIOMÉDICALE

École Doctorale de rattachement : **Ecole Doctorale Pierre Louis de Santé
Publique à Paris**

présentée et soutenue publiquement par

Paul H. Gordon

le 07/11/2012

**Sclérose latérale amyotrophique : mortalité, facteurs prédictifs de
la survie**

Directeur de thèse : Vincent Meininger

JURY:

Professor P. Nigel LEIGH

Président

Professeur Danielle SEILHEAN

Examinateur

Professeur Pierre-Marie PREUX

Rapporteur

Professeur Philippe CORCIA

Rapporteur

Professeur Vincent MEININGER

Directeur de thèse

Scientific publications and communications related to the dissertation

Published articles

Gordon PH, Artaud F, Aouba A, Laurent F, Meininger V, Elbaz A. Changing mortality for motor neuron disease in France (1968-2007): an age-period-cohort analysis. *Eur J Epidemiol* 2011;26:729-37.

Gordon PH, Salachas F, Bruneteau G, Pradat PF, Lacomblez L, Gonzalez-Bermejo J, Morelot-Panzini C, Similowski T, Elbaz A, and Meininger V. Improving survival in a large ALS center cohort. *J Neurol* 2012 In Press

Gordon PH, Salachas F, Lacomblez L, Pradat PF, Bruneteau G, Elbaz A, Meininger V. Predicting survival in ALS at presentation: A 15-year experience. *Neurodegener Dis* 2012. In Press

Abstracts

Gordon PH, Artaud F, Aouba A, Meininger V, Elbaz A. Changing mortality for motor neuron disease in France (1968-2007): an age-period-cohort analysis. *Neurology* 2011;76 (suppl 4): A113

Other related articles published concurrently

Gordon PH, Mehal JM, Holman RC, Rowland LP, Rowland AS, Cheek JE. Incidence of Amyotrophic Lateral Sclerosis among American Indians and Alaska Natives. *Arch Neurol* 2012. In Press

Gordon PH, Mehal JM, Holman RC, Rowland AS, Cheek JE. Parkinson disease among American Indians and Alaska Natives: a nationwide prevalence study. *Mov Disord* 2012. In Press.

Corcia P, Gordon PH. Amyotrophic lateral sclerosis and the clinical potential of dextramipexole. *Ther Clin Risk Manag* 2012. In Press

Gordon PH, Meininger V. How can we improve clinical trials in amyotrophic lateral sclerosis? *Nat Rev Neurol*. 2011;7:650-4. doi: 10.1038/nrneurol.2011.147

Gordon PH, Delgadillo D, Piquard A, Bruneteau G, Pradat PF, Salachas F, Payan C, Meininger V, Lacomblez L. The range and clinical impact of cognitive impairment in French patients with ALS: A cross-sectional study of neuropsychological test performance. *Amyotroph Lateral Scler*. 2011;12:372-378

Gordon PH. Amyotrophic lateral sclerosis: pathophysiology, diagnosis and management. *CNS Drugs*. 2011 Jan 1;25:1-15. doi: 10.2165/11586000-000000000-00000.

Gordon PH, Cheng B, Salachas F, Pradat PF, Bruneteau G, Corcia P, Lacomblez L, Meininger V. Progression in ALS is not linear but is curvilinear. *J Neurol*. 2010;257:1713-7.

Gordon PH, Goetz RR, Rabkin JG, Dalton K, McElhiney M, Hays AP, Marder K, Stern Y, Mitsumoto H. A prospective cohort study of neuropsychological test performance in ALS. *Amyotroph Lateral Scler.* 2010 May 3;11:312-20.

Blasco H, Guennoc AM, Veyrat-Durebex C, Gordon PH, Andres C, Camu W, et al. Amyotrophic Lateral Sclerosis: A hormonal condition? *Amyotroph Lateral Scler* 2012 In Press.

Blasco H, Vourc'h P, Nadjar Y, Ribourtout B, Gordon PH, Guettard YO, Camu W, Praline J, Meininger V, Andres CR, Corcia P; French ALS study group. Association between divalent metal transport 1 encoding gene (SLC11A2) and disease duration in amyotrophic lateral sclerosis. *J Neurol Sci.* 2011;303:124-7.

Corcia P, Petiot P, Stevic Z, Vourc'h P, Morales R, Gordon PH, Pageot N, Andres C, Camu W. Respiratory onset in an ALS family with L144F SOD1 mutation. *J Neurol Neurosurg Psychiatry.* 2011;82:747-9.

Abdelnour-Mallet M, Verschueren A, Guy N, Soriani MH, Chalbi M, Gordon P, Salachas F, Bruneteau G, le Forestier N, Lenglet T, Desnuelle C, Clavelou P, Pouget J, Meininger V, Pradat PF. Safety of home parenteral nutrition in patients with amyotrophic lateral sclerosis: a French national survey. *Amyotroph Lateral Scler.* 2011;12:178-84.

Millecamps S, Salachas F, Cazeneuve C, Gordon P, Bricka B, Camuzat A, Guillot-Noël L, Russaouen O, Bruneteau G, Pradat PF, Le Forestier N, Vandenberghe N, Danel-Brunaud V, Guy N, Thauvin-Robinet C, Lacomblez L, Couratier P, Hannequin D, Seilhean D, Le Ber I, Corcia P, Camu W, Brice A, Rouleau G, LeGuern E, Meininger V. SOD1, ANG, VAPB, TARDBP, and FUS mutations in familial amyotrophic lateral sclerosis: genotype-phenotype correlations. *J Med Genet.* 2010;47:554-60.

Pradat PF, Bruneteau G, Gordon PH, Dupuis L, Bonnefont-Rousselot D, Simon D, Salachas F, Corcia P, Frochet V, Lacorte JM, Jardel C, Coussieu C, Le Forestier N, Lacomblez L, Loeffler JP, Meininger V. Impaired glucose tolerance in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.* 2010;11:166-71.

Blasco H, Corcia P, Moreau C, Veau S, Fournier C, Vourc'h P, Emond P, Gordon P, Pradat PF, Praline J, Devos D, Nadal-Desbarats L, Andres CR. ¹H-NMR-based metabolomic profiling of CSF in early amyotrophic lateral sclerosis. *PLoS One.* 2010;5:e13223.

Limousin N, Blasco H, Corcia P, Gordon PH, De Toffol B, Andres C, Praline J. Malnutrition at the time of diagnosis is associated with a shorter disease duration in ALS. *J Neurol Sci.* 2010;297:36-9.

ABSTRACT

Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder that leads to destruction of motor neurons in the brain and spinal cord, and to death of the patient in less than three years on average from symptom-onset. Riluzole, multidisciplinary care, non-invasive ventilation and nutritional support modestly prolong life, but no cause has been found for most people with ALS so important treatments have not yet been discovered. Clinical trials that test new agents are difficult in ALS because effect sizes are small, the disease is rare, and there are no biomarkers of disease progression; outcome measures are clinical and highly variable. Better characterization of the epidemiology of ALS could improve understanding of the disease and lead to etiologic hypotheses, determine whether patterns of occurrence are changing, and show whether distinct phenotypes exist that could be examined for distinct causes as well as improve the efficiency of clinical trials.

First, we examined the mortality rate from motor neuron disease in France from 1968 to 2007. The crude mortality rate over the study period was 1.74/100,000 person-years, and was higher in men (1.90/100,000) than women (1.58/100,000). Mortality increased with age to peak between 75 and 79 years. The Standardized mortality ratio, after indirect standardization for age and gender, increased from 0.54 (95% CI = .49-.59) in 1968 to 1.26 (95% CI =1.20, 1.32) in 2007. The increasing mortality from MND was better explained by a cohort effect, which involves all individuals born at the same time, independent of their age at death, than by a period effect. This cohort effect was observed graphically and confirmed statistically through Age-Period-Cohort statistical analyses. Changing environmental exposures are a possible explanation for cohort effects, and could be examined in relation to mortality rates in future ecologic studies.

Next we analyzed survival rates and predictors of survival at the ALS Center, Salpêtrière Hospital, Paris, focusing on the survival rate during 2002-2009, and predictors of survival in 1995-2009. No single clinical factor best predicted survival, but a combination of variables, including limb-onset, long duration between symptom-onset and first visit, and high muscle strength as well as function were associate with longer survival. The survival rate improved significantly at the center after 2006. Future studies might better define unique phenotypes by including clinic-pathological correlation. Other center-based as well as community-based studies could determine if survival is improving in ALS generally.

RESUME EN FRANCAIS

La sclérose latérale amyotrophique ou SLA est une affection neurodegenerative conduisant à la mort des motoneurons du cerveau et de la moelle épinière, et responsable du décès des patients en moins de trois ans en moyenne après la survenue des premiers symptômes. Le riluzole, la prise en charge multidisciplinaire, ventilatoire et nutritionnelle, permet d'allonger de façon encore modérée la durée de vie. En l'absence de la découverte des causes de la maladie chez la plupart des patients a considérablement pesé dans les difficultés que nous rencontrons pour découvrir un nouveau traitement.

Les essais thérapeutiques dans cette affection sont difficiles en raison des petits effectifs, du caractère rare de la maladie, de l'absence de marqueurs connus pour évaluer la progression : les seuls marqueurs sont cliniques et montrent une grande variabilité. Une meilleure approche de l'épidémiologie de la SLA pourrait permettre d'améliorer la connaissance de la maladie et pourrait offrir la possibilité de mieux formuler les hypothèses physio pathologiques possibles. Elle permettrait aussi de montrer les modifications des profils évolutifs. Enfin, elle pourrait montrer l'existence de phénotypes distincts, et donc des causes distinctes, ce qui accroîtrait notablement l'efficacité des essais thérapeutiques.

Dans un premier temps, nous avons étudié le taux de mortalité de la SLA en France entre 1968 et 2007. Le taux brut de mortalité pendant cette période a été de 1,74/100.000 avec un taux plus important chez l'homme (1,9/100.000) que chez la femme (1,58/100.000). Le taux de mortalité augmente avec l'âge pour culminer entre 75 et 79 ans. Le rapport standardisé de mortalité, après correction pour l'âge et le sexe, a augmenté de 0,54 (95% IC = .49-.59) en 1968 pour atteindre 1.26 (95% IC =1.20, 1.32) en 2007. Cette augmentation de mortalité liée à la SLA est mieux expliquée par un effet dit cohorte, qui implique tous les sujets nés en même temps, indépendamment de leur âge au moment du décès, plutôt que par un effet dit période. Cet effet cohorte est visible graphiquement et confirmé statistiquement grâce à une analyse statistique Age/Période/Cohorte. Le changement d'exposition à des toxiques environnementaux pourraient expliquer ces effets cohortes, et devrait faire l'objet de futures études écoloquiques.

Nous avons ensuite analysé les taux et les prédicteurs de survie au Centre SLA de la Salpêtrière en se focalisant sur la période 2002-2009 pour la survie et 1995-2009 pour les prédicteurs. Aucune variable clinique n'est meilleure pour prédire la survie, mais une combinaison de variables (incluant notamment le début par les membres, la durée début des symptômes et première visite, et la force musculaire ainsi qu'une échelle fonctionnelle) est associée à une survie prolongée. Ce taux de survie a clairement augmenté depuis 2006. Des études ultérieures permettraient de mieux préciser des phénotypes en incluant des données cliniques et pathologiques. D'autres études fondées sur des cohortes de centre, ou non spécifiques, permettraient de mieux évaluer cette amélioration de la survie.

THANK YOU

The following are just a few of the many friends and colleagues whose support, ideas and work were vital to this dissertation and to whom I give sincere thanks.

Rachida Mimouni for her work compiling several databases at the Salpêtrière Hospital;

Fanny Artaud for her organization and analyses of French mortality data;

Christophe Tzourio, the head of the neuroepidemiology laboratory where the analyses began;

Alexis Elbaz, the mastermind behind many of the ideas;

Vincent Meininger, my friend, who welcomed me to France to be a part of the world class ALS center that he created in the tradition of Charcot, and who made this dissertation possible; and

The committee members, P Nigel Leigh, a giant in the field, for his understanding and making the time to support this effort, Pierre-Marie Preux whose epidemiologic example we have tried to emulate, Danielle Seilhean for her work and time away from a most busy job, and Philippe Corcia, my office mate whose collaboration and friendship have endured.

DEDICATION

This dissertation is dedicated to my wife, Nan, for her love, and to Bud Rowland who inspired me to study ALS.

TABLE OF CONTENTS

1. INTRODUCTION.....	12
1.1. Amyotrophic lateral sclerosis: clinical features, diagnosis and care.....	14
1.1.1. Riluzole.....	20
1.1.2. Multidisciplinary care.....	20
1.1.3. Nutrition.....	21
1.1.4. Respiration.....	22
1.1.5. Palliative care.....	24
1.1.6. Symptomatic therapy.....	24
1.2. Epidemiology.....	26
1.2.1. Incidence and mortality.....	26
1.2.2 Risk factors.....	28
1.3. Measuring progression.....	32
1.4. Clinical features that predict survival.....	33
1.5. Clinical trials.....	35
1.6. Major questions.....	39
2. CHANGING MORTALITY FOR MOTOR NEURON DISEASE IN FRANCE (1968-2007): AN AGE-PERIOD-COHORT ANALYSIS.....	40
2.1. Results.....	41
3. IMPROVING SURVIVAL IN A LARGE ALS CENTER COHORT.....	64
3.1. Results.....	65
4. PREDICTING SURVIVAL IN ALS AT PRESENTATION: A 15-YEAR EXPERIENCE.....	82
4.1. Results.....	83
5. SUMMARY.....	112
6. CONCLUSIONS AND PERSPECTIVE.....	124
7. BIBLIOGRAPHY.....	127

LIST OF TABLES AND FIGURES

Table 1. Summary of Revised El Escorial Diagnostic Criteria for ALS.....	18
Table 2. Summary of proposed diagnostic criteria for PLS	19
Table 3. Treatments used for ALS	25
Table 4. Known mutated genes in Familial ALS.....	30
Table 5. Recent clinical trials in ALS.....	36
Figure 1. French Region Classification	66

LIST OF ABBREVIATIONS

AD = Autosomal dominant
AIC = Akaike's information criterion
ALS = Amyotrophic lateral sclerosis
APC model= Age-period-cohort regression model
AR = Autosomal recessive
BMI = Body mass index
CI = 95% confidence interval
CépiDc = *Centre d'épidémiologie sur les causes médicales de décès*
DF = Degrees of freedom
EU = European Union
HR = Hazard ratio
INSEE = *Institut National de la Statistique et des Etudes Economiques*
LMN = Lower motor neuron
MVIC = Maximum voluntary isometric contraction
NIV = Non-invasive ventilation
UMN = Upper motor neuron
fALS = Familial amyotrophic lateral sclerosis
FDA = U.S. Food and Drug Administration
FTD = Frontotemporal dementia
MEP = Maximal expiratory pressure
MIP = Maximal inspiratory pressure
MMT = Manual muscle testing
MND = Motor neuron disease
MRC = Medical Research Council
MUNE = Motor unit number estimation
NIH = U.S. National Institutes of Health
NIPPV = Nocturnal noninvasive positive-pressure ventilation
NIV = Non-invasive ventilation
UK = United Kingdom
PEG = Percutaneous endoscopic gastrostomy
PLS = primary lateral sclerosis
SNIP = Sniff nasal inspiratory pressure
SMR = Standardized mortality ratio
SOD1 = Cu-Zn superoxide dismutase type 1
TAR = TAR DNA binding protein
U.S. = United States
VC = Vital capacity

INTRODUCTION

1. Introduction

Motor neuron disease (MND) is the general term given to four diseases, primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, and amyotrophic lateral sclerosis (ALS). ALS, the most common form of MND, is a progressive neurodegenerative disorder that leads to ongoing death of motor neurons and associated cells, in the brain and spinal cord. Death of the patient, usually from respiratory failure, most often occurs within three years after the first symptom develops. The rate of progression is highly variable between individuals and appears to be non-linear overall, with more rapid phases early after onset and in the terminal stages.

Research has identified some of the cellular processes that occur after disease onset; mitochondrial dysfunction, protein aggregation, generation of free radicals, excitotoxicity, inflammation and apoptosis all contribute to cell death, but for most patients the underlying cause is unknown, and the sequence and interaction of these cellular events is still largely unexplored. Most authorities consider ALS to be a complex genetic disorder in which multiple genes combine with environmental exposures leading to disease susceptibility, with the contribution of any single factor being small. However, few genetic or environmental risks have been uncovered.

The diagnosis is based on the history and examination showing progressive upper and lower motor neuron signs. Electromyography aids the diagnosis, and additional tests exclude other diseases that might mimic or cause disease of the motor neuron. Until the elucidation of etiologies leads to the development of more robust neuroprotective agents, both pharmacological and nonpharmacological treatments are directed at prolonging life to the extent possible. Riluzole, ventilatory support for respiratory insufficiency, gastrostomy for those with dysphagia and multidisciplinary care can help extend life. Palliative care ensures dignity toward the end stages of the disease. Clinical trials currently aim to slow disease progression by testing drugs that impact one or more of the processes that are initiated after disease onset. Only clinical endpoints are currently validated, which reduces trial efficiency. The identification of really meaningful therapies might only follow elucidation of the causes of ALS. Epidemiological study has an important role in improving the understanding of ALS, better characterizing clinical phenotypes, improving efficiency in measuring progression and

contributing to the ongoing search for etiologies. The objectives of the current work were to improve characterization of the disease by examining mortality rates over time in France, as well as evaluating whether survival has improved and assessing the most sensitive predictors of survival at the Paris ALS center.

1.1. Clinical features, diagnosis and care

ALS begins with limb weakness in about two-thirds of patients.(1) Difficulty walking, foot drop, loss of hand dexterity, and shoulder weakness are typical early symptoms. Limb weakness usually begins asymmetrically and then spreads to contiguous myotomes (2). Approximately one-third of the time, weakness begins in bulbar muscles, usually with dysphagia following dysarthria. Symptoms due to disease of the lower motor neuron (LMN), including weakness, atrophy, cramps and fasciculation, often cause greater disability than the stiffness and slowness associated with upper motor neuron (UMN) degeneration, and predominance of UMN features probably carries a better prognosis.(3) As the disease progresses, meaningful limb function can be lost, leading to dependence on others for daily tasks. Walking and standing, as well as bearing weight for transfers, become impossible for many. Falls are common and can lead to fractures and nursing home placement. Bulbar symptoms can progress to anarthria, and dysphagia can lead to dehydration, malnutrition with weight loss, drooling, and aspiration. Some patients develop weakness of the axial musculature with head drop and kyphosis that cause imbalance due to alteration in the center of gravity, interference with activities such as eating and driving, and pain. Sphincter and sensory function are usually, but not invariably, spared. Cognition is abnormal in 25–50% of patients who receive neuropsychological tests, and approximately 15% develop overt dementia, most often fronto-temporal dementia (FTD).(4, 5) The cognitive abnormalities lead to changes in judgment, personality, language, decision making and affect.(6) The associated abulia and loss of judgment can impair a patient's ability to participate in decisions about medical care and to shorter survival.(7)

Pseudobulbar affect, or emotional lability, a result of loss of the normal inhibition of inappropriate laughter and crying, expressions that depend on complex neural pathways mediating respiration, vocalization, facial movements and emotion, can be a feature of UMN degeneration.(8) Depression and anxiety can be prominent at all stages of the disease, though

perhaps not to the extent expected in those suffering from a terminal illness.(9) Anxiety can be caused by respiratory insufficiency, and depression can lead to insomnia, poor appetite, hopelessness and reduced decision-making ability. ALS is usually described as causing painless weakness, but pain, resulting from loss of mobility, the inability to turn in bed, joint contractures and bedsores, can occur. The psychological and physical discomfort resulting from the inability to move can be overwhelming.(10) In some patients, pain appears to result from the disease itself, likely related to degeneration of sensory tracts or nuclei. Cramps can also be painful and interfere with sleep and physical activity.

Respiratory symptoms usually occur later in the disease. Early symptoms of respiratory decline include weakened cough, orthopnea, and morning headaches due to elevation of carbon dioxide levels during sleep. Shortness of breath occurs first with strenuous tasks, then during mild activity such as dressing or shaving, and eventually during periods of inactivity. Respiratory failure and pulmonary complications of bulbar weakness, such as aspiration pneumonia, are the most common causes of death, though a minority of patients have a sudden death, usually cardiac, in the face of stable respiratory function.(11)

Rarely, ALS begins in respiratory myotomes, which carries the poorest prognosis.(12) Respiratory-onset ALS, making up less than 3% of MND, poses a particular diagnostic dilemma because, early in the course, limb function can be normal. These patients may progress to respiratory failure requiring mechanical ventilation before the underlying diagnosis has been identified. ALS is one cause of cryptogenic respiratory insufficiency in the intensive care unit. These patients may also have early dropped head as a clue to diagnosis, and non-invasive ventilation (NIV) can extend survival.(12) The mechanisms underlying the different sites-of-onset are just beginning to be explored.(13)

The diagnosis is made based on history and examination evidence of progressive UMN and LMN dysfunction. An electromyogram, conducted in the myotomes of three limbs, and bulbar as well as paraspinal muscles, confirms the presence of widespread LMN disease, and can exclude other disorders such as multi-focal motor neuropathy with conduction block that can mimic MND. Widespread sensory nerve conduction abnormalities suggest the presence of Kennedy's disease (X-linked spino-bulbar muscular atrophy), a diagnosis that is now confirmed by gene analysis. Brain and cervical spine MRI are performed to exclude other

conditions that affect the UMN, including cervical spondylosis. The El Escorial diagnostic criteria, developed in 1990 and revised in 1998 (Table 1) are used to standardize enrollment in clinical trials.(14) Recent consensus criteria developed on Awaji Island in Japan may increase the sensitivity of the El Escorial criteria, particularly for bulbar-onset ALS, where limb findings may be sparse.(15) Motor unit number estimation (MUNE) is an electrophysiological technique that can be used to quantify the number of functional LMNs and to assess their decline over time, but the approach is currently limited to research, and has not yet been shown to be more useful than standard clinical outcome measures in trials.(16) Magnetic resonance spectroscopy and transcranial magnetic stimulation examine the functional integrity of the UMN,(17) but are limited to large centers or research protocols, and have not, so far, been shown to deteriorate predictably with clinical decline. Spinal fluid analysis is performed when atypical clinical features suggest a secondary cause such as infection or carcinomatous meningitis. Genetic testing is not a routine part of the evaluation unless there is a family history of the disorder. An experienced ALS specialist and electromyographer make the diagnosis with more than 95% accuracy. Patients with only LMN signs are diagnosed as having progressive muscular atrophy, those with only UMN signs for 4 years or longer as having primary lateral sclerosis (PLS), and those with both UMN and LMN disease are called ALS.

Primary lateral sclerosis makes up approximately 1-3% of MND at most centers.(3, 18) The disorder typically begins in the legs and after age 50, though it can begin in arm or bulbar muscles. Young onset or familial PLS is usually termed hereditary spastic paraparesis, the underlying genetic mutations for which can be identified in many patients (19, 20).

Progression in PLS is slower, function is better and survival is longer than for ALS,(3) but PLS can convert to ALS even after many years of stability. Clues to impending development of ALS and the worse prognosis it brings include focal muscle weakness or atrophy, weight loss, and declining function as well as breathing capacity.(21) Diagnostic criteria have been proposed, but continue to evolve, in part because there is almost no clinico-pathologic evidence that this rare form of MND is an entity distinct from ALS.(3, 22, 23)

Progressive muscular atrophy, first described by Aran in France(24) is a disorder of LMN signs only(25), but patients can sometimes develop UMN involvement, either clinically(26) or at autopsy.(25) The prognosis of isolated LMN signs tends to be better than ALS, but not

measured in decades as PLS can be. Because there is considerable clinical and pathological overlap between the disorders, the term MND is used for all types, ALS, PLS, PMA, in Great Britain; the subdivisions are used in France and the United States.

The onset of ALS can be insidious and time to diagnosis is often more than a year.(27) Practice guidelines(28, 29) suggest that the diagnosis should be given in person, with family or friends present to give support, and that a follow-up appointment be scheduled soon afterward to answer questions. The process of breaking the news can take 45 minutes or longer.(29) Patients are informed about ALS resources, including patient advocacy groups, and a discussion of ongoing research into better treatments conveys hope.(30) Practice parameters also outline common strategies for treatment, but few medications for symptom management have been tested in trials with ALS patients, and there is a wide variety of management practices.(31)

Table 1. Summary of Revised El Escorial Diagnostic Criteria for ALS(14)

Clinically definite ALS	UMN and LMN signs in three regions
Clinically probable ALS	UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs
Laboratory-supported probable ALS	UMN signs in one or more regions and LMN signs defined by EMG in a least two regions
Clinically possible ALS	UMN and LMN signs in one region, or UMN signs in at least two regions, or UMN and LMN signs in two regions with no UMN signs rostral to LMN signs
LMN- lower motor neuron; UMN –upper motor neuron	

Table 2. Summary of proposed diagnostic criteria for PLS(3)

Autopsy-proven PLS	Clinically diagnosed PLS with degeneration in motor cortex and corticospinal tracts; no loss of motor neurons, no gliosis in anterior horn; no Bunina bodies or ubiquitinated inclusions
Clinically pure PLS	Upper motor neuron signs, no focal muscle atrophy or visible fasciculations; no evidence of denervation on EMG > 4 years from symptom onset. Age at onset after 40. Secondary and mimicking conditions excluded by laboratory and neuroimaging
UMN-dominant ALS	Symptoms <4 years, or disability due predominately to UMN signs but with minor EMG denervation or LMN signs on examination that are not sufficient to meet diagnostic criteria for ALS
PLS plus	Predominant UMN signs plus clinical, laboratory, or pathologic evidence of dementia, parkinsonism, or sensory tract abnormalities
Symptomatic lateral sclerosis	Clinically diagnosed PLS with evident possible cause (e.g., HIV infection, paraneoplastic syndrome)

1.1.1. Riluzole

Excess glutamate, an excitatory neurotransmitter, may contribute to neurodegeneration in ALS. Riluzole was first developed as an antiepileptic agent because it inhibits the presynaptic release of glutamate, but its exact mechanism in ALS is unknown.(32) Riluzole is currently the only drug that slows the course of ALS and was approved in 1995. In two randomized controlled trials, riluzole extended survival compared to placebo.(33, 34) In the first trial, 58% of patients in the placebo group and 74% in the riluzole group were still alive at 12 months of follow-up ($p=0.014$), while 37% in the placebo group and 49% in the riluzole group were alive at 21 months ($p=0.046$). The median survival was 449 days in the placebo group and 532 days in the riluzole group at the end of the study. Overall, riluzole reduced mortality by 38.6% at 12 months and 19.4% at 21 months.(33) The deterioration in muscle strength was also slower in the riluzole group ($p=0.028$). Neither study showed benefit in quality of life. In the second trial, a dose ranging study, the adjusted risk of death in the 100 mg riluzole group was 0.65 ($p=0.002$) compared to placebo after 18 months of follow-up.(34) The effect was not apparent to patients.(35) The Cochrane Library conducted a meta-analysis of three published trials that included 876 riluzole-treated and 406 placebo-treated patients.(36, 37) The analysis showed that riluzole in doses of 100 mg/day prolongs survival by approximately 11%, or about 2 months. The long-term safety of riluzole therapy has been shown,(38) including in the elderly and those with advanced ALS.(39) The most common side effects are fatigue, somnolence, nausea, diarrhea and dizziness. Elevation of liver enzymes can occur, but rarely to levels that are clinically meaningful. Serum concentrations of riluzole vary between individuals, probably resulting from different rates of metabolism,(39) but dose-adjustment based on serum measurement, in theory one approach to optimizing treatment, is rarely used in practice. Like other European countries, most patients in France, where the health system covers the cost, take riluzole.(40) More than half of patients in the U.S. take the drug.

1.1.2. Multidisciplinary Care

ALS care is challenging because the disease is progressive and terminal, and there are, as yet, no treatments that reverse symptoms. Standardized multidisciplinary clinics were instituted in France in 2002, and most large centers in developed countries currently use a multidisciplinary approach to care.(41) At least 17 specialized ALS centers now exist across

France. Consensus guidelines have been developed for the diagnosis and care of patients with ALS in France.(42) According to the guidelines, the diagnosis depends on findings of UMN degeneration in areas of amyotrophy with confirmation of LMN degeneration by EMG and exclusion of other conditions. Genetic tests are done in familial cases. Coordinated evaluations are recommended to provide individualized treatments for specific symptoms, including the timing of nutritional and respiratory support.

Data suggest that patients who receive multidisciplinary care may survive longer.(27) Patients are evaluated frequently, typically every three months, so that impending problems are detected and treated early. The specialty care can be obtained through normal consultation, but patients and families in multidisciplinary clinics benefit from having questions answered in one sitting by professionals from different disciplines, conserving energy and time. Typically, professionals at multi-disciplinary clinics also see many patients with ALS, still a rare disease, so their level of experience may be higher than in other settings. Care is centered around the patient's decisions, with a focus on education and support. The neurologist and health team give information to help in treatment decisions, including discussions about advanced directives and treatments for nutritional and respiratory insufficiency.(41) Advanced directives allow patients to make educated decisions in advance about future ventilator support should it become necessary, and help guide the multidisciplinary team in setting goals for care. The neurologist also explains research advances in the field. The neurologist and nurse oversee patient care, physical and occupational therapists evaluate skilled motor function, a dietitian evaluates nutritional status, a speech pathologist assesses bulbar function, a respiratory therapist treats respiratory symptoms, and a social worker assists with health insurance coverage and disability payments. Other professionals affiliated with the clinic usually include a pulmonologist who treats respiratory problems, a gastroenterologist who assists with gastrostomy placement, an orthotist who prescribes braces for those with focal weakness, and a psychiatrist or psychologist who treat symptoms of depression and anxiety. Information is also given to patients regarding services outside the clinic,(41) including home care and hospice. Non-pharmacological therapies include communication devices; gaze - assisted technology; canes, walkers and wheelchairs; home adaptations; and exercise regimens.

1.1.3. Nutrition

Inadequate nutrition, a predictor of survival,(43) can result from impaired swallow, arm weakness that limits the ability to eat, and hypermetabolism.(44) Monitoring weight is the simplest way to assess caloric balance in the clinic, though calculation of body mass index (BMI) using height and weight is also used in research. The risk of aspiration, ability to maintain adequate nutrition and compensatory strategies are assessed by a speech therapist. Management includes postural changes such as the chin tuck, modification of diet consistency, and enteral feeding using a percutaneous endoscopic gastrostomy (PEG) for those with weight loss or symptomatic dysphagia.(45) There may be a lower rate of complications if the procedure is performed while the vital capacity (VC) is still above 50% of predicted or before sniff nasal inspiratory pressure (SNIP) falls below 40 cm H₂O. Radiologically inserted gastrostomy can be done when respiratory compromise is present, allowing patients to use non-invasive ventilation during the procedure. Many patients choose gastrostomy too late in the disease course for a benefit in survival.(46) Parenteral supplementation can be tried for those too ill to receive gastrostomy.(47)

1.1.4. Respiration

As respiratory muscle weakness advances, patients develop symptoms of dyspnea, orthopnea, sleep fragmentation, daytime fatigue, and morning headaches. A weakened cough due to diaphragmatic and bulbar muscle weakness can lead to excess secretions, poor airway clearance, aspiration and pneumonia. The history, physical examination, overnight pulse oximetry and VC are standard assessments and are done serially, as part of the multidisciplinary clinic or referral. The maximal inspiratory and expiratory pressures (MIP and MEP) also correlate with respiratory muscle weakness(45) and become reduced in ALS. A MIP of <60 cm H₂O is a predictor of reduced survival. Sniff nasal inspiratory pressure (SNIP), a noninvasive measure of inspiratory force, estimates intrathoracic pressure and can give an early indication of respiratory muscle strength. It decreases predictably over time in ALS patients, predicts survival and may better reflect hypercapnea than MIP or VC. A transcutaneous carbon dioxide sensor can also be used to assess rising carbon dioxide levels due to muscle weakness.(48)

Nocturnal noninvasive positive-pressure ventilation (NIPPV), often called simply non-invasive ventilation (NIV) because it is the most common form of NIV used in ALS, has become the standard intervention for patients with respiratory insufficiency.(41) The bi-level intermittent positive-pressure ventilator is triggered by the patient's inspiratory efforts and so facilitates physiological function. Because the ventilator is intermittent, it does not overwhelm expiratory efforts with continuous pressure. Patients are counseled on the use of NIV when the VC drops to 50% of predicted or when the MIP falls to <60 cm H₂O,(45) or with the onset of respiratory symptoms. NIV reduces the work of breathing, and improves gas exchange as well as sleep quality,(49) extends survival, particularly in those compliant at least 4 hours per day,(50) enhances quality of life and may improve cognition.(51) Oxygen is usually not prescribed without NIV to prevent inhibiting respiratory drive in the setting of elevated serum carbon dioxide levels. Theoretically, using NIV can reduce energy expenditure from overworked respiratory muscles, and so may not only support respiration but also reduce weight loss.

In 2004, standardized and more aggressive use of NIV was instituted at the ALS Center of the Salpêtrière Hospital.(52) From that time, all patients have received a thorough respiratory examination at each visit. If there are symptoms of respiratory muscle insufficiency (dyspnea, orthopnea) or hypercapnia (morning cephalgia); blood gas measures showing elevated CO₂; VC less than 50% predicted; or nocturnal oxymetry with >10% of time spent <90% saturation (this parameter is considered one of the most important in the practice), the patient is referred to a pulmonologist for prescription of NIV.

Tracheostomy with invasive ventilation is instituted for those who desire long-term survival. The rate varies slightly from country to country, but tracheostomy is generally chosen by less than 5% of patients.(53, 54) Invasive ventilation requires 24-hour supervision and is costly. Many patients refuse tracheostomy because of the loss of independence it entails, the expense or the great emotional and physical burden that is placed on caregivers. Some patients who are unable to decide in advance receive mechanical ventilation emergently due to respiratory failure. Unplanned tracheostomy is often permanent,(55) and patients in France must usually be cared for at home. Decisions need to be made in advance for patients who have tracheostomy should the disease progress to the point where they can no longer communicate even using eye movement. Some patients choose to have respiratory support withdrawn, a

decision that is considered ethical (the Loi Leonetti in France) as long as adequate dosages of opiates and anxiolytics are prescribed to avoid suffering when the ventilator is removed. Other interventions to facilitate breathing and the clearance of secretions include air stacking and assisted cough, either manually or mechanically through an insufflator-exsufflator, and the use of a suction machine.(41) Theophylline, antibacterials, mucolytics, expectorants, and oxygen help to relieve symptoms in some. Pneumonia and yearly influenza immunizations can prevent pulmonary infections.(45)

1.1.5. Palliative Care and Hospice

All of ALS care is palliative because there is no treatment that reverses the progressive course. The care at the end of life is thought to be particularly important to avoid suffering. Approximately 60% of ALS patients die rapidly, often within 24 hours of worsening in their clinical condition and some die suddenly. Advance directives help prevent invasive ventilation being instituted emergently, but the key is ongoing and open communication between the patient and the healthcare team so that a patient understands the disease course and his wishes are known in advance. Anticipating symptoms before they occur is an important part of ALS care. Medications to relieve suffering, including anticholinergic agents, anxiolytics and opioids, can be prescribed in the home under the direction of a hospice team. Narcotic medications are effective for treating pain, nocturnal discomfort and breathlessness long before the terminal phase of the illness.(56) There is no evidence that opioids shorten life, but when relief of distress is the goal, some sedation may be necessary. Palliation at the end of life is usually done at home, but inpatient palliative care teams can be used for those patients who do not wish to die at home. Hospice teams not only provide symptom management through the use of medications, but also emotional support for patients and families.

1.1.6. Symptomatic treatments

A wide variety of medications are used to treat symptoms due to ALS (Table 3), but most are used off label and have not been tested specifically in ALS. Some treatments have been shown to improve quality of life and a few may extend life.

Table 3. Treatments used for ALS

<u>Modality</u>	<u>Indication</u>	<u>Administration</u>
*Non-invasive ventilation	Respiratory insufficiency	Nighttime and during symptoms
Gastrostomy	Dysphagia and malnutrition	Daily calorie supplements
*Multidisciplinary care	All symptoms of ALS	Every three monthly visits
*Riluzole	ALS	50 mg bid
*Dextromethorphan/quinidine	Pseudobulbar affect	20mg/10mg bid
Amitriptyline		12.5-125 mg qhs
SSRI antidepressants		20-100 mg qd
Mirtazapine		15-30 mg qhs
Buspirone	Anxiety	10 mg tid
Diazepam		2-10 mg tid
Lorazepam		0.5-2 mg tid
Mirtazapine		15-30 mg qhs
SSRI antidepressants		10-100 mg qd
Diazepam	Cramps	2-10 mg tid
Phenytoin		100-300 mg qhs
Vitamin E		400 IU tid
Mirtazapine	Depression	15-30 mg qhs
SSRI antidepressants		20-100 mg qd
Tricyclic antidepressants		12.5-150 mg qhs
Venlafaxine		37.5-75 mg qd
Amantadine	Fatigue	100 mg qAM, qnoon
Bupropion SR		150-450 mg qd
Fluoxetine		20-80 mg qd
Pemoline		18.75-93.75 mg qd
Pyridostigmine		60 mg tid
Venlafaxine		75-225 mg qd
Amitriptyline	Sialorrhea	12.5-125 mg qhs
Atropine sulfate		0.4 mg q4-6h
		1-2 ophthalmic drops SL q4-6h
Diphenhydramine		25-50 mg tid
Hyoscyamine sulfate		0.125-0.25 mg q4h

Scopolamine transdermal patch		0.5 mg q72h
Baclofen	Spasticity	10-60 mg tid
Benzodiazepines		2-10 mg tid
Dantrolene		25-100 mg tid
Tizanidine		2-8 mg tid
Amitriptyline	Urinary urgency	12.5-75 mg qhs
Oxybutynin		2.5-5 mg bid
		3.9 mg patch qd
Tolterodine		1-2 mg bid

Bid = twice daily; IU = international units; qAM = every morning qd = daily; qhs = every day qt bedtime; qid = four times daily; qnoon = every day at noon; qhx = every x hours; SL = sublingual; SR = slow release; SSRI = serotonin-specific reuptake inhibitor; tid = three times daily.

*shown to have a beneficial effect in ALS

1.2. Epidemiology

The causes of ALS have proved difficult to identify, in part because the disease is rare,(57) but also because the nerve cells are fragile and ephemeral, and determinants may act in sequence over decades, so that once the illness develops, the causes might be long since passed. However, different forms may have different causes, genetic or environmental, that could act more or less in concert and at varying time points. For most patients, the cause of the disease is unidentified. Even after disease onset when more is known about the pathophysiology,(58) the timing, interaction and location of different mechanisms is unknown.(59) One disease pathway could be active, or even protective, in one body area while another is active in a different region.

1.2.1. Incidence and mortality

ALS is the most common form of MND, but it still rare, with incidence rates ranging from 1.2-4.0 per 100,000 person-years (60-64). The incidence increases with age, peaking between

70 and 80 years, and then decreases, and ALS is thought to be more common in men than women (63, 65). The incidence of ALS appears stable across Caucasian populations, but the disease may be rarer in certain ethnic populations, including Asians, black Africans and Hispanics.(66)

Some reports suggest that the incidence has increased with time (65, 67), but this finding has not been confirmed in all studies (61, 63, 64, 68, 69). A 22-year study in New Zealand identified 393 patients, and found that the incidence increased by 3% per year from 1.6 to 3.3 per 100,000 population during the study period.(67) A population-based study in Sweden also showed increasing incidence over time.(65, 67) In that study, 3481 patients were identified over the 15 year period from 1991-2005. The incidence increased significantly by approximately 2% per year from 2.32 to 2.98/100,000 ($p=0.002$). Other studies of incidence have suggested stable rates, but most of these examined smaller samples over shorter time periods.(61, 63, 64, 68-70) Longer and larger studies may be needed for adequate power to detect changing rates. The two studies showing increasing incidence were conducted over 15 and 22 years (65, 67).

Because population-based incidence studies are difficult and expensive to conduct, and may not provide adequate numbers of patients to detect change over time, mortality rates have been used as a surrogate for incidence. Mortality studies are based on examination of death certificates, which have variable correlation with incidence, depending on the quality of the study.(71, 72) Marin and colleagues identified features of mortality studies that ensure high quality data, including clear definition of the population at risk, identification of criteria for exclusion of cases, presentation of data on the accuracy of death certificates in the country of study and for the relevant period of time, inclusion of data based on ‘underlying’ and ‘contributory’ causes, comparison of ALS mortality among calendar dates, consistent coding of data when based on different ICD codes, and confirmation that the health care and certificate reporting systems are comparable and of high quality across regions.(72) The accuracy of death certificates reporting has ranged from 72-91% in studies conducted in the U.S., but the accuracy of death certificate reporting has not yet been examined in France.

Study of changing rates over time can provide clues to features that influence disease occurrence. Although mortality may underestimate incidence, mortality studies based on

existing death certificate databases have the advantage of including larger sample sizes during longer periods than is usually possible in studies of incidence, providing strong power for the examination of change over time. In studies from different parts of the world, mortality has increased over time (73-75). A study carried out in France from 1968 to 1982 (76) showed that the mortality rates from MND increased from 0.71 per 100,000 person-years in 1968 to 1.52 in 1982. There was also a decreasing sex ratio with time, indicating that the rates increased more in women than men. Research from other countries has shown similarly increasing mortality rates over time. Mortality due to ALS has increased in the U.S. (75), Finland (74), Norway (73), Britain (77) and Italy (78). A more pronounced trend in women, with a decreasing sex ratio over time, was found in the U.S. (75), Britain (77), Norway (73) and Finland (74). Noonan and colleagues found an increasing mortality rate in the U.S. from 1969 to 1998. Overall rates increased by 46% during the 30 year period. While rates stabilized during the last 10 years of the study in men, they continued to increase in women and grew by 60% overall in women. Rates were also lower among African Americans and Hispanics, and increased in a southeast to northwest gradient geographically.

Increasing mortality rates, compared to largely stable incidence rates, could be due to inadequate power in the incidence studies; the mortality rates could reflect a real increase in ALS over time, related to changing susceptibility patterns in a population dying less from other diseases, or related to changing environmental exposures in the population. This latter hypothesis also explains the greater increase in rates in women than men. An alternative explanation is that the diagnosis of ALS has gotten better with time, particularly in women, and that the accuracy of death certificate reporting has improved with time.

1.2.2 Risk factors

ALS is thought to be a complex genetic disorder in which genetic and environmental risk factors combine in the pathogenesis, with the contribution of any single factor being small. Indications of a small but real genetic contribution to sporadic ALS come from analysis of twin data showing an estimate of heritability in sALS of 0.61 (95% CI 0.38-0.78);(79) gender predominance among certain phenotypes;(80) and aggregation of neurodegenerative disorders in family members of ALS patients.(81, 82) Relatives of patients with non-inherited ALS have an increased risk of developing the disease, suggesting a possible genetic influence to

susceptibility.(65) Co-segregation of ALS with other neurodegenerative disorders in families also suggests common genetic risks,(81) but genome-wide association studies (GWAS) have yet to demonstrate any single gene that reproducibly accounts for most sALS.(83-87)

Multiple genome-wide association studies (GWAS) have been carried out to identify candidate risk genes,(88-92) but the contribution of individual genes to ALS seems very small and GWAS have, so far, explained very little of the genetic contribution to the disease. Several genes that have been identified have not been confirmed in replication studies.(83-87) The GWAS are difficult to conduct in ALS; testing for multiple genes requires statistical correction to avoid excessive type I error and sample sizes must be very large to detect small genetic effects.(93)

Between 5% and 10% of cases are inherited (familial ALS; fALS) as a Mendelian trait, of which 15–20% are due to one of more than 100 mutations in the Cu-Zn superoxide dismutase type 1 (SOD1) gene.(94) Under normal circumstances SOD1 is responsible for reducing oxidative stress by converting superoxide anions to hydrogen peroxide. The mechanisms of mutant SOD1 toxicity to motor neurons are still unknown. After discovery of the mutated gene in fALS, an animal model was developed that has contributed to better understanding of cellular processes that occur, at least in this genetic form of ALS, after disease onset.(95) The rodent model, developed using an overexpression of the human mutated SOD-1 gene, has become a major source of drug screening, but many of the negative trials in humans have followed positive studies in the ALS model. These discordant findings have raised questions about the utility of the rodent models and support the need for the development of other models based on different genes. Consensus criteria are now published on the use of the SOD-1 model to standardize drug testing in rodents,(96) and additional models using TARDBP or FUS mutated genes are under development. Currently 12 different genes, the most common being SOD1, FUS and TARDBP, have been identified in familial ALS.(93) The genes explain approximately 25-35% of fALS. The mutations can be inherited in an autosomal dominant, autosomal recessive or X-linked manner. Genetic loci have been labeled ALS1 through ALS13 (Table 4).(94) Mutations in the fused in sarcoma (FUS) gene account for approximately 5% of fALS.(97)

Table 4. Known mutated genes in Familial ALS

Locus	Chromosome	Gene	Inheritance	Phenotype
ALS1	21q22.1	SOD1	AD, AR	ALS, PMA
ALS2	2q33.2	ALS2	AR	Juvenile ALS, Juvenile PLS
ALS3	18q21	Not defined	AD	ALS
ALS4	9q34	SETX	AD	ALS, dHMN
ALS5	15q21.1	SPG11	AR	Juvenile ALS
ALS6	16q11.2	FUS	AD, AR, De Novo	ALS, ALS-FTD
ALS7	20p13	Not defined	AD	ALS
ALS8	20q13.3	VAPB	AD	ALS, PMA
ALS9	14q11.2	ANG	AD	ALS, ALS-FTD, PBP
ALS10	1p36.2	TARDBP	AD	ALS, ALS-FTD
ALS11	6q21	FIG4	AD	ALS, PLS
ALS12	10p15-p14	OPTN	AD, AR	ALS
ALS13	12q24	ATXN2	AD	ALS
	9p21.2	C9orf72	AD	ALS, FTD, ALS-FTD

ALS: Amyotrophic Lateral Sclerosis- PLS: Primary Lateral Sclerosis – PMA: Progressive Muscular Atrophy – FTD: Frontotemporal Dementia – dHMN: distal Hereditary Motor Neuropathy- PBP: Progressive Bulbar Palsy.

AD: Autosomal Dominant- AR: Autosomal Recessive

TAR DNA binding protein (TDP-43), a ubiquitously expressed nuclear protein that regulates messenger RNA transcription and splicing, is found in inclusions in the brains of ALS patients and most forms of FTD.(98) Mutations in the TDP gene have been identified in some patients with fALS or sALS,(99) suggesting a possible pathogenic link, but the inclusions have also been identified in other conditions, so their exact role is unknown.(100)

Similarly, despite the examination of many environmental factors, there is currently very little evidence to support the contribution of any major environmental risk factor in most cases of sALS. Accepted risks include age, with most cases occurring above age 50 years, male gender and likely cigarette smoking.(101-106) A 2004 prospective study using the Cancer Prevention Study II cohort of the American Cancer Society found a higher risk in women, however, but not men.(107) A recent metanalysis of 15 case-control studies and five cohort studies, found an association in women but an overall insignificant association between smoking and ALS.(108) The same authors found higher risk associated with cigarette smoking in women but not men in a nested case-control study.(109) A 2009 evidence-based review found one article providing class II evidence(104) and one article providing class III evidence(106), both supporting an increased risk of ALS in smokers.(110) The review concluded that smoking is a risk factor for sALS because of concordance among results in better-designed studies. A recent pooled analysis of five large cohorts, the Nurses' Health Study, the Health Professionals Follow-up Study, the Cancer Prevention Study II Nutrition Cohort, the Multiethnic Cohort, and the National Institutes of Health – AARP Diet and Health Study found modest but significant associations with active smoking, former smoking, duration of smoking, and quantity of cigarettes.(111)

Among environmental risk factors besides smoking, some reports show positive associations with athleticism (112), in particular professional sports players, or exposure to pesticides (113), and being a veteran of the first Gulf war.(112, 114) A study of 7325 professional soccer players in Italy from 1970-2001 identified five ALS cases during 137,078 person-years of follow-up, yielding a standardized mortality ratio of 6.5 (2.1-15.1), with a dose-response relationship for time played.(115) Others have disagreed with the analyses,(116) but the association with athleticism and exercise (112, 117) as well as head trauma(118, 119) has been repeated by other groups.

However, the major causes of ALS are still unidentified. It could be that risks have not yet been examined in correct sequence, for example, if they interact over a lifetime, or that science has not yet developed an ability to detect the important risks.

1.3. Measuring progression

Measuring disease progression in ALS is complicated because there are no biomarkers yet, as there are for diseases like HIV infection or cancer; measures are clinical, and progression varies from person to person. Clinical outcomes are inherently less sensitive than biomarkers, and because of inter-individual variability, clinical research studies must examine many patients over a long period to reliably detect progression.

Survival is a definitive outcome in a disorder in which death is a prominent manifestation, and survival has long been considered the standard measure of outcome in ALS. Databases in Europe and the U.S. can be used to check the survival status of patients who are lost to follow-up, reducing missing data from clinical studies. There are also disadvantages to using survival to measure progression, however. Varying patterns of practice at different hospitals can influence survival,(120) and the definition of survival can vary depending on whether death alone or tracheostomy are used.(54) Survival studies also require great size to detect changes; adequate numbers of events must occur. Therefore studies of survival are large, long and expensive.

By the late 1990s, measurements of strength were validated as surrogates for survival. Maximum voluntary isometric contraction (MVIC), a quantitative measure of isometric muscle strength, was used in a number of clinical trials,(121-123) but reliability was low without examiner training, the equipment was expensive, and patients with advanced ALS could not perform the test, introducing variability and high quantities of missing data. MVIC was subsequently supplanted by manual muscle testing (MMT) as a measure of strength. MMT has been shown to be a sensitive and reproducible means to measure progression in ALS, and MMT of 34 muscle groups predicts survival.(124) MMT was the primary outcome measure in a phase III trial of insulin-like growth factor.(125) MMT also can be burdensome to patients, however, particularly as the disease progresses, and strength testing is not known to elicit functionally meaningful information.

Functional scales gained popularity as outcome measures because of their simplicity, measurement of functionally meaningful activities, and low cost. The ALS functional rating scale (ALSFERS),(126) was developed in 1996. The scale measures activities of daily living, is reliable, and correlates with survival. It takes about 5 minutes to administer and the simplicity of administration can minimize missing data.

The ALSFRS was revised in 1999 to include more substantive questions on respiratory function. The ALSFRS-R,(127) used as a primary outcome measure in phase II(128, 129) and phase III(130, 131) trials, is also used in clinics.(132) The ALSFRS-R can be administered to patients or caregivers, in person or over the telephone, and a self-administered version has been shown to be reliable.(133) The ALSFRS-R has small within-patient variability. The baseline score and slope have been shown to predict survival, though the slope is not strictly linear for all patients.(134) A deterioration of nine points can be appreciated by patients using an analogue scale for perceived change.(135)

Measures of respiratory function can also be used to assess progression in ALS. Assessments of pulmonary function predict survival in large studies, and are used as part of enrollment criteria for clinical research.(136) Pulmonary function helps determine the timing of nutritional, respiratory and palliative treatments in the clinical management of patients.(45) Vital capacity (VC) was used as a primary endpoint in a trial of brain-derived neurotrophic factor,(137) and was one of the co-primary endpoints in a phase III trial of xaliproden.(138) VC provides a limited assessment of only one function, however, and measuring VC requires a trained evaluator and special equipment.(139)

1.4. Clinical features that predict survival

ALS is an incurable disease that is rapidly progressive for most patients. Population-based studies estimate median survival times of 30 months from symptom-onset and 19 months from diagnosis,(140) but the disease can be unpredictable, with some patients surviving months and others decades.(80) No phenotypes have been shown to have uniformly unique survival patterns that might suggest unique causes. Until causes and more robust therapies are discovered, anticipating survival time is important to patients, physicians and researchers.

A variety of clinical factors have been reported to be associated with shorter survival in ALS, including older age, bulbar-onset, and a shorter interval from onset of symptoms to diagnosis.(141-147) Poor strength and motor function (132, 145) or breathing capacity,(145, 148, 149) as well as weight loss (44, 150) and female gender (142, 151, 152) may also predict shorter survival.

Patients with older age and bulbar-onset have been consistently reported to have shorter survival rates, both in clinic-based,(44, 141, 143, 145, 146, 149, 153) and population-based (142, 144, 148, 152, 154) studies. Bulbar-onset occurs with increased frequency in older age groups,(155) but this association is not thought to fully explain the worse prognosis of those with bulbar-onset symptoms.(148) The delay between symptom onset and first visit, a surrogate for the rapidity of disease progression, has also been shown to predict survival, with shorter intervals having worse prognosis.(141-145, 147, 149, 155-159) Motor function, as assessed by strength or functional scale scores (132, 145, 146, 149) also predicts survival. Some studies indicate that breathing capacity is also an important predictor (44, 146, 148, 149, 160) of survival. A cluster analyses of multiple variables indicated that the strongest predictors in one sample were site-of-onset and interval from onset to first evaluation.(159) A calculation of the rate of progression as first visit using the ALSFRS-R score and time from symptom onset has also been shown to predict survival.(161, 162)

Findings are less consistent for gender and psychosocial factors. While most studies have shown no effect of gender on outcome, two population-based and several small retrospective studies found worse outcome in women.(142, 151, 152) Psychosocial stressors including perceived stress, depression, hopelessness and poor mood may portend worse prognosis,(163) and cognitive impairment has been associated with shorter survival.(7) Some research indicates that being underweight could also lead to shorter survival time,(44, 150) and other studies show that multidisciplinary care,(27) early use of non-invasive ventilation (NIV),(50) and nutritional support(164) could contribute to improved prognosis.

In clinical trials, Cox proportional hazards models using stepwise entry of clinical variables have examined predictors of survival. The original trials of riluzole showed that age, disease duration, breathing capacity, bulbar dysfunction, and scores on tiredness as well as stiffness

scales predicted survival.(33) In a phase III trial of pentoxifylline, age; disease duration; and lower BMI, ALSFRS-R, strength and VC predicted shorter survival.(165)

Two studies have also reported improvements in survival over time. In a center based study, the rate of functional decline and survival both improved in patients seen after 1999 compared to 1984-1999.(166) That study used Kaplan-Meier and Cox proportional hazards methodology to examine survival rate and time to functional decline in 1041 patients seen over 20 years. The investigators found improved survival of approximately one year and slower deterioration on the Appel Scale in contemporary patients. Patients' clinical and demographic features also changed with time, but the improved survival persisted when these variables were controlled for in the analyses; there was no effect of riluzole, gastrostomy or NIV use in that study. The authors speculated that the course of ALS itself may have improved with time or that unmeasured clinical factors could have been at play. An analysis of patients enrolled in the placebo arm of clinical trials conducted between 1999-2005 also showed improved survival over time.(167) Time from symptom onset differed among the trials and trial participants are different than ALS patients as a whole, possibly participating more in dedicated clinics, so there is bias in the sample. However, evolving methods of care may have contributed to improved outcome.

1.5. Clinical trials

Only one neuroprotective agent has been clearly shown to be effective in ALS.(33, 34) At least 30 other efficacy trials have been negative or shown the drug to be detrimental (Table 5). There is a small margin of error in therapeutic trials in ALS, in which the disorder is heterogeneous and disabling. ALS trials are also hard to conduct because the disease is rare, correct doses are difficult to define, outcomes are clinical, and progressive weakness can lead to excessive missing data. An error in design, conduct or analysis can invalidate the results of a trial, wasting years of effort and millions of dollars.(59)

Table 5. Recent Clinical Trials in ALS

Drug	Trial Design	Mechanism	Sample	Endpoint	Outcome
Lithium	Phase II	Anti-glutamatergic	Up to 171	Survival/ALSFRS-R	Negative
Glatiramer	Phase III	Immune modulator	360	ALSFRS-R	Negative
Ceftriaxone	Dose selection/efficacy	Anti-glutamatergic	600	Survival/ALSFRS-R	Ongoing
Memantine	Phase II	Anti-glutamatergic	63	ALSFRS-R	Negative
Arimoclomol	Phase II	Heat shock protein inducer	84	Safety	Adequate safety
Talampanel	Phase II	Anti-glutamatergic	59	Arm strength	Non-significant improvement
CoQ10	Phase II Dose selection/futility	Antioxidant/mitochondrial cofactor	185	ALSFRS-R	Negative
Minocycline	Phase III	Anti-inflammatory/anti-apoptotic	412	ALSFRS-R	Negative
Xaliproden	Phase III	Anti-apoptotic	Up to 1210	Survival Breathing capacity	Negative
Celecoxib	Phase III	Anti-inflammatory	300	Arm strength	Negative
Gabapentin	Phase III	Antiglutamatergic	204	Arm strength	Negative
Riluzole	Phase III	Anti-glutamatergic, unknown	Up to 959	Survival	Positive

Perhaps the area that currently poses the greatest obstacle to ALS researchers both in Europe and North America, is how best to translate basic science findings into clinical applications. Increasing focus is being given to how to establish the scientific justification for entering a drug into a clinical trial and how to identify the correct dose for neuroprotection in early phase trials before proceeding to a phase III trial.(128, 168) Standard approaches for testing drugs in animals have been proposed,(96) and new designs for drug and dose selection are being tested(169).

Because of the great expense and time required, a strong scientific rationale must be present before embarking on a large clinical trial. In ALS, preclinical researchers utilize *in vitro* and *in vivo* models, including motor neuron and spinal cord tissue screens, which provide more rapid results but may incompletely reflect complex *in vivo* pathophysiology. The transgenic mouse model is probably the most widely accepted means of establishing the scientific merit of an investigational agent. Questions regarding the mouse model include the timing of administration, how best to define dose and pharmacokinetics profiles that translate to dosing in humans, and what degree of improvement in the murine model is adequate justification for proceeding to human trials.(96, 170). The transgenic model based on overexpression of mutations in the SOD1 gene may not be an adequate representation of sporadic ALS, which has different causes and so may be a different disease. The SOD1 model, for example, has none of the inclusions that are considered pathognomonic for sporadic ALS. Models based on other gene mutations or screening of potential drugs in a series of models could add to the scientific justification for testing a new agent in people. Generalizability to models of other neurodegenerative diseases is also used to support testing a new drug.

Slow recruitment, historically more of a problem in the U.S. than Europe and when the drug is available for other indications, can hamper trials for rare disorders such as ALS in which there are few eligible patients. One of the greatest threats to the validity of a trial is loss-to-follow-up and missing data. Missing data reduce study power, the ability to detect a benefit of a drug if one exists, and if occurring in one treatment arm more than another, lead to biased, incorrect conclusions. Loss-to-follow-up has been a particular problem in the U.S. where competition is great between studies and there is a strong movement among patients to play a leading role in their own medical decision making.

The European Union (EU) has moved to standardize trial oversight and drug approval across Europe through the European Medicines Evaluation Agency (EMA) and the Clinical Trials Directive (http://eudract.emea.europa.eu/docs/directive/Directive_2001_20_EC.pdf). Its mission is to protect public health by using resources from the EU to evaluate new drugs, offer advice on research and development, inform health professionals, develop transparent procedures to facilitate access to new medicines, and control safety of medicines for humans as well as animals (<http://www.emea.europa.eu/>). The Clinical Trials Directive, issued in 2001 by the EU,(171) placed emphasis on speeding research and development, harmonizing procedures among countries, increasing the transparency of clinical research, and enforcing patient protection. While the EU has established standards for the conduct of trials and drug development, individual trial oversight is regulated by the specific countries. In France, for example, L'Agence Française de Sécurité Sanitaire des Produits de Santé (<http://afssaps.sante.fr>) oversees trial approval and drug development analogous to the Food and Drug Administration in the U.S.

The EU has also created the European Clinical Trials Database (EudraCT), which was established in accordance with the Clinical Trials Directive and contains all clinical trials commencing in the EU from May 2004 onwards. Applications are made through a website (<http://eudract.emea.europa.eu>) where the sponsor of a trial receives a EudraCT number providing authorization for a clinical trial, and gives notification of amendments to the trial as well as declaration of the end of the trial. EudraCT also provides ethics committee opinion on the trial and contains a database for trial data.

Perhaps the greatest difference between U.S. and European-based trials lies in the sources of funding. While most ALS trials in the world are supported by pharmaceutical companies, the NIH clinical trials division has established public funding for investigator-initiated clinical trials in the U.S.; large ALS trials outside the U.S. have been funded almost exclusively by pharmaceutical companies, or occasionally by a patchwork of government and charity agency organizations. In the UK, for example, trials are supported by drug companies, charities and the UK government. Pharmaceutical companies run their own trials and sometimes supply the drug free of charge for an investigator-initiated trial. The U.K. government can fund research through the Medical Research Council (MRC), the National Health Service and the Health Technology Assessment Programme (HTA). The MRC (<http://www.mrc.ac.uk/index.htm>) is a publicly-funded organization that supports research across the entire spectrum of medical

sciences, in universities and hospitals, and in MRC research units in the UK and in Africa. The Motor Neuron Disease Association can also contribute, but generally not in terms of multi-million euro amounts needed to fund an entire trial. Similar efforts to establish government funding of ALS research are underway in France, but most European trials are still sponsored by pharmaceutical companies.(131, 138, 165) The 2008 economic crisis in Europe and the United States has reduced the amount governments can spend on all types of research, lowering the success rate for grant applicants and, at times, rendering decisions by peer reviewers more arbitrary as they struggle to decide which of many applicants to allocate funding.(172)

1.6. Major questions

It is likely that better treatments and preventative measures will be discovered after the causes of this incurable condition are found. The disease is still mysterious in that no strong causal associations have been found for most forms of ALS. Better characterization of the disease, including change in occurrence over time, could lead to hypotheses for new associations. Hindering successful clinical trials, in addition to absence of known etiologies, is lack of an efficient way to measure disease progression. There is an ongoing search for reliable biomarkers of disease progression, but, as yet, none have been identified, and so researchers still use clinical endpoints, reducing trial efficiency. Better definition of disease phenotypes, along with identification of the most sensitive predictors of survival, could lead, not only to improved trial efficiency, but to identification of unique patient characteristics that could suggest like risks. Epidemiologic studies could better characterize changes in disease occurrence over time, disease characteristics and predictors of survival, along with contributing to the search for causes. The objectives of the current projects were to characterize change in mortality due to ALS in France while examining potential reasons for variation, determine whether the survival rate has changed in French patients, and assess baseline predictors of survival in the patient population at the Salpêtrière Hospital.

**CHANGING MORTALITY FOR MOTOR
NEURON DISEASE IN FRANCE (1968-
2007): AN AGE-PERIOD-COHORT
ANALYSIS**

2. CHANGING MORTALITY FOR MOTOR NEURON DISEASE IN FRANCE (1968-2007): AN AGE-PERIOD-COHORT ANALYSIS

2.1. Results

Some (65, 67), but not all (61, 63, 64, 68, 69) studies indicate that the incidence of ALS and MND have increased over time. Mortality has consistently increased in different studies (73-75). Studies of mortality may underestimate incidence, but they have the advantage of large sample sizes studied during long periods, providing good power to examine change. Study of mortality rates can contribute to the descriptive epidemiology of the disease, and examination of reasons for changing rates might lead to new hypotheses for etiologies.

A previous mortality study conducted in France showed that the mortality rate increased from 0.71/100,000 in 1968 to 1.52/100,000 in 1982.(76) A study from the United States showed that mortality rate increased from 1.25/100,000 in 1969 to 1.82/100,000 in 1998.

Our project examined mortality from MND in France during 1968-2007 and used a form of Poisson regression known as Age-Period-Cohort (APC) modeling to determine whether the variables age, period of death, or cohort of birth best explained the changing mortality rates.(173, 174). A period effect influences all individuals during a period of time independently of their age, and can be explained by social, medical, or economic factors, including improved treatment or diagnosis. A cohort effect, seen as a change in the rates for a cohort of individuals born during the same period of time, can be due to changing environmental exposures.

37,624 deaths from MND were recorded in people aged 40 to 89 years during 1968-2007. The crude mortality rate over the whole study period was 1.74 per 100,000 person-years; 1.90/100,000 in men and 1.58 in women.

Standardized mortality ratios (SMRs), taken as the ratio of the number of observed deaths to the number of expected deaths each year using the overall population (1968-2007) as the reference (indirect standardization), increased with time, from 54 (95% CI = 49-59) in 1968 to 126 (95% CI = 120-132) in 2007. This trend was similar for each gender, but the sex ratio declined over time from 1.80 in 1968 to 1.45 in 2007. The mortality rates began to increase

with time period in subjects aged 60-64, a trend that strengthened with advancing age. The rates also increased according to birth cohorts.

In APC analyses, the model including age only (model 1) showed that mortality increased to a peak between 75 and 79 years (ratio of deviance to degrees of freedom for the model = 34.86). The age-drift model (model 2) estimated that the relative risk (RR) per one year increase in age was 1.018 (95% CI=1.017-1.019) and that mortality increased 19.6% every 10 years (ratio of deviance to degrees of freedom = 13.03). The age-period model (model 3) showed that mortality increased during the study period (ratio of deviance to degrees of freedom = 12.23). The age-cohort model (model 4) showed that the RR of dying from MND increased with time; this model fit the data better than the other models (ratio of deviance to degrees of freedom = 1.09), suggesting that a cohort effect best explained the increasing mortality rate in France. In analyses stratified by sex, the cohort effect was more pronounced in women than in men, corresponding to the decrease in male to female gender ratio over time.

The study showed that mortality from MND increased in France, independent of the aging of the population, and that this increase is best explained by birth cohort. Environmental factors are one explanation for the cohort effect seen in these data. Improved diagnosis in older age groups and women could also contribute to the findings. Future studies could examine whether changes in mortality rates are associated with varying levels of selected environmental exposures, and use APC Poisson regression to study data from other countries.

Changing mortality for motor neuron disease in France (1968–2007): an age-period-cohort analysis

Paul H. Gordon^{1,2,4,5}✉, Fanny Artaud^{1,2}, Albertine Aouba³, Françoise Laurent³, Vincent Meininger^{2,4} and Alexis Elbaz^{1,2}

(1) INSERM, U708, 75013 Paris, France

(2) UPMC Univ Paris 06, UMR_S 708, 75005 Paris, France

(3) Inserm-CépiDc, Le Vésinet, France

(4) Fédération des Maladies du Système Nerveux, AP-HP, Hôpital de la Salpêtrière, Paris, France

(5) INSERM, Unité U708, Neuroépidémiologie, Hôpital de la Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France

✉ Paul H. Gordon

Email: paul.Gordon@psl.aphp.fr

Received: 27 February 2011 **Accepted:** 31 May 2011 **Published online:** 15 June 2011

Abstract

The incidence and mortality of motor neuron disease (MND) increase with age and appear to have increased with time. The examination of period and cohort effects using age-period-cohort (APC) models can help characterize temporal trends. Our objective was to describe mortality from MND in France (1968–2007), and to examine the role of age, period of death, and birth-cohort on changes in mortality. The number of people who died from MND and population statistics (1968–2007) were extracted from French national records. Annual standardized (age/sex) mortality ratios (SMRs) were computed. Using Poisson regression, APC models examined the relationship between mortality rates and age, period of death, and birth-cohort in subjects aged 40–89 years. Deviance/degrees-of-freedom ratios evaluated model fit; ratios close to one indicated adequate fit. Between 1968 and 2007, 38,863 individuals died from MND (mortality rate = 1.74/100,000); 37,624 were aged 40–89 years. SMRs increased from 54 (95% CI = 49–59) in 1968 to 126 (120–132) in 2007. Male-to-female ratios declined from 1.80 in 1968 to 1.45 in 2007. Changing mortality rates were best explained by cohort effects (deviance/degrees-of-freedom = 1.09). The relative risk of dying from MND increased markedly for persons born between 1880 and 1920, and more slowly after 1920. In conclusion, mortality rates for MND increased between 1968 and 2007, and more rapidly in women than men. This increase was better explained by the birth-cohort of individuals than by period effects. Changing environmental exposures may be a possible explanation and these findings warrant the continued search for environmental risk factors for MND.

Electronic supplementary material The online version of this article (doi:[10.1007/s10654-011-9595-0](https://doi.org/10.1007/s10654-011-9595-0)) contains supplementary material, which is available to authorized users.

Keywords Amyotrophic lateral sclerosis – Motor neuron disease – Mortality – Epidemiology – Temporal trend

Abbreviations *AIC*

Akaike's information criterion

- *ALS*

Amyotrophic lateral sclerosis

- *APC model*

Age-period-cohort model

- *ICD*

International classification of diseases

- *MND*

Motor neuron disease

- *SMR*

Standardized mortality ratio

Introduction

The motor neuron diseases (MNDs), of which is amyotrophic lateral sclerosis (ALS) is the most common, are overall rare, with incidence rates ranging between 1.2 and 4.0 per 100,000 person-years [1–5]. The incidence increases with age, peaking between 70 and 80 years, and then decreases. In addition, MND is thought to be more common in men than women [4, 6].

Some reports have suggested that the incidence has increased with time [6, 7], but this finding has not been confirmed in all studies [2, 4, 5, 8, 9]. Reports of mortality rates mirror incidence studies and have shown that mortality from MND has increased over time in different parts of the world [10–12]. Although they may underestimate incidence, mortality studies based on administrative databases have the advantage of including large sample sizes during long periods, providing robust power for the examination of change over time.

MND is thought to be a complex disorder in which genetic and environmental risk factors combine in the pathogenesis. Relatives of patients with ALS have an increased risk of developing the disease [6]. Among environmental risk factors, the most robust evidence is available for smoking [13, 14], but some reports show positive associations with athleticism [15] or exposure to pesticides [16]. However, the major causes of MND are unidentified, and epidemiologic descriptive studies can contribute to a better understanding of the disease.

Period and cohort effects have been examined in other diseases, particularly cancer, to provide clues to the factors underlying changing rates [17, 18]. A period effect, which affects all individuals during a period of time independently of their age, can be explained by social, medical, or economic factors, including improved treatment or diagnosis. A cohort effect, seen as a change in the rates for a cohort of individuals born during the same period of time, can be due to changing environmental exposures. Age-period-cohort (APC) models have been proposed as a statistical tool to disentangle the role of these three time factors, and, to our knowledge, have not been used previously to study MND.

The objectives of the current study were to describe the mortality from MND in France during the period 1968–2007, determine whether a previously-identified increasing trend [19] continued after 1982, and assess the effects of age, period of death, and cohort of birth on mortality.

Methods

Data collection

We obtained the number of deaths from MND in France between January 1, 1968, and December 31, 2007, from the *Centre d'épidémiologie sur les causes médicales de décès* (CépiDc; <http://www.cepdc.vesinet.inserm.fr>), and the French population statistics for the same period from the *Institut National de la Statistique et des Etudes Economiques* (INSEE; <http://www.insee.fr>). Overseas territories were not included in the analyses.

CépiDc collects, analyzes, and disseminates the statistics on causes of death in France. The data are created using information gathered from death certificates, and are compiled according to the International Classification of Diseases (ICD-8 from 1968 to 1978, ICD-9 from 1979 to 1999, and ICD-10 beginning in 2000). CépiDc provided the data on all individuals for whom the codes 348 (ICD-8), 335.2 (ICD-9), or G12.2 (ICD-10) were entered as the primary or associated cause of death. These codes incorporate different forms of MND; diseases other than ALS contained in the codes are rarer still, and comprise progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, and primary lateral sclerosis. The data included the years of death and of birth, sex, and district (French *département*) of residence. Overseas districts were excluded from the analyses because of less consistent vital statistics reports and census data than on the European continent.

INSEE, which collects and disseminates information on the French economy and society, including population statistics derived from the census, provided the population numbers by year, age, sex, and district. From these data, person-years were calculated by 5-years age groups [20].

Mortality rates

We computed crude and age- and sex-standardized mortality rates. Annual standardized mortality ratios (SMRs, 95% confidence intervals, CI), calculated as the ratio of the observed number of deaths to the number of expected deaths each year using the overall population (1968–2007) as the reference (indirect standardization), examined change over time. SMRs were computed overall and then separately for each gender; the sex ratio was taken as the ratio of SMRs in men and women.

Age-period-cohort model

Three time factors are usually considered to characterize trends in mortality rates: (1) age; (2) date of death (i.e., period); and (3) date of birth (i.e., cohort) [21].

We created graphics to represent the data visually, and used APC regression models to summarize model parameters. APC models characterized rates as a combination of time factors, describing the magnitude of the rates and their variation by age, period, and cohort [22]. The models assessed which combination of the three time factors best described the data.

Data were tabulated by 5-years age groups and calendar periods (supplementary table 1). There were few deaths below 40 and above 89 years of age, so we restricted the analyses to subjects aged 40–89 years (10 age groups and eight calendar periods). Seventeen 10-years cohorts were defined by subtracting periods from the center of each age group. The 1983–1987 period and the 1923 birth cohort were taken as the reference. Plots of mortality rates according to age, period, and birth cohort were constructed.

We used Poisson regression to model mortality rates using a model-building procedure that sequentially fit models with the following terms: model 1, age; model 2, age + drift; model 3, age + period; model 4, age + cohort; model 5, age + period + cohort (“Appendix”) [17, 18]. Model 1 corresponded to the null hypothesis of no temporal variation. Model 2 fit a simple linear time trend (drift) not attributable to period or cohort influences. In the case that model 2 did not describe the data adequately, models 3–5 were used to examine period or cohort effects.

The goodness-of-fit of the models was assessed through both deviance and Akaike’s information criterion (AIC). Ratios of deviance to the number of degrees of freedom that were closer to 1 and lower AIC values indicated a better fit. Models were compared using the difference between their deviances; under the null hypothesis, this difference followed a chi-square distribution whose degrees of freedom were computed as the difference between degrees of freedom from the two models.

Analyses were performed overall and stratified by sex. To determine whether the observed changes were similar in men and women, we tested for interactions between sex and period or cohort effects by introducing multiplicative terms in the Poisson regression models.

We used the GENMOD and *glm* procedures in SAS v9.1 (SAS Institute, Inc., Cary, NC) and R software (R Development Core Team; R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>) respectively.

Results

Between January 1, 1968, and December 31, 2007, 38,863 deaths from MND were recorded in France. Of these, 37,624 occurred in people aged 40–89 years. The crude mortality rate over the whole study period was 1.74 per 100,000 person-years, and was higher in men (1.90 per 100,000) than women (1.58 per 100,000). Mortality increased with age to peak between 75 and 79 years and then decreased (Fig. 1); it was higher in men than women at all ages.

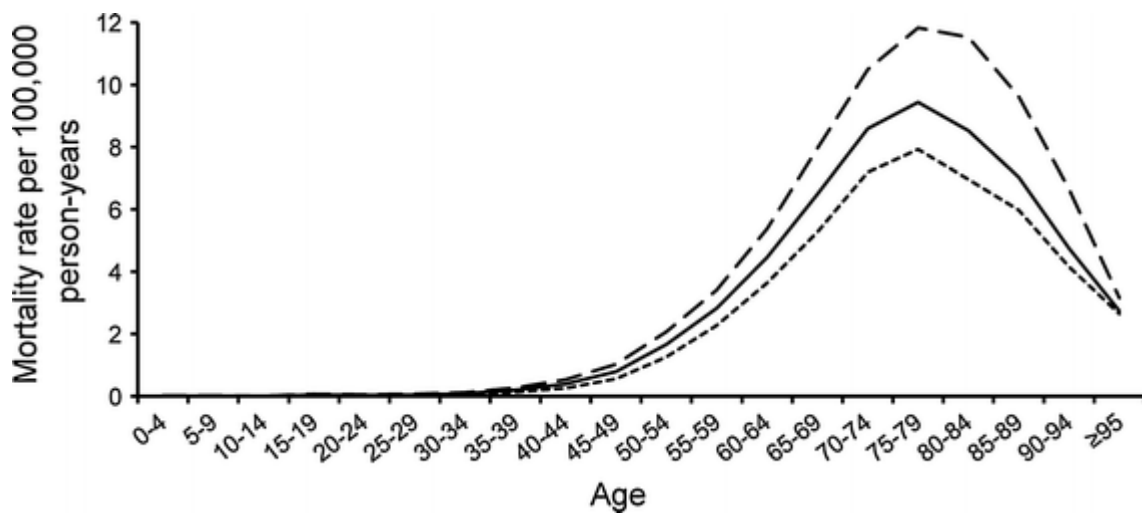


Fig. 1 Age- and sex-specific mortality rates from MND per 100,000 person-years in France between 1968 and 2007 (*solid line overall; long-dashed line men; short-dashed line women*)

SMRs increased progressively with time, ranging from 54 (95% CI = 49–59) in 1968 to 126 (95% CI = 120–132) in 2007 (Fig. 2a). This trend was similar when examined separately for each sex (Fig. 2b, c), but was steeper in women than men; the sex ratio declined over time from 1.80 in 1968 to 1.45 in 2007 (Fig. 2d).

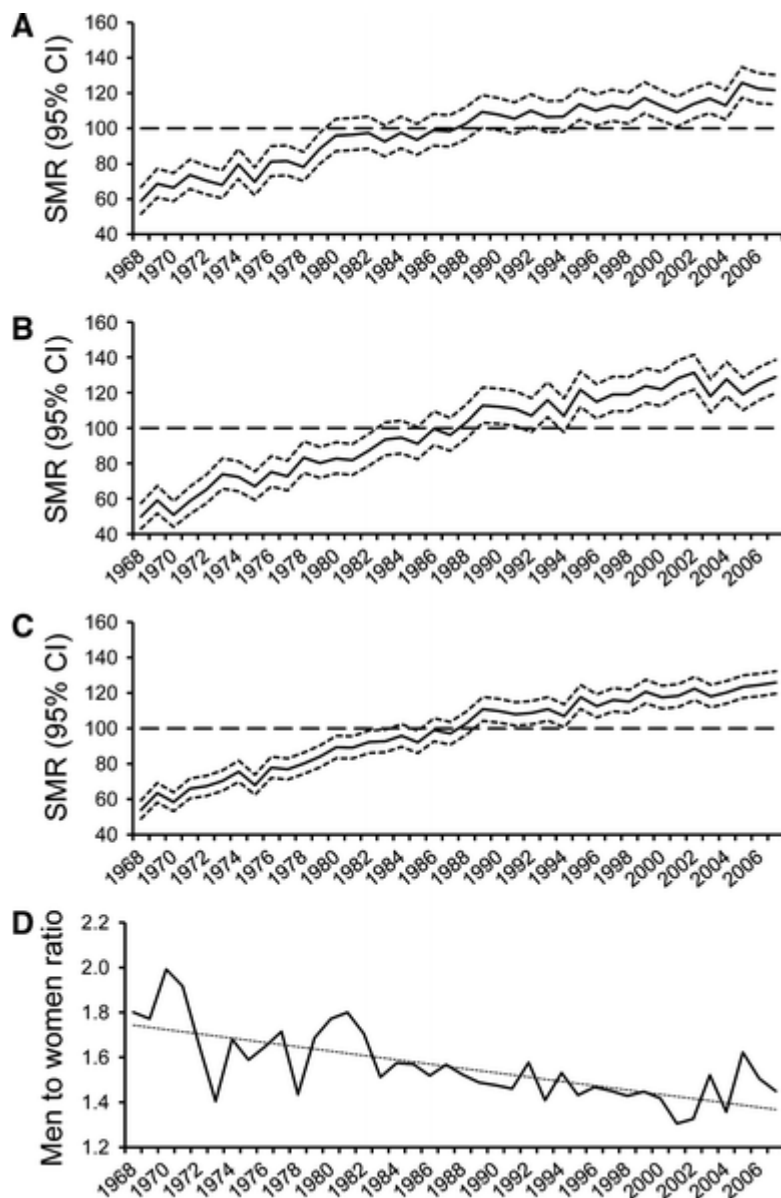


Fig. 2 Standardized mortality ratios (SMR, *solid line*; the *long dashed line* represents the reference) from MND and 95% CI (*short dashed line*) in France between 1968 and 2007, **a** overall, **b** in men, **c** in women, and **d** men to women ratio (*solid line*) and regression line of ratio on year (*dotted line*)

A graphic presentation of mortality rates by age and time period (Fig. 3a, b) showed that the rates began to increase with time period in subjects aged 60–64 and that this trend strengthened with advancing age; the curves for mortality rates in each age group were not parallel as the period of death increased. In addition, the peak tended to move towards older age groups as time period increased. Similar trends were noted in men and women (data not shown).

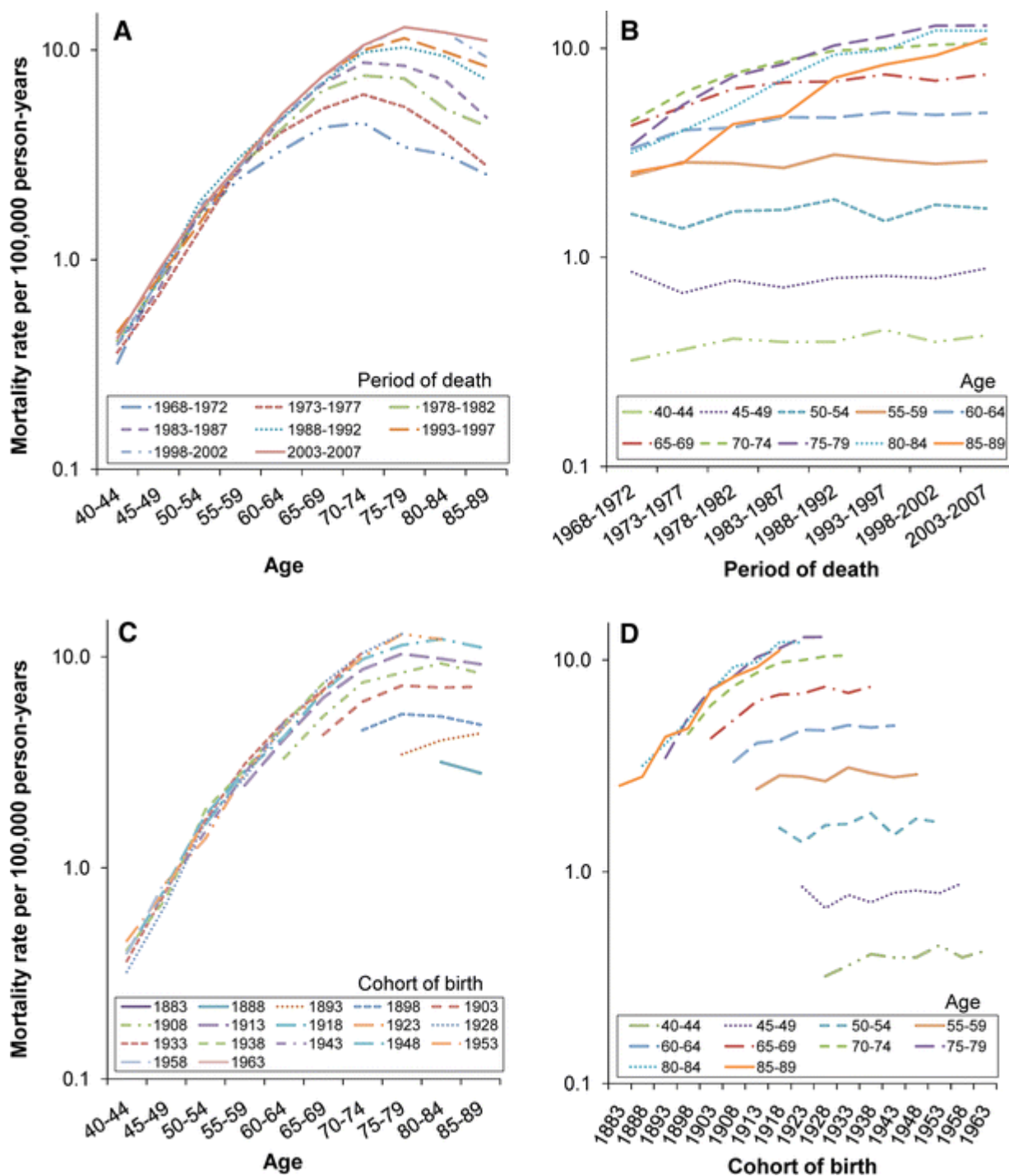


Fig. 3 Mortality rates from MND in France between 1968 and 2007 by age group, time-period of death, and birth cohort. The *top panels* show mortality rates connected within periods of death (a) or within age groups at death (b). The *bottom panels* show age-specific mortality rates from MND in France for the birth cohorts 1883–1963 connected within cohorts of birth (c) or within age groups at death (d). Mortality rates (per 100,000 person-years) are shown on the logarithmic scale

A similar presentation by age and birth cohort showed an increase in mortality according to birth cohorts that was more pronounced for people born between 1883 and 1918 (Fig. 3c, d). This pattern translated into curves that were parallel across birth cohorts for a given age group (Fig. 3d). Similar trends were noted in men and women (data not shown).

In APC analyses (Table 1), the model including age only (model 1) confirmed that mortality increased to a peak between 75 and 79 years and then decreased (supplementary table 2). This model fit the data poorly (ratio of deviance to degrees of freedom = 34.86). The age-drift model (model 2) estimated that the relative risk (RR) per 1 year increase in age was 1.018 (95% CI = 1.017–1.019) and that mortality increased 19.6% every 10 years. This model also fit the data poorly (ratio of deviance to degrees of freedom = 13.03), suggesting the presence of non-linear time trends. The age-period model (model 3) showed that mortality increased during the study period (supplementary table 2), but also had a poor fit (ratio of deviance to degrees of freedom = 12.23). The age-cohort model (model 4) showed that the RR of dying from MND increased markedly for those born between 1880 and 1920 (Fig. 4; supplementary table 2); people born in 1893 were 69% (95% CI = 66–71%) less likely to die from MND than those born in 1923, independently of their age at death. Between 1920 and 1960, the increase remained significant ($P = 0.0013$) but at a slower rate (Fig. 4). The ratio of deviance to degrees of freedom of this model (1.09) indicated an excellent fit to the data. A comparison of the deviance and the AIC for all models (Table 1) showed that the age-cohort model fit the data significantly better than the age-drift or age-period models. Moreover, the age-period-cohort model added nothing in terms of deviance to the age-cohort model; the addition of the variable period to the age-cohort model was not useful.

Table 1 Age-period-cohort analysis: assessment of the goodness-of-fit of the models

	DF	Deviance	Deviance/DF	AIC	Comparison of models	<i>P</i> value
Overall						
Age	70	2,440.15	34.86	3,072		
Age-drift	69	899.10	13.03	1,533	Age-drift vs. age	<0.05
Age-period	63	770.77	12.23	1,417	Age-period vs. age-drift	<0.05
Age-cohort	54	58.94	1.09	732	Age-cohort vs. age-drift	<0.05
Age-period-cohort	48	57.82	1.20	732	Age-period-cohort vs. age-cohort	0.98
Women						
Age	70	1,473.31	21.05	2,040		
Age-drift	69	539.46	7.82	1,108	Age-drift vs. age	<0.05
Age-period	63	447.48	7.10	1,028	Age-period vs. age-drift	<0.05
Age-cohort	54	55.32	1.02	654	Age-cohort vs. age-drift	<0.05
Age-period-cohort	48	50.55	1.05	661	Age-period-cohort vs. age-cohort	0.57
Men						
Age	70	971.83	13.88	1,556		
Age-drift	69	400.08	5.80	986	Age-drift vs. age	<0.05
Age-period	63	348.70	5.53	946	Age-period vs. age-drift	<0.05
Age-cohort	54	73.37	1.36	689	Age-cohort vs. age-drift	<0.05

	DF	Deviance	Deviance/DF	AIC	Comparison of models	P value
Age-period-cohort	48	65.78	1.37	693	Age-period-cohort vs. age-cohort	0.27

DF degrees of freedom, AIC Akaike information criterion

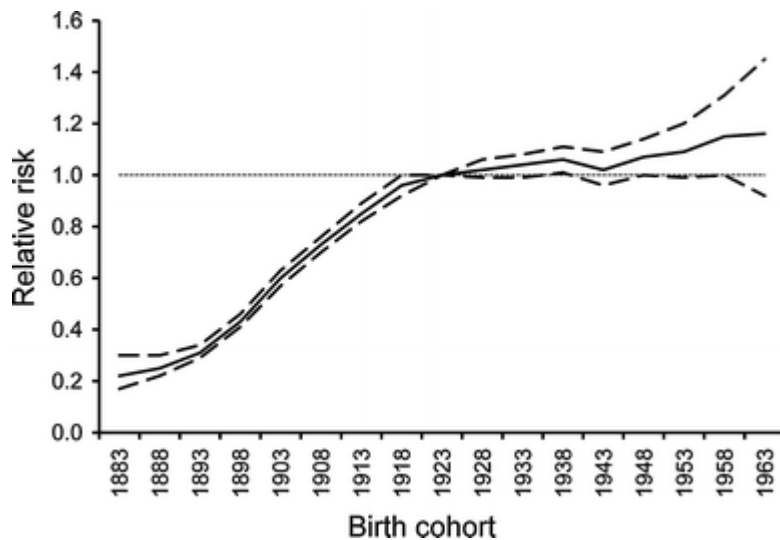


Fig. 4 Age-adjusted relative risk (solid line) and 95% CI (long dashed line) of mortality by MND in France between 1968 and 2007 by birth cohort (age-cohort model); the short dashed line represents the reference (1923 birth cohort)

In analyses stratified by sex, the cohort effect was more pronounced in women than in men; the increase in mortality with advancing birth cohorts was steeper in women than men (supplementary table 2; P for interaction = 0.0049), corresponding to the decrease in male to female sex ratio over time.

In sensitivity analyses, we performed the APC analysis separately in persons aged 40–69 and 70–89 years old at the time of death (supplementary table 3), and in persons who died before and after 1990 (supplementary table 4); the age-cohort model provided the best fit to the data in all the strata. We also performed sensitivity analyses restricted to each of the three time periods during which the different ICD codes were used, and obtained results similar to those described above for each of the periods (data not shown).

Discussion

This study analyzed a large sample of individuals who died from MND in France over a period of 40 years. The mortality rate for MND increased from 1968 to 2007 and this increase was better explained by the period of birth of individuals (cohort effect) than by the time of their death (period effect). Mortality rates were higher among men than women throughout the study period, but the cohort effect was more pronounced in women and the sex-difference in mortality diminished with time. No other studies of ALS or MND have, to our knowledge,

used age-period-cohort modeling to help determine why the mortality of these diseases is changing.

Our findings are consistent with other reports. The results extend those of a study carried out in France from 1968 to 1982 [19], which showed that the mortality rates from MND increased from 0.71 per 100,000 person-years in 1968 to 1.52 in 1982. This trend continued from 1983 to 2007 in the current study. We also verified the decreasing sex ratio with time detected in the earlier study. Additionally, our findings agree with research in other countries. Mortality rates have increased in the US [12], Finland [11], Norway [10], Britain [23] and Italy [24]. Similar to our study, a more pronounced trend in women, with a decreasing sex ratio over time, has been found in the US [12], Britain [23], Norway [10] and Finland [11]. These data provide consistency of findings, not only between countries, but also between different health care systems and study designs. Several population-based studies have also shown increasing incidence of MND over time Sweden [6, 7]. Other studies of incidence have suggested stable rates, but most of these studies identified up to several hundred people over periods up to 10 years [2, 4, 5, 8, 9, 25]. Longer and larger studies may be needed for adequate power to detect changing rates. Two studies showing increasing incidence were conducted over 15 and 22 years [6, 7].

In our study, the increasing mortality from MND was better explained by a cohort effect, which involves all individuals born at the same time, independently of their age at death, than by a period effect. This cohort effect was observed graphically and confirmed statistically through APC analyses; there was a marked increase for cohorts born before 1923, but the increase continued for cohorts born after that date, notably for persons born after 1945 who died from MND in recent years. A visual inspection of graphs from the US [12] and Sweden [6] shows similar patterns suggestive of a birth cohort effect rather than a period effect in those studies.

Changing environmental exposures are a possible explanation for cohort effects. It is likely that environmental risk factors for diseases such as MND act at younger ages and require prolonged exposures. Therefore, changes in population exposures are likely to manifest after many years and not occur simultaneously in all age groups. Variations in the frequency and intensity of exposure across birth cohorts may account for the observed differences in mortality in our study; individuals from one generation have exposure levels that are different from other generations, explaining why the age-cohort model provided the best description of the data [17]. If this hypothesis is true, our findings suggest that environmental factors linked to the development of MND: (1) have increased over the past century; (2) are more frequent in men than in women; and (3) have become increasingly frequent in women as time passed. One way to investigate this hypothesis would be through ecological studies examining whether changing environmental exposures (e.g., temporal trends in smoking and occupational exposures such as pesticides) account in part for the observed temporal trends in mortality from MND.

In contrast to cohort effects, period effects are explained by factors that impact all individuals during a period of time, independently of their age. Medical discoveries, changes in diagnostic methods, or development of new drugs are likely to translate into period effects. It is, however, possible that age-dependent period effects (i.e., a period effect that is restricted to certain age groups) could mimic a cohort effect, and APC models cannot distinguish between the two scenarios. If improved identification of a disease occurred over time for certain, but

not all, age groups, then an interaction between age and period would manifest as a cohort effect [17]. Therefore, an alternative explanation for our findings is that patients with MND have been better identified over time, in particular among the older age groups and women. As in other countries, the number of centers in France that specialize in MND has increased with time, which has likely led to heightened awareness among the medical community. Some studies have suggested that this phenomenon may be more pronounced in women than in men [26]. It is unclear to what extent the changing number of specialists affects reporting of MND on death certificates [12], but it seems unlikely to account entirely for our findings. First, we performed analyses stratified by age and found that the age-cohort model provided the best fit to the data in persons who died from MND before age 70 years and in whom MND started 2–3 years earlier on average. While there is evidence of under-diagnosis and under-reporting of MND in death certificates, this is likely to be more pronounced in older people [26]. Therefore, the cohort effect seen in younger persons is less likely to be entirely explained by improved diagnosis over time. Second, in the US there was an inverse correlation between mortality from MND and the geographical distribution of neurologists; access to specialty care was not a determinant of the variation in mortality rates [12]. Third, in France the first centers specializing in ALS appeared after 1990, which has probably led to better diagnosis and patient identification and resulted in increased death certification after that date. We performed separate analyses in persons who died before and after 1990 and found that the age-cohort model provided the best fit in both groups; in particular, the age-cohort model fit the data best before 1990. Therefore, the development of specialty centers does not explain the increase in ALS mortality seen before that time. Fourth, the increasing trend in mortality from MND in France is consistent with worldwide trends seen in many countries with different health systems and different methods for death certification.

As in most studies, we observed a decrease in mortality rates of MND after age 80. This suggests that susceptibility to MND may be age-dependent but we cannot exclude other explanations, such as under-ascertainment in the oldest age groups or competing causes of mortality. Gompertzian analyses have suggested that decline in mortality rates from ALS in the elderly may be explained by the existence of a susceptible population to which ALS deaths are limited and whose frequency decreases over time [27]. Based on this model and its underlying assumptions, it has been suggested that the evolving ALS mortality pattern may be attributable to increasing life expectancy; mortality rates would be expected to increase over time in the older age groups, while they would decrease in the younger age groups [28]. In our data, mortality increased in the older age groups over time, but it also increased, although less markedly, in younger age groups. In addition, in the Gompertzian framework, the nature of susceptibility is of unknown origin and may be due to environmental causes occurring early in life, which is not in contradiction with a possible cohort effect [28].

The strengths of this study include the large sample size, long study period, and statistical approach using APC models. The study also has limitations. Although mortality studies offer the opportunity to examine a disease over long periods of time and in large numbers of patients, which is usually not possible in population-based studies of incidence, mortality data have imperfect sensitivity and specificity. However, in the case of MND, mortality data are generally considered reliable [29]. The diagnosis is straightforward for neurologists and requires only standard equipment for confirmation, making mortality data for MND a better reflection of incidence than for other neurological diseases [12]. Autopsies have shown that there are very few false positives (people incorrectly diagnosed with MND during life) [30], and there are no autopsy studies that detected undiagnosed MND. Studies based on death

certificates indicate 72–97% accuracy [10, 31–33]. The highest true positive rates, where mortality rates are highly consistent with incidence data, occur in studies that use high-quality methodology, including a defined population and data collected based on underlying and contributory causes, as was done in the current study [34]. We excluded overseas territories where death certificate reporting and census data may be less consistent. The population of the French overseas territories represents 2–3% of the total French population and the number of cases in overseas territories is likely to be small compared to the total number of patients with MND. Nevertheless, our findings apply only to the part of France that is located in the European continent. The mortality rates of MND in our study are higher than incidence rates of ALS reported in a single region of France during 1997–2007 based on patients followed at a referral center [3]. A direct comparison to the incidence data from that study showed that 264 patients died from MND between 1997 and 2007, yielding a mortality rate of 3.32/100,000 (vs. an ALS incidence of 2.5/100,000 in Limousin); the mortality rate for ages 45–74 during the same time was 5.18 based on 153 deaths (vs. an ALS incidence of 4.7 in Limousin). The crude mortality rate of MND for the years 1994–1995 was 3.00/100,000, very close to the ALS incidence rate of 3.2/100,000 reported in Limousin in an earlier study that also surveyed neurologists and other hospitals [35]; this study, using a capture-recapture method, estimated that approximately 60% of the patients with ALS had been identified. There are no data, however, that describe the accuracy of death certificate reporting in France. A study that identified incident cases from six population-based registries from three European countries (Ireland, UK, Italy) in the years 1998–1999 found a homogeneous incidence rate of 2.16 per 100,000 [36], similar to our overall mortality rate of 2.2/100,000 during the years 1998–2002. Mortality rates in our study were similar to or slightly lower than incidence rates below 70 years, but became higher in older age groups when incidence and mortality were highest. Another limitation is the change in ICD codes that occurred twice during the study. However, we noted no discontinuity of rates, and more important, a period effect would have occurred had the changes in ICD had a significant impact, which was not the case. In addition, when we performed analyses restricted to periods that used the same coding system, we observed results that were similar to those from the main analyses.

The data from this study suggest that the mortality from MND is increasing, independently of the aging of the population, and that this increase is better explained by birth cohort than time period. Although we cannot exclude that improved diagnosis in the older age groups and women contributes to our findings, environmental influences may be a possible explanation for the cohort effect seen in these data. Future studies could examine whether changes in mortality rates are associated with varying levels of selected environmental exposures, and apply APC analyses to data from other countries to assess whether similar patterns are observed elsewhere.

Appendix: age-period-cohort models

The mortality rates λ_{ijk} for age i , period j , and cohort k ($k = j - i$) are $\lambda_{ijk} = m_{ijk} / T_{ijk}$, where m_{ijk} is the expected number of deaths and T_{ijk} the number of person-years for the ijk combination. The observed number of deaths, n_{ijk} , is considered to arise from a Poisson distribution with mean m_{ijk} . Age-period-cohort models assume that the three time factors, age, period, and cohort have an additive effect on the logarithm of the rates and can be generally written as $\log \lambda_{ijk} = \mu + \alpha_i + \beta_j + \gamma_k$, where age effects are represented by α_i ,

period effects by β_j , and cohort effects by γ_k . Poisson regression is used to model mortality rates using person-years as an offset.

Clayton and Schifflers [17, 18] have proposed a sequential procedure (supplementary figure 1). Models of increasing complexity, depending on which terms are included in the regression model, are sequentially fitted to the data:

- Model 1: Age

- Model 2: Age-Drift (the drift parameter fits a simple linear trend in mortality with time)

- Model 3: Age-Period

- Model 4: Age-Cohort

- Model 5: Age-Period-Cohort

Model 1 assesses whether mortality changes with age. Model 2 evaluates whether there are additional linear trends that cannot ascribed to period or cohort effects. If this model does not fit adequately the data, then more complex models can be evaluated. Model 3 evaluates the presence of period effects and model 4 tests for cohort effects. If none of these models fits the data adequately, model 5, which includes age, period, and cohort effects, is fitted.

The goodness-of-fit of the models is assessed through ratios of deviance to the degrees of freedom; ratios that are closer to one indicate a better fit. A lower value of the Akaike's information criterion (AIC) also indicates a better fit. Models can be compared using the difference between their deviances; under the null hypothesis, this difference follows a chi-square distribution whose degrees of freedom are computed as the difference between degrees of freedom from the two models that are compared.

Electronic supplementary material

Below is the link to the electronic supplementary material.

[Supplementary material 1 \(DOCX 65 kb\)](#)

References

- 1 Annegers JF, Appel S, Lee JR, Perkins P. Incidence and prevalence of amyotrophic lateral sclerosis in Harris County, Texas, 1985–1988. *Arch Neurol.* 1991;48:589–93.

[PubMed](#) [ChemPort](#)

- 2 Beghi E, Millul A, Micheli A, Vitelli E, Logroscino G. Incidence of ALS in Lombardy, Italy. *Neurology*. 2007;68:141–5.

[PubMed](#) [crossref](#) [ChemPort](#)

- 3 Marin B, Gil J, Preux PM, Funalot B, Couratier P. Incidence of amyotrophic lateral sclerosis in the Limousin region of France, 1997–2007. *Amyotroph Later Scler*. 2009;10:216–20.

[crossref](#)

- 4 Alonso A, Logroscino G, Jick SS, Hernan MA. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. *Eur J Neurol*. 2009;16:745–51.

[PubMed](#) [crossref](#) [ChemPort](#)

- 5 Chio A, Mora G, Calvo A, Mazzini L, Bottacchi E, Mutani R. Epidemiology of ALS in Italy: a 10-year prospective population-based study. *Neurology*. 2009;72:725–31.

[PubMed](#) [crossref](#) [ChemPort](#)

- 6 Fang F, Valdimarsdottir U, Bellocco R, Ronnevi LO, Sparen P, Fall K, et al. Amyotrophic lateral sclerosis in Sweden, 1991–2005. *Arch Neurol*. 2009;66:515–9.

[PubMed](#) [crossref](#)

- 7 Murphy M, Quinn S, Young J, Parkin P, Taylor B. Increasing incidence of ALS in Canterbury, New Zealand: a 22-year study. *Neurology*. 2008;71:1889–95.

[PubMed](#) [crossref](#) [ChemPort](#)

- 8 Sorenson EJ, Stalker AP, Kurland LT, Windebank AJ. Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925 to 1998. *Neurology*. 2002;59:280–2.

[PubMed](#)

- 9 Mandrioli J, Faglioni P, Merelli E, Sola P. The epidemiology of ALS in Modena, Italy. *Neurology*. 2003;60:683–9.

[PubMed](#)

- 1 Seljeseth YM, Vollset SE, Tysnes OB. Increasing mortality from amyotrophic lateral sclerosis in Norway? *Neurology*. 2000;55:1262–6.

[PubMed](#) [ChemPort](#)

- 1 Maasilta P, Jokelainen M, Loytonen M, Sabel CE, Gatrell AC. Mortality from amyotrophic lateral sclerosis in Finland, 1986–1995. *Acta Neurol Scand*. 2001;104:232–5.

[PubMed](#) [crossref](#) [ChemPort](#)

- 1 Noonan CW, White MC, Thurman D, Wong LY. Temporal and geographic variation in United States

2 motor neuron disease mortality, 1969–1998. *Neurology*. 2005;64:1215–21.



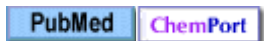
1 Nelson LM, McGuire V, Longstreth WT Jr, Matkin C. Population-based case-control study of
3 amyotrophic lateral sclerosis in western Washington State. I. Cigarette smoking and alcohol
consumption. *Am J Epidemiol*. 2000;151:156–63.



1 Gallo V, Bueno-De-Mesquita HB, Vermeulen R, Andersen PM, Kyzozis A, Linseisen J, et al.
4 Smoking and risk for amyotrophic lateral sclerosis: analysis of the EPIC cohort. *Ann Neurol*.
2009;65:378–85.



1 Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity
5 athletics in ALS. *Neurology*. 2002;59:773–5.



1 Sutedja NA, Veldink JH, Fischer K, Kromhout H, Heederik D, Huisman MH, et al. Exposure to
6 chemicals and metals and risk of amyotrophic lateral sclerosis: a systematic review. *Amyotroph*
Later Scler. 2009;10:302–9.



1 Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: age-period and age-cohort
7 models. *Stat Med*. 1987;6:449–67.



1 Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: age-period-cohort models.
8 *Stat Med*. 1987;6:469–81.



1 Durrleman S, Alperovitch A. Increasing trend of ALS in France and elsewhere: are the changes
9 real? *Neurology*. 1989;39:768–73.



2 Hill C, Doyon F. Age in completed years versus age reached during the year. *Rev Epidemiol Sante*
0 *Publique*. 2005;53:205–8.



2 Holford TR. The estimation of age, period and cohort effects for vital rates. *Biometrics*.
1 1983;39:311–24.



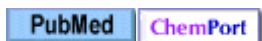
2 Carstensen B. Age-period-cohort models for the Lexis diagram. *Stat Med*. 2007;26:3018–45.



2 Dean G, Elian M. Motor neuron disease and multiple sclerosis mortality in Australia, New Zealand
3 and South Africa compared with England and Wales. *J Neurol Neurosurg Psychiatr.* 1993;56:633–7.



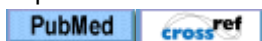
2 Chio A, Magnani C, Schiffer D. Amyotrophic lateral sclerosis mortality in Italy, 1958 to 1987: a
4 cross-sectional and cohort study. *Neurology.* 1993;43:927–30.



2 O'Toole O, Traynor BJ, Brennan P, Sheehan C, Frost E, Corr B, et al. Epidemiology and clinical
5 features of amyotrophic lateral sclerosis in Ireland between 1995 and 2004. *J Neurol Neurosurg
. Psychiatr.* 2008;79:30–2.



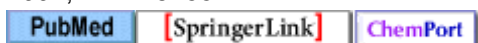
2 Ragonese P, Filippini G, Salemi G, Beghi E, Citterio A, D'Alessandro R, et al. Accuracy of death
6 certificates for amyotrophic lateral sclerosis varies significantly from north to south of Italy:
. implications for mortality studies. *Neuroepidemiology.* 2004;23:73–7.



2 Riggs JE. Longitudinal Gompertzian analysis of amyotrophic lateral sclerosis mortality in the US,
7 1977–1986: evidence for an inherently susceptible population subset. *Mech Ageing Dev.*
. 1990;55:207–20.



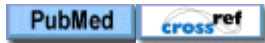
2 Neilson S, Robinson I, Alperovitch A. Rising amyotrophic lateral sclerosis mortality in France 1968–
8 1990: increased life expectancy and inter-disease competition as an explanation. *J Neurol.*
. 1994;241:448–55.



2 Chio A, Magnani C, Oddenino E, Tolardo G, Schiffer D. Accuracy of death certificate diagnosis of
9 amyotrophic lateral sclerosis. *J Epidemiol Community Health.* 1992;46:517–8.

. [HYPERLINK "http://dx.doi.org.ezproxyhhs.nihlibrary.nih.gov/10.1136/jech.46.5.517"](http://dx.doi.org.ezproxyhhs.nihlibrary.nih.gov/10.1136/jech.46.5.517) \t
"_blank" INCLUDEPICTURE
"http://www.springerlink.com.ezproxyhhs.nihlibrary.nih.gov/content/gt231752274r786p/crossref
_link.gif" * MERGEFORMATINET [HYPERLINK "http://chemport.cas.org/cgi-
bin/sdcgi?APP=ftslink&action=reflink&origin=springer&version=1.0&coi=1%3ASTN%3A280%3ADya
K3s7itl2htw%253D%253D&md5=366d0a590eb86fad10ac81e1ae58a5af"](http://chemport.cas.org/cgi-bin/sdcgi?APP=ftslink&action=reflink&origin=springer&version=1.0&coi=1%3ASTN%3A280%3ADyaK3s7itl2htw%253D%253D&md5=366d0a590eb86fad10ac81e1ae58a5af) \t "_blank"
INCLUDEPICTURE
"http://www.springerlink.com.ezproxyhhs.nihlibrary.nih.gov/content/gt231752274r786p/chempo
rt_link.gif" * MERGEFORMATINET

3 Marin B, Couratier P, Preux PM, Logroscino G. Can mortality data be used to estimate amyotrophic
4 lateral sclerosis incidence? *Neuroepidemiology.* 2011;36:29–38.



3 Preux PM, Druet-Cabanac M, Couratier P, Debrock C, Truong T, Marcharia W, et al. Estimation of
5 the amyotrophic lateral sclerosis incidence by capture-recapture method in the Limousin region of
. France. J Clin Epidemiol. 2000;53:1025–9.



3 Logroscino G, Traynor BJ, Hardiman O, Chio A, Mitchell D, Swingler RJ, et al. Incidence of
6 amyotrophic lateral sclerosis in Europe. J Neurol Neurosurg Psychiatr. 2010;81:385–90.

Supplementary table 1: Mortality rates (per 100,000 person-years) from MND in France during the period 1968-2007 by age group and period of death

Age group	Period of death																Overall	
	1968-1972		1973-1977		1978-1982		1983-1987		1988-1992		1993-1997		1998-2002		2003-2007			
	n*	MR	n	MR	n	MR	n	MR	n	MR	n	MR	n	MR	n	MR	n	MR
<40	106	0.07	91	0.06	87	0.05	103	0.06	100	0.06	102	0.06	74	0.05	56	0.04	719	0.06
40-44	54	0.32	59	0.36	61	0.41	62	0.39	83	0.39	96	0.45	84	0.39	93	0.42	592	0.40
45-49	138	0.85	111	0.67	124	0.78	105	0.72	123	0.79	169	0.81	167	0.79	188	0.88	1125	0.79
50-54	178	1.61	217	1.37	265	1.66	261	1.68	270	1.89	226	1.49	364	1.78	357	1.71	2138	1.66
55-59	312	2.46	302	2.85	427	2.82	412	2.68	465	3.10	406	2.92	416	2.80	592	2.88	3332	2.82
60-64	439	3.31	483	4.05	418	4.17	671	4.67	681	4.65	706	4.92	642	4.79	692	4.90	4732	4.46
65-69	509	4.27	631	5.22	698	6.40	637	6.87	929	6.94	1026	7.49	947	6.99	961	7.49	6338	6.49
70-74	419	4.48	629	6.13	797	7.54	839	8.70	812	9.73	1216	9.99	1305	10.41	1337	10.52	7354	8.59
75-79	219	3.44	391	5.34	601	7.31	728	8.41	835	10.31	816	11.37	1357	12.82	1429	12.84	6376	9.43
80-84	124	3.17	172	4.02	264	5.21	417	7.14	597	9.32	608	9.79	690	12.15	1065	12.11	3937	8.52
85-89	46	2.55	57	2.81	101	4.33	135	4.76	251	7.21	338	8.35	371	9.23	401	11.10	1700	7.04

90-94	12	2.26	13	2.04	22	2.95	29	3.18	63	5.23	70	4.38	124	6.47	121	5.98	454	4.75
≥95	6	6.34	2	1.63	3	1.94	2	1.05	7	2.64	13	3.38	9	1.67	24	3.64	66	2.74
Overall	2562	1.00	3158	1.20	3868	1.44	4401	1.59	5216	1.84	5792	2.00	6550	2.22	7316	2.39	38863	1.74

n, number of deaths from MND; MR, mortality rates

Supplementary table 2: Age-period-cohort (APC) models, overall and in men and women

	Overall	Women	Men
Age	Model 1 (age): mortality rate per 100,000		
40-44	0.40	0.26	0.54
45-49	0.79	0.56	1.03
50-54	1.66	1.25	2.07
55-59	2.82	2.27	3.40
60-64	4.46	3.64	5.38
65-69	6.49	5.27	7.96
70-74	8.59	7.19	10.49
75-79	9.44	7.93	11.83
80-84	8.52	6.96	11.53
85-89	7.04	5.98	9.62
Period of death	Model 3 (age-period): RR (95% CI)		
1968-1972	0.64 (0.61- 0.67)	0.59 (0.55- 0.64)	0.69 (0.65- 0.74)
1973-1977	0.77 (0.73- 0.80)	0.76 (0.71- 0.81)	0.78 (0.73- 0.83)
1978-1982	0.91 (0.87- 0.95)	0.87 (0.82- 0.93)	0.94 (0.89- 1.00)
1983-1987	1.00 (reference)	1.00 (reference)	1.00 (reference)
1988-1992	1.13 (1.08- 1.18)	1.15 (1.08- 1.22)	1.11 (1.05- 1.18)
1993-1997	1.18 (1.13- 1.23)	1.22 (1.15- 1.29)	1.14 (1.08- 1.20)
1998-2002	1.24 (1.19- 1.29)	1.31 (1.24- 1.39)	1.17 (1.11- 1.23)
2003-2007	1.28 (1.24- 1.33)	1.30 (1.23- 1.38)	1.25 (1.19- 1.32)
Cohort of birth	Model 4 (age-cohort): RR (95% CI)		
1883	0.22 (0.17-0.30)	0.21 (0.14-0.31)	0.25 (0.15-0.40)

1888	0.25 (0.22-0.30)	0.23 (0.19-0.28)	0.31 (0.25-0.38)
1893	0.31 (0.29-0.34)	0.30 (0.26-0.34)	0.36 (0.31-0.41)
1898	0.43 (0.41-0.46)	0.42 (0.38-0.45)	0.46 (0.42-0.51)
1903	0.60 (0.57-0.63)	0.55 (0.52-0.59)	0.66 (0.62-0.71)
1908	0.73 (0.70-0.76)	0.72 (0.67-0.76)	0.74 (0.70-0.79)
1913	0.85 (0.82-0.89)	0.81 (0.77-0.86)	0.89 (0.85-0.94)
1918	0.96 (0.92-1.00)	0.95 (0.90-1.01)	0.96 (0.91-1.02)
1923	1.00 (reference)	1.00 (reference)	1.00 (reference)
1928	1.02 (0.99-1.06)	1.03 (0.97-1.08)	1.02 (0.97-1.08)
1933	1.04 (1.00-1.08)	1.04 (0.98-1.11)	1.03 (0.97-1.09)
1938	1.06 (1.01-1.11)	1.04 (0.97-1.13)	1.06 (0.99-1.13)
1943	1.02 (0.96-1.09)	1.01 (0.92-1.11)	1.02 (0.94-1.10)
1948	1.07 (1.00-1.14)	1.01 (0.91-1.13)	1.10 (1.01-1.20)
1953	1.09 (1.00-1.20)	0.93 (0.80-1.09)	1.19 (1.06-1.34)
1958	1.15 (1.00-1.31)	1.05 (0.84-1.33)	1.21 (1.03-1.43)
1963	1.16 (0.92-1.45)	1.13 (0.76-1.67)	1.19 (0.90-1.57)

Relative risks (RR) and 95% CI were computed using Poisson regression (adjusted for age) and correspond to the difference in mortality for a given period or cohort compared to the reference period or cohort.

IMPROVING SURVIVAL IN A LARGE ALS CENTER COHORT

3. IMPROVING SURVIVAL IN A LARGE ALS CENTER COHORT

3.1. Results

Research indicates that the median survival time for ALS is 30 months from onset and 19 months from diagnosis(140). Multidisciplinary care,(27) early use of non-invasive ventilation (NIV),(50) and nutritional support(164) may improve outcome. Riluzole use extends survival (36).

Different clinical factors are associated with worse outcome, including older age at onset, bulbar-onset, and a shorter interval from onset of symptoms to diagnosis (141-147). Poor strength and motor function (132, 145), breathing capacity (145, 148, 149), weight loss (44, 150) and female gender (142, 151, 152) may also predict shorter survival rates.

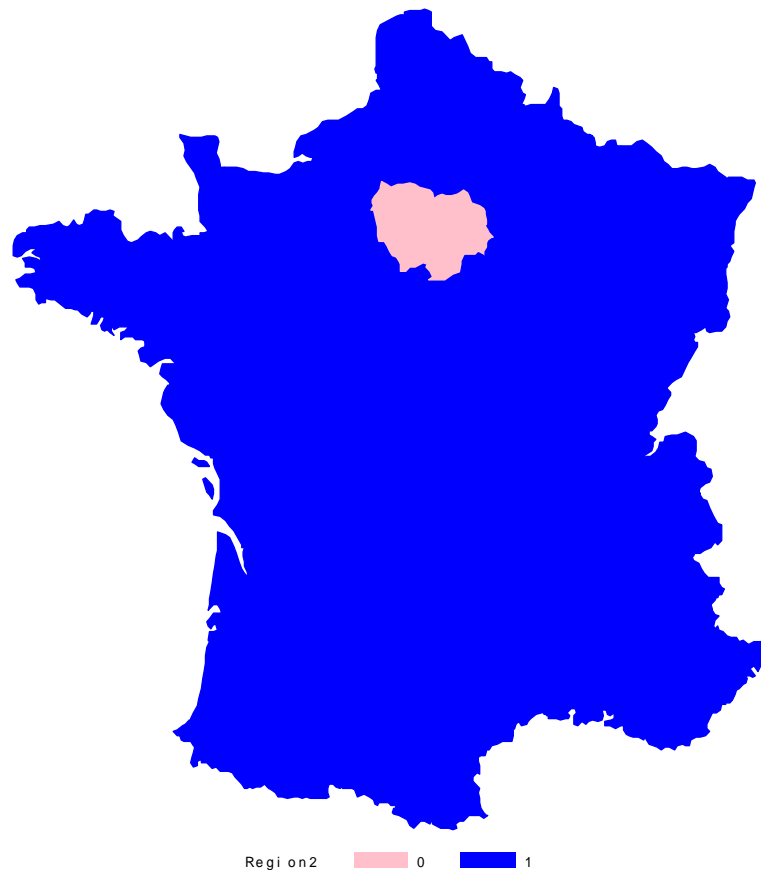
In the 1860s and 70s, Jean-Martin Charcot described different forms of motor neuron disease at the Salpêtrière Hospital, now the largest ALS referral center in France.(175) In 1989, the center developed an electronic database for patients' clinical information; in 1995, a standardized multidisciplinary approach was developed for patient care; In 2002, multidisciplinary care was standardized at centers across France; and in 2004, the Paris center began a more aggressive approach to respiratory management.

The objective of this second part of the research was to analyze survival during 2002- 2009, the years after multidisciplinary care was standardized, to determine whether rates have changed at the Paris center.

Our classification for the French geographic regions is shown in Figure 1.

Figure 1. Region Classification

2 regions, 0 = IDF (75, 92, 93, 94, 77, 78, 91, 95); 1 = REST of France.



The analyses were based on 2037 patients seen in 2002-2009. Clinical parameters changed during that time: patients became older at first visit, were more likely to reside in Paris, came to the clinic sooner after symptom-onset, and had higher baseline ALSFRS-R scores as well as BMI.

On December 31, 2009, 1471 patients had died. Median survival was 2.83 years from onset and 1.65 years from first visit. Survival varied according to year of first visit; ($p < 0.0001$). In Cox proportional hazards models, patients seen after 2007 had better survival. Compared to patients first seen before 2004, the HR of death was 0.97 (95% CI=0.85-1.11, $p=0.6721$) for patients first seen in 2004-2005, 0.96 (95% CI=0.83-1.10, $p=0.5125$) for 2006-2007, and 0.56 (95% CI=0.46-0.69, $p < 0.0001$) after 2007, while adjusting for other predictors of survival.

Limb-onset, longer interval between onset and first visit, and higher ALSFRS-R scores were also associated with better survival ($p < 0.0001$). In multivariable analyses, survival remained significantly better after 2007. Analyses of splines curves showed that survival improved starting in 2006.

Use of NIV also increased after 2006 and could explain the improved survival after that date. Longer observation is needed to determine whether the improved survival persists. Studies of the impact of NIV in population-based studies could determine whether the improvement is being seen in ALS patients generally.

Improving survival in a large French ALS center cohort

Paul H. Gordon^{1,2,4}✉, François Salachas⁴, Gaelle Bruneteau⁴, Pierre-François Pradat⁴, Lucette Lacomblez^{2,4,6}, Jesus Gonzalez-Bermejo^{3,5}, Capucine Morelot-Panzini^{3,5}, Thomas Similowski^{3,5}, Alexis Elbaz^{1,2} and Vincent Meininger^{2,4}

- (1) INSERM, unité U708, F-75013, Neuroépidémiologie, Hôpital de la Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France
- (2) UPMC Univ Paris 06, UMR_S 708, AP-HP, Hôpital de la Salpêtrière, Paris, France
- (3) ER10, AP-HP, Hôpital de la Salpêtrière, Paris, France
- (4) Département des Maladies du Système Nerveux, AP-HP, Hôpital de la Salpêtrière, Paris, France
- (5) Service de Pneumologie et Réanimation Médicale, AP-HP, Hôpital de la Salpêtrière, Paris, France
- (6) Département de Pharmacologie, AP-HP, Hôpital de la Salpêtrière, Paris, France

✉ Paul H. Gordon

Email: paul.gordon@psl.aphp.fr

Received: 3 October 2011 **Revised:** 26 December 2011 **Accepted:** 27 December 2011 **Published online:** 19 January 2012

Abstract

The aim of this work was to determine whether survival changed during 2002–2009 at a French amyotrophic lateral sclerosis (ALS) center. We included all patients with ALS who were seen consecutively at the center from January 2002–May 2009. Participants were followed from date of first visit through death, date of censoring, or December 31, 2009, whichever occurred first. Cox proportional hazard models computed hazard ratios (HR; 95% confidence interval CI) of death, and flexible modeling of continuous predictors (splines) assessed trends in survival. We analyzed a total of 2,037 ALS patients, of whom 1,471 died before the end of follow-up. Median survival was 2.83 years from onset and 1.65 years from first visit. Compared to patients first seen before 2004, the HR of death was 0.97 (95% CI = 0.85–1.11, $p = 0.6721$) for patients first seen in 2004–2005, 0.96 (95% CI = 0.83–1.10, $p = 0.5125$) for 2006–2007, and 0.56 (95% CI = 0.46–0.69, $p < 0.0001$) after 2007, while adjusting for other survival predictors. Spline analysis confirmed that survival remained stable during 2002–2006, then markedly improved. The proportion of patients receiving non-invasive ventilation (NIV) increased from 16 (2004) to 51% (2008). At this large ALS center, survival improved after 2006. Because more aggressive use of NIV was the principal therapeutic adaptation, our data suggest that better survival resulted from improved respiratory care.

Electronic supplementary material The online version of this article (doi:[10.1007/s00415-011-6403-4](https://doi.org/10.1007/s00415-011-6403-4)) contains supplementary material, which is available to authorized users.

Keywords Amyotrophic lateral sclerosis – Survival – ALSFRS-R – Non-invasive ventilation

Introduction

Fifteen years after regulatory approval of riluzole, amyotrophic lateral sclerosis (ALS) is still rapidly progressive for most patients. Population-based studies estimate median survival times of 30 months from onset and 19 months from diagnosis [1]. Some studies indicate that multidisciplinary care [2], early use of non-invasive ventilation (NIV) [3, 4], and nutritional support [5] could contribute to improved prognosis.

We investigated whether survival in ALS changed between 2002 and 2009 at a French ALS referral center.

Methods

Patients

Multidisciplinary care for ALS was standardized at French ALS centers as part of a national program starting in 2002. Multidisciplinary clinic usually occurs every 3 months with various specialists making recommendations about different aspects of treatment. In 2002, the revised ALS Functional Rating Scale (ALSFRS-R) [6] was also instituted to assess functional status, and in 2004, a more systematic approach to NIV was implemented. All patients are evaluated at each visit with clinical examination, arterial blood gases, and nocturnal oxymetry, and referred to the home mechanical ventilation unit of the department of respiratory medicine for possible institution of NIV once any parameter becomes abnormal. Other therapies, including percentage of patients taking riluzole and prescribed gastrostomy, were stable during the study period.

Our analyses are based on all patients who lived in France with a final diagnosis of probable (laboratory or clinically) or definite ALS (revised El Escorial criteria) [7], and seen consecutively at the ALS center of the Salpêtrière Hospital between January 2002 and May 2009. Data collection and reporting was approved by the French data protection agency (Commission Nationale Informatique et Liberté); the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Covariates

From the computerized database maintained at the center, we extracted socio-demographic data (region of residence, sex) and clinical variables that could influence prognosis (date/age at first symptom of weakness; date/age at first visit to the center; site of symptom onset; body mass index, BMI, at first visit; ALSFRS-R score at first visit) [8]. Patients were followed for mortality through contacts with their families or treating physicians and official vital status records.

Statistical analysis

Descriptive statistics examined participants' baseline characteristics by quartiles of year of first visit. Groups were compared using the Mantel–Haenszel Chi-square test for trend (proportions) and analysis of variance using linear contrasts (continuous variables).

For survival analyses, participants were followed from date of first visit through death, date of censoring, or December 31, 2009, whichever occurred first; in sensitivity analyses, we assessed survival starting from symptom onset rather than from first visit. Survival was plotted by quartiles of year of first visit using the Kaplan–Meier method; the logrank test was used for significance testing. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI). Because age at first visit was a strong predictor of survival, we used age as the time-axis [9]. The proportional hazards assumption was verified using Schoenfeld residuals. The proportion of patients living in the Paris region increased with year of first visit; therefore, all analyses were adjusted for region of residence (Paris region vs. rest of France). Continuous predictors were categorized according to quartiles of their distribution. We first performed analyses in which each covariate was entered individually. We then performed multivariable analyses by including all covariates in the same model and using a backwards selection procedure (*p* value of 0.10 for retaining a variable in the model); sex, year of first visit (in quartiles), and region of residence were forced in the model.

Due to the large sample size, we were able to model continuous variables in a more flexible way using splines. We used the mvrs multivariable modeling procedure implemented in STATA 11 that allows modeling natural cubic splines for several variables at the same time [10]. The results of these analyses are presented graphically.

Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and STATA 11 (StataCorp, College Station, TX, USA).

Results

Vital status was not available for 59 (2.8%) of the 2,096 patients seen between January 2002 and May 2009; the analyses are based on 2,037 patients.

As time passed, patients became older at first visit, were more likely to reside in Paris, came to the clinic sooner after symptom-onset, and had higher baseline ALSFRS-R scores and BMI (Table 1).

Findings were similar in analyses stratified by region.

Table 1 Patients' characteristics by time period of first visit

Characteristics	Year of first visit				<i>p</i> *
	≤2003	2004–2005	2006–2007	>2007	
	<i>n</i> = 443	<i>n</i> = 577	<i>n</i> = 558	<i>n</i> = 459	
Mean age, years (SD)	59.5 (12.5)	61.8 (12.3)	62.2 (12.5)	63.0 (12.7)	<0.0001
Male sex, % (<i>n</i>)	53.7 (238)	57.0 (329)	50.2 (280)	57.5 (264)	0.7832
Limb onset, % (<i>n</i>)	73.6 (326)	70.9 (409)	67.2 (375)	69.5 (319)	0.0870

Characteristics	Year of first visit				p*
	≤2003	2004–2005	2006–2007	>2007	
	n = 443	n = 577	n = 558	n = 459	
Residence outside Paris region, % (n)	46.0 (204)	41.1 (237)	38.5 (215)	36.4 (167)	0.0022
Mean time to first visit (SD), months	16.4 (16.1)	16.6 (18.3)	14.4 (17.8)	12.8 (10.9)	<0.0001
Mean BMI (SD), kg/m ²	25.1 (4.2)	25.1 (4.3)	25.3 (4.1)	24.0 (4.1)	0.0026
Mean ALSFRS-R at first visit (SD)	37.4 (6.4)	37.7 (6.3)	38.4 (5.9)	38.3 (6.4)	0.0070

The cut-offs for the time periods were determined based on the quartiles of the distribution

* p values were computed using the Mantel–Haenszel Chi-square test for trend for proportions and analysis of variance using linear contrasts for continuous variables

On December 31, 2009, 1,471 of the patients had died. Median survival was 2.83 years from onset of weakness and 1.65 years from first visit. Survival varied according to year of first visit; ($p < 0.0001$, Supplementary Figure 1); the curve for patients seen after 2007 separated from the curves for earlier periods soon after the first visit. In Cox proportional hazards models (Table 2, model 1), patients seen after 2007 had better survival: compared to patients first seen before 2004, the HR of death was 0.97 (95% CI = 0.85–1.11, $p = 0.6721$) for patients first seen in 2004–2005, 0.96 (95% CI = 0.83–1.10, $p = 0.5125$) for 2006–2007, and 0.56 (95% CI = 0.46–0.69, $p < 0.0001$) after 2007, while adjusting for other survival predictors. Limb-onset, longer interval between onset and first visit, and higher ALSFRS-R scores were also associated with better survival ($p < 0.0001$). Similar patterns were noted in analyses stratified by region of residence (Supplementary Tables 1, 2) or when survival was assessed from onset (data not shown). In multivariable analyses (Table 2, model 2), survival remained significantly better after 2007. Analyses based on flexible modeling of continuous variables (Fig. 1) showed that survival was stable between 2002 and 2006, then markedly improved. Survival also improved with increasing baseline ALSFRS-R score and delay between onset and first visit (Supplementary Figure 2).

Table 2 Baseline predictors of survival after first visit

Covariate	Coding	Deaths (n)	Median survival (years)	Model 1 ^{a,*}		Model 2 ^{b,*}	
				HR (95% CI)	p value	HR (95% CI)	p value
Region of residence	Rest of France	586	1.73	1.00 (reference)	–	1.00 (reference)	–
	Paris region	885	1.59	1.01 (0.91–1.12)	0.8650	0.96 (0.86–1.07)	0.4543
Year of first visit ^c	≤2003	414	1.60	1.00 (reference)	–	1.00 (reference)	–
	2004–2005	505	1.49	0.97 (0.85–1.11)	0.6721	0.97 (0.85–1.11)	0.6721
	2006–2007	413	1.60	0.96 (0.83–1.10)	0.5125	0.96 (0.83–1.10)	0.5125

Covariate	Coding	Deaths (n)	Median survival (years)	Model 1 ^{a,*}		Model 2 ^{b,*}	
				HR (95% CI)	p value	HR (95% CI)	p value
	>2007	139	–	0.56 (0.46–0.65)	<0.0001	0.56 (0.46–0.69)	<0.0001
Sex	Women	685	1.54	1.00 (reference)	–	1.00 (reference)	–
	Men	786	1.77	0.96 (0.86–1.06)	0.4042	1.04 (0.94–1.16)	0.4362
Site of onset	Bulbar	485	1.37	1.00 (reference)	–	1.00 (reference)	–
	Limb	986	1.84	0.74 (0.67–0.83)	<0.0001	0.68 (0.61–0.77)	<0.0001
Time to first visit (months) ^c	≤7.0	373	1.61	1.00 (reference)	–	1.00 (reference)	–
	7.1–10.6	360	1.52	1.01 (0.87–1.17)	0.8877	0.95 (0.82–1.09)	0.4493
	10.7–17.0	381	1.63	0.88 (0.76–1.02)	0.0869	0.80 (0.70–0.93)	0.0032
	>17.0	357	1.84	0.74 (0.64–0.86)	<0.0001	0.56 (0.48–0.66)	<0.0001
ALSFRS-R score at first visit ^c	≤35	466	0.92	1.00 (reference)	–	1.00 (reference)	–
	36–39	378	1.35	0.74 (0.65–0.85)	<0.0001	0.69 (0.60–0.80)	<0.0001
	40–42	333	1.93	0.50 (0.44–0.58)	<0.0001	0.46 (0.40–0.53)	<0.0001
	>42	290	2.41	0.42 (0.35–0.49)	<0.0001	0.33 (0.28–0.39)	<0.0001
BMI at first visit (kg/m ²) ^c	<18.5	125	1.53	1.08 (0.90–1.32)	0.4039	–	–
	18.5–24.9	710	1.69	1.00 (reference)	–	–	–
	25–29.9	496	1.65	1.10 (0.98–1.23)	0.1147	–	–
	≥30.0	139	1.55	1.08 (0.90–1.29)	0.4275	–	–

* HR (95% CI) and *p* values were computed using a Cox proportional hazards model with age as the time axis. All the variables met the proportionality assumption

^aA separate Cox model was built for each covariate and adjusted for region of residence

^bMultivariable model. All covariates were included in the initial model; we used a backwards stepwise selection procedure with a *p* value of 0.10 for retaining a variable in the model. Sex, year of first visit, and region of residence were forced in the model. BMI was not retained in the model (*p* = 0.4024)

°Cut-offs were determined based on the quartiles of the distribution of the covariates; cut-offs for BMI were defined by the World Health Organization

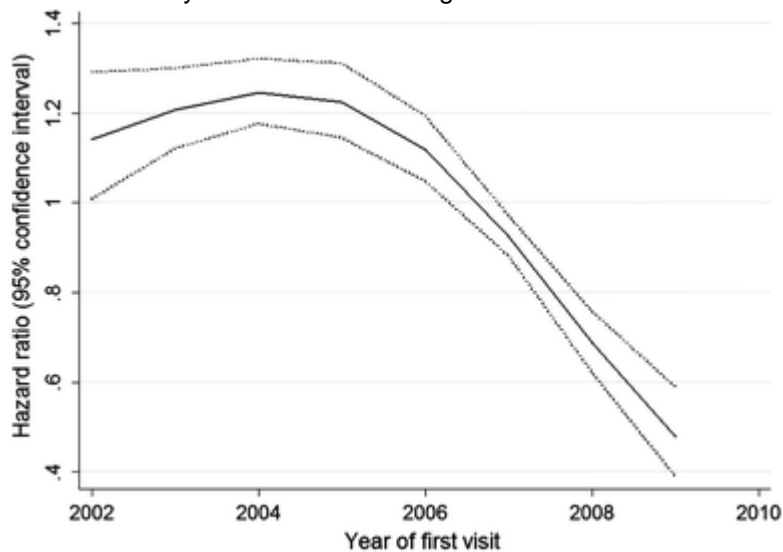


Fig. 1 Hazard ratio of death from a multivariable Cox proportional hazard model including year of first visit modeled as a natural cubic spline. The *solid line* represents the hazard ratio and the *dotted lines* represent the 95% confidence interval

Discussion

We found a changing survival pattern over time at a French ALS referral center. After adjusting for covariates that influence prognosis, patients first seen after 2007 had a reduced risk of death compared to earlier years. The median survival after disease onset was nearly 24 months longer in the most contemporary cohort than in the reference group.

The main potential explanations are changes in patients' characteristics or in respiratory therapy. Patients' characteristics evolved over time, but in analyses adjusted for changing characteristics using a flexible method to model continuous variables, survival was still significantly better in more recent years. In addition, while patients' characteristics changed progressively over the study period, mortality was stable between 2002 and 2006 and the improvement in survival was restricted to the last years. Finally, we performed analyses restricted to patients residing in the Paris region, who are more likely to be representative of all ALS patients, and found similar results. It is therefore unlikely that changing characteristics of the patients entirely explains improved survival.

In recent years, more aggressive respiratory management has been instituted at the center. The proportion of patients receiving NIV increased from 16% in 2004 to 31% in 2006 and to 51% in 2008, while the medical team and other methods of care remained the same, strongly suggesting that the dramatic increase in the use of NIV contributed to the improved survival seen in recent years. The approach to other therapies, including riluzole (98% of patients in each time period), gastrostomy (approximately 12% of patients in each time period; $p = 0.6862$ for the difference between periods and $p = 0.8688$ for the effect of gastrostomy on survival), and multi-disciplinary care, was stable during the study.

Other studies have also reported improvements in survival over time. In a center-based study, the rate of functional decline and survival both improved in patients seen after 1999 compared to 1984–1999 [11]. That study used Kaplan–Meier and Cox proportional hazards methodology to examine survival rate and time to functional decline in 1,041 patients seen over 20 years. The investigators found improved survival of approximately 1 year and slower deterioration on the Appel Scale in contemporary patients. Patients’ clinical and demographic features, as in our study, also changed with time, but the improved survival persisted even when these variables were controlled for in the analyses; there was no effect of riluzole, gastrostomy, or NIV use in that study. The authors speculated that the course of ALS itself may have improved with time or that unmeasured clinical factors could have been at play. An analysis of patients enrolled in the placebo arm of clinical trials conducted between 1999 and 2005 also showed improved survival over time [12]. It is unclear, however, to what extent potential selection biases and evolving methods of care contributed to these findings.

Strengths of this study include the large number of patients who were consecutively recruited and who underwent standardized assessment of several ALS prognostic factors. The main limitations of the study are that the data derive from a single referral center and do not represent the French ALS population as a whole, and that we did not include a population-based sample; however, we adjusted our analyses for important prognostic factors and analyses restricted to patients residing in Paris yielded similar conclusions. Parameters of respiratory care could not be included in the analyses. There were large numbers of missing values for vital capacity that varied according to time, and use of NIV was not recorded directly in the database. Direct measures of respiratory function and treatment were therefore not available for use as covariates, and attempts to include them in the analyses would have introduced bias and excessive missing data. The link between use of NIV and survival rate resulted from descriptive statistics showing concurrent increases. Other variables that changed during the study were controlled for in the analyses, and the period of the study was chosen because other treatments, including multi-disciplinary care, were stable. The standard of multi-disciplinary care was set in 2002 and was unchanged other than increased use of NIV thereafter. No new treatments besides NIV were introduced and there were no positive trials impacting survival between 2002 and 2009.

In this large center-based cohort, survival improved markedly after 2006, likely due to increased NIV use. Longer observation of these patients is needed to determine whether the improved survival pattern persists. Detailed studies of the impact of NIV on survival in ALS are needed in population-based studies to determine whether the improvement is being seen in ALS patients generally.

Conflicts of interest None.
























Electronic supplementary material

Below is the link to the electronic supplementary material.

[Supplementary material 1 \(DOC 84 kb\)](#)

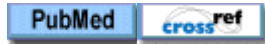
[Supplementary material 2 \(JPEG 44 kb\)](#)

References

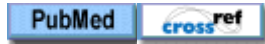
1. Logroscino G, Traynor BJ, Hardiman O et al (2008) Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry* 79:6–11
  
2. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O (2003) Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000. *J Neurol Neurosurg Psychiatry* 74:1258–1261
  
3. Aboussouan LS, Khan SU, Banerjee M, Arroliga AC, Mitsumoto H (2001) Objective measures of the efficacy of noninvasive positive-pressure ventilation in amyotrophic lateral sclerosis. *Muscle Nerve* 24:403–409
  
4. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ (2006) Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol* 5:140–147
 
5. Chio A, Finocchiaro E, Meineri P, Bottacchi E, Schiffer D (1999) Safety and factors related to survival after percutaneous endoscopic gastrostomy in ALS. ALS percutaneous endoscopic gastrostomy study group. *Neurology* 53:1123–1125
 
6. Cedarbaum JM, Stampler N, Malta E, Fuller C et al (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS study group (Phase III). *J Neurol Sci* 169:13–21
  
7. Brooks BR, Miller RG, Swash M, Munsat TL (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 1:293–299
  
8. Chio A, Logroscino G, Hardiman O et al (2009) Prognostic factors in ALS: a critical review. *Amyotroph Lateral Scler* 10:310–323
 
9. Thiebaut AC, Benichou J (2004) Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 23:3803–3820
 
10. Royston P, Sauerbrei W (2007) Multivariable modeling with cubic regression splines: a principled

approach. *Stata J* 7:45–70

11. Czaplinski A, Yen AA, Simpson EP, Appel SH (2006) Slower disease progression and prolonged survival in contemporary patients with amyotrophic lateral sclerosis: is the natural history of amyotrophic lateral sclerosis changing? *Arch Neurol* 63:1139–1143



12. Qureshi M, Schoenfeld DA, Paliwal Y, Shui A, Cudkowicz ME (2009) The natural history of ALS is changing: improved survival. *Amyotroph Lateral Scler* 10:324–331



Supplementary Table 1. Baseline Predictors of Survival After First Visit: Analyses Restricted to Patients Residing in the Paris Region

Covariate	Coding	N deaths	Median	Model 1*†		Model 2*‡	
			survival (years)	HR (95% CI)	p-value	HR (95% CI)	p-value
Year of first visit§	≤2003	222	1.66	1.00 (reference)	--	1.00 (reference)	--
	2004-2005	305	1.45	1.04 (0.87-1.24)	0.9862	0.95 (0.79-1.14)	0.5734
	2006-2007	261	1.47	1.00 (0.83-1.20)	0.9973	0.92 (0.77-1.12)	0.4141
	>2007	97	--	0.64 (0.50-0.81)	0.0003	0.55 (0.43-0.71)	<0.0001
Sex	Women	421	1.44	1.00 (reference)	--	1.00 (reference)	--
	Men	464	1.70	0.96 (0.84-1.10)	0.5659	1.08 (0.94-1.25)	0.2602
Site of onset	Bulbar	312	1.32	1.00 (reference)	--	1.00 (reference)	--
	Limb	573	1.83	0.77 (0.67-0.89)	0.0004	0.69 (0.60-0.81)	<0.0001
Time to first visit (months)§	≤7.0	246	1.52	1.00 (reference)	--	1.00 (reference)	--
	7.1-10.6	233	1.47	1.01 (0.84-1.21)	0.9485	0.94 (0.79-1.12)	0.4980
	10.7-17.0	217	1.60	0.86 (0.71-1.04)	0.1104	0.78 (0.64-0.94)	0.0093
	>17.0	189	1.95	0.73 (0.60-0.89)	0.0016	0.54 (0.44-0.67)	<0.0001
ALSFRS-R score at first visit§	≤35	280	0.85	1.00 (reference)	--	1.00 (reference)	--
	36-39	217	1.23	0.76 (0.63-0.91)	0.0028	0.73 (0.61-0.88)	0.0008
	40-42	187	1.97	0.53 (0.44-0.64)	<0.0001	0.46 (0.38-0.56)	<0.0001
	>42	197	2.40	0.44 (0.36-0.53)	<0.0001	0.34 (0.28-0.42)	<0.0001
BMI at first visit (kg/m ²)§	<18.5	85	1.38	1.08 (0.85-1.37)	0.5200	--	--
	18.5-24.9	432	1.67	1.00 (reference)	--	--	--
	25.0-29.9	293	1.61	1.11 (0.96-1.29)	0.1702	--	--
	≥30	75	1.52	1.01 (0.79-1.30)	0.9284	--	--

* HR (95% CI) and p-values were computed using a Cox proportional hazards model with age as the time axis. All the variables met the proportionality assumption.

† A separate Cox model was built for each covariate.

‡ Multivariable model. All covariates were included in the initial model; we used a backwards stepwise selection procedure with a p-value of 0.10 for retaining a variable in the model. Sex and year of first visit were forced in the model. BMI was not retained in the model (P=0.2830).

§ Cutoffs were determined based on the quartiles of the distribution of the covariates; cutoffs for BMI defined by the World Health Organization.

Supplementary Table 2. Baseline Predictors of Survival After First Visit: Analyses Restricted to Patients Residing in the Rest of France

Covariate	Coding	N deaths	Median	Model 1*†		Model 2*‡	
			survival (years)	HR (95% CI)	p-value	HR (95% CI)	p-value
Year of first visit§	≤2003	192	1.55	1.00 (reference)	--	1.00 (reference)	--
	2004-2005	200	1.53	0.93 (0.76-1.14)	0.4872	0.99 (0.81-1.22)	0.9350
	2006-2007	152	1.74	0.92 (0.74-1.14)	0.4517	0.94 (0.75-1.17)	0.5649
	>2007	42	--	0.47 (0.34-0.66)	<0.0001	0.43 (0.31-0.61)	<0.0001
Sex	Women	264	1.64	1.00 (reference)	--	1.00 (reference)	--
	Men	322	2.47	1.00 (0.85-1.19)	0.9632	1.02 (0.86-1.21)	0.8008
Site of onset	Bulbar	173	1.54	1.00 (reference)	--	1.00 (reference)	--
	Limb	413	1.84	0.72 (0.60-0.86)	0.0004	0.67 (0.55-0.81)	<0.0001
Time to first visit (months)§	≤7.0	127	1.76	1.00 (reference)	--	1.00 (reference)	--
	7.1-10.6	127	1.66	1.02 (0.80-1.31)	0.8522	1.00 (0.79-1.28)	0.9665
	10.7-17.0	164	1.65	0.94 (0.74-1.18)	0.5722	0.86 (0.68-1.09)	0.2224
	>17.0	168	1.80	0.75 (0.60-0.95)	0.0172	0.58 (0.45-0.74)	<0.0001
ALSFRS-R score at first visit§	≤35	186	1.01	1.00 (reference)	--	1.00 (reference)	--
	36-39	161	1.56	0.70 (0.56-0.87)	0.0011	0.62 (0.50-0.78)	<0.0001
	40-42	146	1.90	0.48 (0.38-0.60)	<0.0001	0.45 (0.36-0.56)	<0.0001
	>42	93	2.42	0.40 (0.31-0.51)	<0.0001	0.32 (0.24-0.41)	<0.0001
BMI at first visit (kg/m²)§	<18.5	40	1.89	1.00 (0.71-1.40)	0.9815	--	--
	18.5-24.9	278	1.76	1.00 (reference)	--	--	--
	25.0-29.9	203	1.68	1.05 (0.87-1.26)	0.5984	--	--
	≥30	64	1.62	1.14 (0.86-1.50)	0.3648	--	--

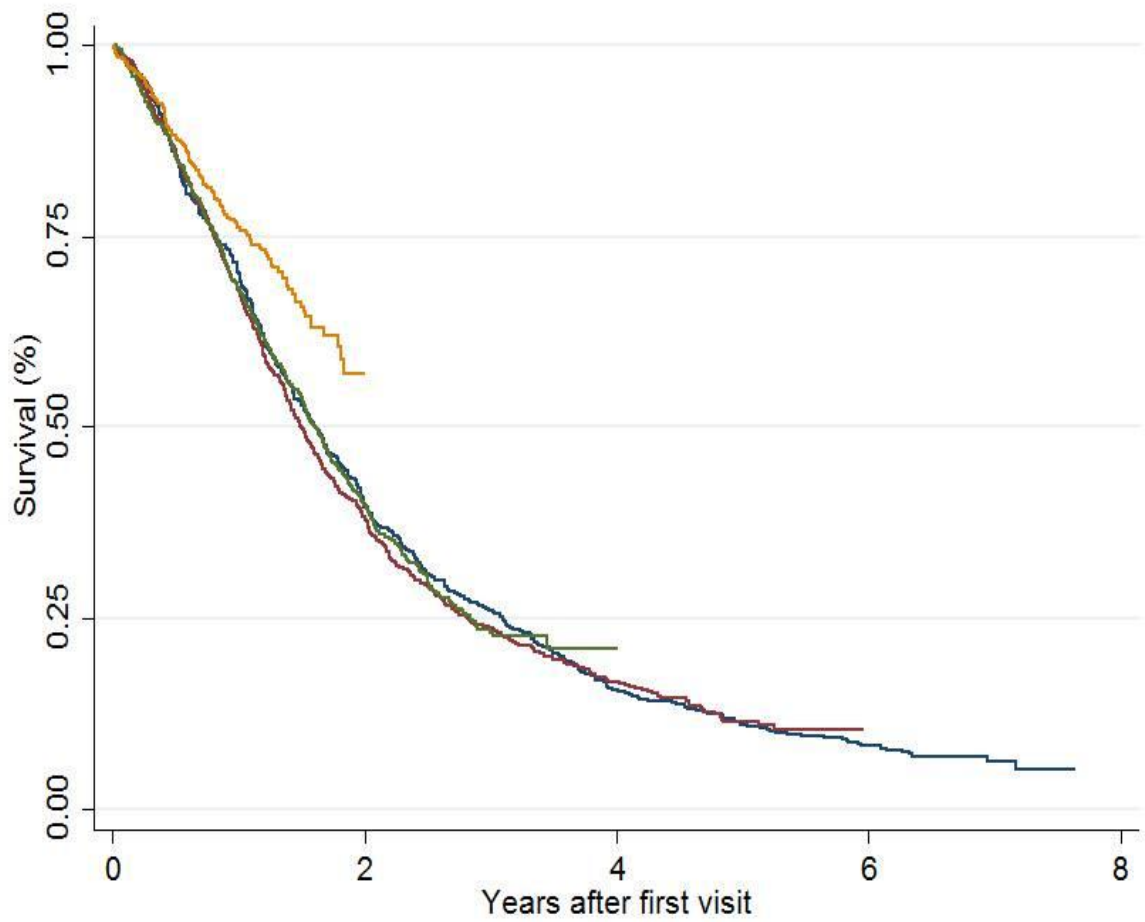
* HR (95% CI) and p-values were computed using a Cox proportional hazards model with age as the time axis. All the variables met the proportionality assumption.

† A separate Cox model was built for each covariate.

‡ Multivariable model. All covariates were included in the initial model; we used a backwards stepwise selection procedure with a p-value of 0.10 for retaining a variable in the model. Sex and year of first visit were forced in the model. BMI was not retained in the model (P=0.9999).

§ Cutoffs were determined based on the quartiles of the distribution of the covariates; cutoffs for BMI defined by the World Health Organization.

eFigure 1: Kaplan-Meier survival curves in ALS patients by time period of first visit (<2003, blue line; 2004-2005, red line; 2006-2007, green line; >2007, orange line) (logrank test, $P < 0.001$)



**PREDICTING SURVIVAL IN ALS AT
PRESENTATION: A 15-YEAR
EXPERIENCE**

4. PREDICTING SURVIVAL IN ALS AT PRESENTATION: A 15-YEAR EXPERIENCE

4.1. Results

Amyotrophic lateral sclerosis (ALS) is still an incurable disorder without known cause. No unique phenotypes have been identified that have clearly distinct survival patterns to suggest common etiologies. Survival prediction is important to patients, physicians and researchers.

We analyzed baseline features to report patient and disease prognostic factors at the ALS Center at the Salpêtrière Hospital from 1995, the year multidisciplinary care was developed through 2009. This dataset included 3830 patients. We analyzed a separate dataset starting in 2002 that included 2037 patients.

Patients residing in Paris were older ($p < 0.0001$), more likely to be women ($p = 0.012$) and to have bulbar-onset ($p = 0.0097$), weigh less ($p < 0.0001$), and have better strength ($p < 0.0001$) than those residing in the rest of France.

Similar to the previous project, we found that as time passed, patients became older ($p = 0.0007$), were more likely to reside in Paris ($p < 0.0001$), came to the clinic sooner after symptom-onset ($p < 0.0001$), and were stronger at baseline ($p < 0.0001$).

3211 patients had died by the end of the follow-up. Median survival after disease onset was of 2.80 years overall, and was shorter for patients from the Paris region (2.66 years) than the rest of France (3.00 years) (logrank, $p = 0.0004$). The median survival times from first visit to the center were 1.60 years overall (1.68 years for Paris and 1.52 years for the rest of France; Logrank $p = 0.0033$). The HR of death from a Cox-model was 0.88 (95% CI=0.82-0.95, $p < 0.0001$) for the Paris region versus the rest of France, a difference explained mainly by age at first visit: in a Cox model with age as the time axis, the HR of death for the Paris region was no longer significant (HR=1.01, 95% CI=0.94-1.09, $p = 0.70$).

Age at baseline was a strong predictor of survival (logrank, $p < 0.0001$). The HR of death per an increase of 10 years was 1.36 (95% CI=1.32-1.40, $p < 0.0001$). Age was therefore used as the time axis in subsequent analyses.

In univariate Cox Proportional Hazards models adjusted for region of residence and age, limb-onset ($p < 0.0001$), time to first visit longer than 18 months ($p < 0.0001$), better muscle strength ($p < 0.0001$), and the year of first visit beyond 2006 ($p < 0.0001$) were associated with better survival; higher BMI at baseline was associated with worse survival ($p = 0.012$). Similar patterns were noted in analyses stratified by region of residence.

Using stepwise entry in Multivariable Cox Proportional Hazards models, living in the Paris region was no longer associated with worse survival and BMI was not retained in the final model. Gender was not associated with survival in univariate analyses, but men had worse survival in the multivariate models. The time periods 1995-1998 and greater than 2006 had better survival than the reference period. Limb-onset, increasing time to first visit, and increasing MMT score were also associated with better survival. Analyses based on region of residence and the shorter time period (2002-2009) yielded similar findings except that survival improved in recent years only.

In this large center-based study, similar to other reports, site-of-onset, strength, age, and time to first visit, were the strongest predictors of survival. The patients with the longest survival were younger, had limb-onset and high motor function, and took more than 18 months to reach the center. Future studies might better define subgroups based on clinicopathological correlation. However, clear subtypes may only be defined after etiologies are discovered.

Predicting Survival in ALS at Presentation: a 15-Year Experience

Paul H. Gordon, MD, François Salachas, MD, Lucette Lacomblez, MD, Nadine Le Forestier, MD, Pierre-François Pradat, MD, PhD, Gaëlle Bruneteau, MD, Alexis Elbaz, MD, PhD, and Vincent Meininger, MD, PhD

UPMC Univ Paris 06, UMR_S 708 (PHG, AE, VM); INSERM, U708, F-75013 (AE); AP-HP, Hôpital de la Salpêtrière, Département des Maladies du Système Nerveux (PHG, PFP, GB, FS, LL, VM); UPMC Univ Paris 06, Département de Pharmacologie (LL); and INSERM, U 678 (LL) Paris, France.

Key words: amyotrophic lateral sclerosis, survival, manual muscle testing, prognostic factors

Accepted for publication in: Neurodegenerative Diseases

Date of acceptance: June 8, 2012

Character count (title): 96

Word count (abstract): 233

Word count (text): 2917

Correspondance:

Paul H. Gordon, MD
Fédération des Maladies du Système Nerveux
Centre référent maladie rare SLA
Hôpital de la Pitié-Salpêtrière
47-83, Boulevard de l'Hôpital
75651 Paris France
paul.gordon@psl.aphp.fr

ABSTRACT

Objective: To describe the clinical features at first evaluation that best predict survival in the ALS population from the Salpêtrière Hospital, 1995-2009.

Methods: Data are collected and entered into a clinical database from all patients seen at the Paris ALS Center. Variables analyzed were demographic and baseline information, strength testing (MMT; 1995-2009), ALS Functional Rating Scale (ALSFRS-R; 2002-2009) and survival status. Chi-square and ANOVA assessed differences in variables by region and across time period. Univariate and multivariate Cox proportional hazards models determined which variables best predicted survival. Flexible modeling of continuous predictors (splines) assessed trends in survival for different variables.

Results: 3885 patients with ALS were seen in 1995-2009, of whom 2037 had ALSFRS-R scores. Age, weight, strength, and site of onset varied by region of residence. The proportion of patients living outside Paris, the time to first visit, patient age, and motor function differed across time periods. In Cox models, site of onset, time to first visit greater than 18 months, strength and the year of visit after 2006 predicted survival (all p-values<0.0001). Compared to patients first seen in 1999-2002, the hazard ratio of death was 1.04 (95% CI= 0.95-1.14) for 2003-2006, and 0.76 (95% CI= 0.66-0.87) after 2006, while adjusting for other predictors of survival. The use of non-invasive ventilation increased during 2004-2006 from 16-51% of patients.

Conclusions: Older age, bulbar-onset, shorter delay to first visit and poor motor function at first visit predicted shorter survival rates in this large center-based sample from France, showing marked consistency across time and region of residence. Survival improved after 2006, concurrent with increasing rates of non-invasive ventilation use. Clinico-pathologic correlation could better define subgroups, but identification of etiologies may be needed to elucidate individual forms of ALS with unique survival patterns.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is still an incurable disorder that is rapidly progressive for most patients. The median survival is less than three years from onset (140), but the disease can be unpredictable, with some patients surviving several months and others decades. No unique phenotypes have been identified that have clearly distinct survival patterns to suggest common etiologies.

Numerous studies have reported a variety of factors that are associated with shorter survival, including older age at onset, bulbar-onset symptoms, and a shorter interval from onset of symptoms to diagnosis (141-147). Poor strength and motor function (132, 145) or breathing capacity (145, 148, 149), as well as weight loss (44, 150) and female sex (142, 151, 152) have also been reported to predict shorter survival rates in some studies.

We analyzed baseline features and survival rates to report patient and disease prognostic factors at the ALS Center at the Salpêtrière Hospital, the largest ALS referral center in France.

METHODS

Patients

Multidisciplinary care was instituted at the Center in 1995. Since that time, patients have been referred to the Center from throughout France, and then referred by one of the Center neurologists for multidisciplinary care, where patients are evaluated by specialists on different aspects of ALS. In 2005, a more aggressive approach to respiratory care was taken in which patients were referred for prescription of non-invasive ventilation once they develop evidence of respiratory insufficiency by clinical, respiratory function or arterial blood gas examination.

Our analyses are based on all patients who lived in France, met revised El Escorial criteria for definite, probable or laboratory-supported probable ALS(14) and who were seen consecutively at the ALS Center from the Salpêtrière Hospital between January 1, 1995 and May 31, 2009. Patients who had a diagnosis other than ALS were excluded.

Data collection and analysis was approved by the Commission Nationale Informatique et Liberté, which oversees the ethical protection and reporting of research data in France.

Covariates

The following socio-demographic and clinical variables were extracted for all patients from the Center's database: region of residence; gender; date and age at first symptom of weakness; date of and age at first visit to the center; site of symptom onset; body mass index (BMI, kg/m²) at first visit; manual strength testing (MMT) score of 30 muscles using the Medical Research Council Scoring at first visit (124); and, beginning in 2002, the revised ALS Functional Rating Scale score (ALSFRS-R) (127) at first visit.

Mortality

Patients were followed for mortality both through contacts with their families or treating physicians and through the national mortality register until December 31, 2009. Mortality was taken as the time of death and did not include tracheostomy in the definition. Tracheostomy rate was less than 5% throughout the study.

Statistical analysis

Two separate sets of analyses were performed: (i) analyses based on the entire study period in which the baseline MMT score was available for all patients (MMT dataset); (ii) analyses based on patients recruited in 2002 and after for whom a baseline ALSFRS-R was available (ALSFRS-R dataset). For both datasets, we excluded patients for whom the delay between the first visit and the first available MMT or ALSFRS-R score was longer than 6 months.

Descriptive statistics examined participants' baseline characteristics by region of residence, Paris and suburbs (Paris region) vs. the rest of France, and time period defined by the quartiles of its distribution. To assess whether patients' characteristics varied by time period according to their region of residence, we repeated these analyses in patients living in the Paris region and in patients who lived in the rest of France. The Mantel-Haenszel chi-square test for trend (proportions) and analysis of variance using linear contrasts for continuous variables compared differences in groups defined by region of residence and by time period.

For survival analyses, participants were followed from entry through death or date of censoring alive or December 31, 2009, whichever occurred first. Survival was plotted by baseline characteristics using the Kaplan-Meier method. The logrank test was used for statistical testing. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Because age at study entry was a strong predictor of survival, we used age as the time-axis (176). The proportional hazards assumption was

verified using Schoenfeld residuals. All analyses were first performed overall while adjusting for region of residence (Paris region *versus* rest of France); analyses were subsequently stratified by region of residence.

We first conducted univariate analyses in which each covariate was entered separately. We then performed multivariate analyses including variables associated with mortality at the 0.05 significance level and we used a backwards stepwise selection procedure with a p-value of 0.10 for staying in the model. Sex, time period (in quartiles) and region of residence were forced in these models.

Due to the large sample size, we also modeled continuous predictors in a flexible way using splines (177). We used the *mvars* multivariable modeling procedure implemented in STATA 11 that allows modeling natural cubic splines for several variables at the same time(178); all models were adjusted for region of residence and sex and used age as the time axis. The results of these analyses are presented graphically.

The analyses were performed using SAS v9.2 (SAS Institute, INC., Cary, North Carolina) and STATA 11 (StataCorp LP, Texas, USA).

RESULTS

Patients

Of 3990 patients living in France with a final diagnosis of ALS and seen consecutively at the Salpêtrière ALS center between January 1, 1995, and May 31, 2009, we were unable to obtain the vital status for 105 (2.6%); we also excluded 55 (1.4%) patients for whom the delay between the first visit and the first available MMT score was longer than 6 months. The MMT dataset therefore included 3830 patients. Of 2096 patients seen between January 1, 2002, and May 31, 2009, we were unable to obtain the vital status for 59 (2.8%); the delay between the first visit and the first available ALSFRS-R score was shorter than 6 months for all patients. The ALSFRS-R dataset therefore included 2037 patients, whose survival rate was previously reported (52). Thirty six patients were present only in the ALSFRS-R dataset, 1829 patients were present only in the MMT dataset, and 2001 patients were present in both datasets.

Baseline Differences by Region

Analysis of baseline differences by region of residence using the MMT dataset (1995-2009)(Table 1) showed that patients residing in Paris were older ($p<0.0001$), more likely to be women ($p=0.012$) and to have bulbar-onset ($p=0.0097$), weigh less ($p<0.0001$), and have better strength ($p<0.0001$) than those residing in the rest of France. Findings were similar in analysis of the ALSFRS-R dataset (2002-2009; Table 1), except gender and function as defined by the ALSFRS-R score were balanced between regions.

Baseline Differences by Time Period

Analysis of the MMT dataset showed that as time passed, patients became older ($p=0.0007$), were more likely to reside in Paris ($p<0.0001$), came to the clinic sooner after symptom-onset ($p<0.0001$), and were stronger at baseline ($p<0.0001$) (Table 2). Similar findings were

observed for the ALSFRS-R dataset (Table 2); baseline BMI also differed by time period in this dataset ($p=0.0026$). Findings were similar when analyses were stratified by region in each dataset (supplementary table 1).

Survival

Of the 3830 patients included in the MMT dataset, 3211 (1795 from the Paris region and 1416 from the rest of France) had died by the end of the follow-up. Median survival after disease onset was of 2.80 years overall; it was shorter for patients from the Paris region (2.66 years) than for those from the rest of France (3.00 years) (logrank, $p=0.0004$). The median survival times from first visit to the center were 1.60 years overall, 1.68 years for those residing in Paris and 1.52 years for those from the rest of France (Logrank $p=0.0033$ for the difference between regions; Figure 1). The HR of death from a Cox-model was of 0.88 (95% CI=0.82-0.95, $p<0.0001$) for the Paris region versus the rest of France; this difference was mainly explained by age at first visit: in a Cox model with age as the time axis, the HR of death for the Paris region was no longer significant (HR=1.01, 95% CI=0.94-1.09, $p=0.70$).

Of 2037 patients in the ALSFR-R dataset, 1471 (885 from Paris and 586 from the rest of France) had died by study conclusion. Median survival times were 2.83 years from onset and 1.65 from first visit overall; 2.72 years from onset and 1.60 years from first visit for those residing in Paris; and 3.01 years from onset and 1.74 years from first visit for those residing outside Paris. A significant difference in median survival after first visit by region (Logrank $p=0.023$) was again explained by age at first visit: in a Cox model using age as the time axis, the HR of death for the Paris region was not significantly different than from the rest of France (HR =0.99, 95% CI=0.89-1.10, $p=0.86$).

Predictors of survival

Age at baseline was a strong predictor of survival (supplementary figure 1, logrank, $p < 0.0001$). The HR of death per an increase of 10 years was 1.36 (95% CI=1.32-1.40, $p < 0.0001$).

In univariate Cox Proportional Hazards models (MMT dataset) adjusted for region of residence and using age as the time axis, limb-onset ($p < 0.0001$), time to first visit longer than 18 months ($p < 0.0001$), higher muscle strength ($p < 0.0001$), and the year of first visit beyond 2006 ($p < 0.0001$) were associated with better survival, while higher BMI at baseline was associated with worse survival ($p = 0.012$) (Table 3). Similar patterns were noted in analyses stratified by region of residence.

In the ALSFRS-R dataset (Table 3), univariate models showed that limb-onset ($p = 0.0004$), time to first visit longer than 17 months ($p < 0.0001$), higher MMT ($p < 0.0001$), higher ALSFRS-R ($p < 0.0001$) scores, and year of first visit later than 2007 ($p < 0.0001$) predicted better survival. The ALSFRS-R was a significant predictor of survival when examined by quartiles or its median value of 39. In a cox model controlling for age and region, patients with a score higher than 39 had 0.54 times the hazard (95% CI = 0.48-0.60) as those with scores ≤ 39 ($p < 0.0001$). Higher BMI was associated with poorer survival but this association was not significant and BMI was not included in the multivariable model. Similar patterns were noted in analyses stratified by region of residence.

Multivariable Cox Proportional Hazards Models

The results of the multivariable analysis are shown in Tables 4 and 5. In analyses based on the MMT dataset, after adjustment for the other covariates, living in the Paris region was no longer associated with worse survival and BMI was not retained in the final model. While gender was not associated with survival in univariate analyses, men had worse survival than women after including the other covariates in the model, in particular MMT and site of onset.

The time periods 1995-1998 and greater than 2006 had better survival than the reference period. Limb-onset, increasing time to first visit, and increasing MMT score were all associated with better survival. These findings are summarized graphically using spline modeling in left part of Figure 2. The HR for the major predictors of survival were very similar no matter where the patients originated.

Analyses based in the ALSFRS-R dataset (Table 5) yielded similar findings except that gender was not associated with survival and survival improved in recent years only. These findings are summarized graphically using spline modeling in the right part of Figure 2; as shown in the top figure, the HR of death decreased markedly starting in 2006. The findings were also similar for patients from Paris and from throughout France.

DISCUSSION

Patients with older age and bulbar-onset have been consistently reported to have shorter survival rates, both in clinic-based (44, 141, 143, 145, 146, 149, 153), and population-based (142, 144, 148, 152, 154) studies. Bulbar-onset occurs with increased frequency in older age groups (155), but this association does not appear to fully explain the worse prognosis of those with bulbar-onset symptoms (148). The worse outcome in patients with bulbar-onset ALS could be related to poorer compliance with NIV, increased airway obstruction and aspiration due to excessive secretions or greater association with extra-motor findings including dementia (5). The delay between symptom onset and first visit, a surrogate for the rapidity of disease progression, has also been shown to predict survival, with shorter intervals portending worse prognosis (141-145, 147, 149, 155-159). Motor function, as assessed by strength or functional scale scores (132, 145, 146, 149) also predicts survival. Some studies indicate that breathing capacity is also an important predictor (44, 146, 148, 149, 160) of survival. A cluster analysis of multiple variables indicated that the strongest predictors in one sample were site-of-onset and interval from onset to first evaluation (159). Findings are less consistent for gender and psychosocial factors. While most studies have shown no effect of gender on outcome, two population-based and several small retrospective studies found worse outcome in women (142, 151, 152). Psychosocial stressors including perceived stress, depression, hopelessness and poor mood may portend worse prognosis (163), and cognitive impairment has been associated with shorter survival (7). Some studies indicate that being underweight could also lead to shorter survival time (44, 150).

The survival rates in this study are consistent with those from studies of other populations, which have ranged from 1.6-4.0 years after disease-onset (80, 142, 144, 154). The survival rate was slightly longer in those residing outside Paris, probably due to the greater percentage of younger patients and patients with limb-onset in this group, a reflection

of who is best able to travel to the Center from outside Paris. Another large Center-based study covering a period of 20 years and 1034 patients showed a median survival time of 3.45 years from symptom onset (145). In that population, younger age, limb onset, longer time to diagnosis, better baseline functional scale score, higher baseline breathing capacity, and lower rate of change prior to first visit were significantly associated with longer survival.

Our findings confirm and extend those of earlier studies to the French population at the Salpêtrière Hospital. Similar to previous studies, while controlling for other variable that changed during the study period, our patients with limb-onset symptoms, younger age, better motor function as measured by manual strength testing or the ALSFRS-R score, and those with greater interval between symptom onset and first visit to the center had better survival rates. In particular, those who took longer than 18 months to reach the center had a significantly better outcome. The hazard ratios were similar for the major variables, irrespective of where or when the patients originated, showing the consistent importance of these predictors across time and geographic location. We examined vital capacity but determined that a large number of missing values varied by time period, and so the analysis of breathing capacity was deemed unreliable. In our study, men were found to have a worse outcome in a single multivariate analysis, and having overweight BMI, a marker of poor health, predicted worse survival in two univariate analyses, but was not a significant predictor of survival in multivariate analyses. In contrast to several other studies, we found no effect of being underweight (44, 150). Measures of psychosocial stress and cognitive impairment were not collected in the database. Similarly, there were too few data to reliably assess the effect of smoking, family history and other medical illnesses on survival.

Patients originating from in and outside of Paris had different clinical features, with those travelling from outside Paris more likely to be men, and being younger, more likely to have limb-onset, taking longer to reach the center, being heavier, and having less strength; all

likely a reflection of who is best able to travel long distances and need additional time in the disease course to reach the Center. These contrasting characteristics did not translate into significant differences in survival rate between regions in multivariate analyses, however.

Our data also showed a changing survival pattern over time. The survival rate improved significantly at the Center after 2006, when the data were examined both graphically and in statistical analyses. Possible explanations are the changing clinic population and modification in respiratory therapy after that time. The patient population evolved over time, with patients becoming stronger, taking less time to reach the center, becoming older, and being more likely to reside in Paris; important influences changed with time and these factors could have influenced the changing survival pattern we detected. Increased strength predicts better survival, while increased age and shorter time to first visit portend worse survival. It is likely that, as the center became better known during the mid and late 1990s, patients were referred sooner and more often, and that the clinic population became more representative of the ALS population in France. It is also possible that unknown confounders changed with time; not all clinical data were collected in the database and not all prognostic factors can be measured in this still mysterious disease. But even when known confounders were controlled for in multivariate Cox models, survival still significantly improved after 2006. Beginning during 2005, more aggressive respiratory management was instituted at the center. The proportion of patients receiving NIV, which has been shown to prolong survival (179), increased each year, from 16% in 2004 to 31% in 2006 and 51% in 2008 (52). Since all other parameters of standard care such as use of riluzole, tracheostomy, nutritional control, as well as speech and physical therapies were unchanged before and after this date, it is likely that the increase in the use of NIV contributed to the improved survival seen starting in 2006 (52).

The strengths of this study are the analysis of a large consecutively evaluated sample seen over 15 years and the very low proportion of lost to follow up for survival data. The study also has weaknesses. The data derive from a single center and so may not represent the French ALS population as a whole. The evolving patient characteristics make it impossible to determine with certainty whether the markedly improved survival during recent years represents a truly improved rate or whether the change is due partly or entirely to the evolving makeup of the sample. Specific data on use of NIV, including mean ventilation time per day and the proportion of patients using NIV for longer than 20 hours per day, were not available for analysis.

Even with changing population patterns, traditionally-reported predictors of survival were also identified in this French sample, no matter where the patients originated or in what time period. In this large center-based cohort, cardinal predictors of survival, including site-of-onset, strength, age, time to first visit, also proved to be the strongest predictors of survival. The subgroup with the longest survival pattern included younger patients with limb-onset and high motor function, who took longer than 18 months to reach the center. Future studies might better define subgroups based on clinicopathological correlation. However, clear subtypes may only be defined after etiologies are discovered. After 140 years of study, ALS still presents with elusive heterogeneity, in which certain clinical features in combination determine outcome better than any single defining characteristic.

Legend

Figure 1. Kaplan-Meier Survival Curve by Region of Residence (Paris region, solid line; rest of France, dotted line).

Figure 2. Multivariable Cox Proportional Hazards Models Including Continuous Variables Modeled as Restricted Cubic Splines.

Table 1. Patients' Characteristics by Region of Residence

Characteristics	MMT dataset, region		p*	ALSFRS-R dataset, region		p*
	Paris region	Outside Paris		Paris region	Outside Paris	
	N=2153	N=1677		N=1214	N=823	
Mean age, yrs (SD)	63.3 (12.5)	58.5 (12.1)	<0.0001	63.6 (12.6)	58.8 (11.8)	<0.0001
Male sex, % (n)	53.0 (1141)	57.1 (957)	0.0121	53.8 (653)	55.6 (458)	0.4080
Limb onset, % (n)	68.2 (1469)	72.1 (1209)	0.0097	68.0 (826)	73.3 (603)	0.0114
Mean time to first visit (SD), months	16.0 (18.8)	17.1 (19.1)	0.0651	14.5 (15.9)	15.9 (16.9)	0.0691
Mean BMI (SD), kg/m ²	24.6 (3.9)	25.2 (4.0)	<0.0001	24.6 (4.0)	25.3 (4.5)	0.0013
Mean MMT (SD)	123.5 (19.7)	119.0 (19.8)	<0.0001	129.3 (19.3)	125.4 (18.3)	<0.0001
Mean ALSFRS-R (SD)	--	--	--	38.1 (6.5)	37.8 (5.8)	0.3215

* P-values were computed using the Mantel-Haenszel chi-square test for categorical variables and analysis of variance using linear contrasts for continuous variables.

Table 2. Patients' Characteristics by Time Period

Characteristics	MMT dataset, year of first visit				p*	ALSFRS-R dataset, year of first visit				p*
	1995-1998	1999-2002	2003-2006	>2006		≤2003	2004-2005	2006-2007	>2007	
	N=1056	N=893	N=1159	N=722		N=440	N=575	N=558	N=459	
Mean age, yrs (SD)	60.7 (12.4)	60.5 (12.7)	61.3 (12.5)	62.6 (12.6)	0.0007	59.5 (12.5)	61.8 (12.3)	62.2 (12.5)	63.0 (12.7)	<0.0001
Male sex, % (n)	54.2 (572)	56.1 (501)	54.4 (631)	54.6 (394)	0.9900	53.7 (238)	57.0 (329)	50.2 (280)	57.5 (264)	0.7832
Limb onset, % (n)	68.5 (723)	71.1 (635)	71.8 (832)	67.6 (488)	0.9141	73.6 (326)	70.9 (409)	67.2 (375)	69.5 (319)	0.0870
Residence outside Paris, % (n)	47.7 (504)	48.8 (4360)	40.4 (468)	37.3 (269)	<0.0001	46.0 (204)	41.1 (237)	38.5 (215)	36.4 (167)	0.0022
Mean time to first visit (SD), months	18.7 (23.7)	17.5 (18.3)	15.6 (16.2)	13.4 (15.2)	<0.0001	16.4 (16.1)	16.6 (18.3)	14.4 (17.8)	12.8 (10.9)	<0.0001
Mean BMI (SD), kg/m ²	24.8 (3.8)	24.9 (3.8)	25.0 (4.2)	24.6 (4.2)	0.3855	25.1 (4.2)	25.1 (4.3)	25.3 (4.1)	24.0 (4.1)	0.0026
Mean MMT (SD)	109.4 (16.4)	122.5 (19.1)	126.4 (19.4)	130.6 (17.8)	<0.0001	126.2 (18.5)	125.2 (20.8)	129.5 (17.9)	130.4 (17.8)	<0.0001
Mean ALSFRS-R (SD)	--	--	--	--	--	37.4 (6.4)	37.7 (6.3)	38.4 (5.9)	38.3 (6.4)	0.0070

* P-values were computed using the Mantel-Haenszel chi-square test for categorical variables and analysis of variance using linear contrasts for continuous variables.

Table 3. Baseline Predictors of Survival: Univariate Models, MMT dataset

Characteristics		All France		Paris region		Rest of France	
		HR (95% CI)*	p*	HR (95% CI)	p	HR (95% CI)	p
Year of first visit ‡	1995-1998	0.94 (0.86-1.03)	0.1881	0.86 (0.76-0.98)	0.0204	1.01 (0.88-1.15)	0.9114
	1999-2002	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--
	2003-2006	1.02(0.93-1.12)	0.6388	0.98 (0.86-1.11)	0.7460	1.06 (0.93-1.22)	0.3745
	>2006	0.76 (0.66-0.86)	<0.0001	0.79 (0.67-0.93)	0.0045	0.68 (0.55-0.84)	0.0005
Sex	Male vs female	1.01 (0.94-1.08)	0.8540	1.02 (0.92-1.12)	0.7403	1.01 (0.91-1.13)	0.8115
Site of onset	Limb vs bulbar	0.68 (0.63-0.74)	<0.0001	0.66 (0.60-0.73)	<0.0001	0.71 (0.63-0.80)	<0.0001
Time to first visit (months) ‡	≤7.3	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--
	7.4-11.6	1.04 (0.94-1.15)	0.4548	1.05 (0.93-1.20)	0.4177	1.04 (0.89-1.22)	0.5885
	11.7-18.7	0.96 (0.87-1.06)	0.4216	0.94 (0.82-1.07)	0.3406	1.00 (0.86-1.17)	0.9423
	>18.7	0.66 (0.60-0.73)	<0.0001	0.60 (0.53-0.69)	<0.0001	0.72 (0.61-0.84)	<0.0001
BMI (kg/m²)	<18.5	1.10 (0.96-1.28)	0.1777	1.04 (0.87-1.25)	0.6373	1.19 (0.92-1.54)	0.1745
	18.6-25.0	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--
	25.1-30.0	1.10 (1.02-1.19)	0.0121	1.09 (0.98-1.22)	0.0990	1.12 (1.00-1.26)	0.0494
	>30	1.17 (1.04-1.33)	0.0118	1.15 (0.97-1.37)	0.1173	1.20 (1.00-1.43)	0.0518
MMT ‡	≤112	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--
	113-123	0.68 (0.62-0.75)	<0.0001	0.64 (0.56-0.73)	<0.0001	0.73 (0.64-0.84)	<0.0001
	124-136	0.62 (0.56-0.68)	<0.0001	0.65 (0.57-0.74)	<0.0001	0.59 (0.51-0.68)	<0.0001
	>136	0.58 (0.52-0.64)	<0.0001	0.62 (0.54-0.70)	<0.0001	0.52 (0.44-0.61)	<0.0001

HR (95% CI) and p-values were computed using a Cox proportional hazards models with age as the time axis.

* Adjustment for region of residence (Paris region *versus* rest of France).

† The p-value for the interaction between each covariate and the region of residence was computed by including a multiplicative term in the model.

‡ Groups were defined based on the quartiles of the distribution of the corresponding variables.

Table 3 continued. Baseline Predictors of Survival: Univariate Models (ALSFRS-R dataset)

Characteristics		All France		Paris region		Rest of France	
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Year of first visit ‡	≤ 2003	1.03 (0.90-1.17)	0.6721	0.96 (0.81-1.15)	0.6872	1.07 (0.88-1.32)	0.4872
	2004-2005	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--
	2006-2007	0.98 (0.86-1.12)	0.7897	0.96 (0.82-1.14)	0.6751	0.99 (0.80-1.22)	0.9155
	>2007	0.58 (0.48-0.70)	<0.0001	0.77 (0.67-0.89)	<0.0001	0.72 (0.60-0.86)	0.0004
Sex	Male vs female	0.96 (0.86-1.06)	0.4042	0.96 (0.84-1.10)	0.5659	1.00 (0.85-1.19)	0.9632
Site of onset	Limb vs bulbar	0.74 (0.67-0.83)	<0.0001	0.77 (0.67-0.89)	0.0004	0.72 (0.60-0.86)	0.0004
Time to first visit (months) ‡	≤7.0	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--
	7.1-10.6	1.01 (0.87-1.17)	0.8877	1.01 (0.84-1.21)	0.9485	1.02 (0.80-1.31)	0.8522
	10.7-17.0	0.88 (0.76-1.02)	0.0869	0.86 (0.71-1.04)	0.1104	0.94 (0.74-1.18)	0.5722
	>17.0	0.74 (0.64-0.86)	<0.0001	0.73 (0.60-0.89)	0.0016	0.75 (0.60-0.95)	0.0172
BMI (kg/m²)	<18.5	1.08 (0.90-1.32)	0.4039	1.08 (0.85-1.37)	0.5200	1.00 (0.71-1.40)	0.9815
	18.6-25.0	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--
	25.1-30.0	1.10 (0.98-1.23)	0.1147	1.11 (0.96-1.29)	0.1702	1.05 (0.87-1.26)	0.5984
	>30	1.08 (0.90-1.29)	0.4275	1.01 (0.79-1.30)	0.9284	1.14 (0.86-1.50)	0.3648
MMT ‡	≤120	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--
	121-131	0.70 (0.61-0.81)	<0.0001	0.75 (0.61-0.91)	0.0033	0.65 (0.53-0.80)	<0.0001
	132-142	0.62 (0.54-0.72)	<0.0001	0.68 (0.56-0.82)	<0.0001	0.57 (0.45-0.71)	<0.0001
	>142	0.51 (0.44-0.59)	<0.0001	0.56 (0.46-0.68)	<0.0001	0.44 (0.34-0.57)	<0.0001
ALSFRS-R ‡	≤35	1.00 (ref.)	--	1.00 (ref.)	--	1.00 (ref.)	--

	36-39	0.74 (0.65-0.85)	<0.0001	0.76 (0.63-0.91)	0.0028	0.70 (0.56-0.87)	0.0011
	40-42	0.50 (0.44-0.58)	<0.0001	0.53 (0.44-0.64)	<0.0001	0.48 (0.38-0.60)	<0.0001
	>42	0.42 (0.35-0.49)	<0.0001	0.44 (0.36-0.53)	<0.0001	0.40 (0.31-0.51)	<0.0001

HR (95% CI) and p-values were computed using a Cox proportional hazards models with age as the time axis.

* Adjustment for region of residence (Paris region *versus* rest of France).

† The p-value for the interaction between each covariate and the region of residence was computed by including a multiplicative term in the model.

‡ Groups were defined based on the quartiles of the distribution of the corresponding variables

Table 4. Baseline Predictors of Survival: Multivariable Models MMT dataset

Covariate	Coding	All France		Paris region		Rest of France	
		HR (95 % CI)	p-value	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Region of residence	Paris region vs rest of France	0.95 (0.88-1.02)	0.1738	--	--	--	--
Year of first visit	1995-1998	0.71 (0.64-0.78)	<0.0001	0.67 (0.58-0.76)	<0.0001	0.74 (0.64-0.85)	<0.0001
	1999-2002	1.00 (ref)	--	1.00 (ref)	--	1.00 (ref)	--
	2003-2006	1.04 (0.95-1.14)	0.4081	0.99 (0.87-1.12)	0.8681	1.08 (0.94-1.24)	0.2739
	>2006	0.76 (0.66-0.87)	<0.0001	0.78 (0.65-0.92)	0.0033	0.70 (0.55-0.86)	0.0011
Sex	Men vs women	1.17 (1.08-1.26)	<0.0001	1.20 (1.09-1.33)	0.0002	1.15 (1.03-1.29)	0.0129
Site of onset	Limb vs bulbar	0.67 (0.62-0.72)	<0.0001	0.66 (0.59-0.73)	<0.0001	0.67 (0.60-0.76)	<0.0001
Time to first visit (months)	≤7.3	1.00 (ref)	--	1.00 (ref)	--	1.00 (ref)	--
	7.4-11.6	0.96 (0.86-1.06)	0.3762	0.98 (0.86-1.11)	0.7282	0.94 (0.80-1.11)	0.4885
	11.7-18.7	0.86 (0.78-0.95)	0.0027	0.87 (0.76-0.99)	0.0418	0.85 (0.72-0.99)	0.0406
	>18.7	0.54 (0.48-0.60)	<0.0001	0.51 (0.44-0.59)	<0.0001	0.57 (0.48-0.67)	<0.0001
MMT Score	≤112	1.00 (ref)	--	1.00 (ref)	--	1.00 (ref)	--
	113-123	0.57 (0.52-0.62)	<0.0001	0.54 (0.47-0.62)	<0.0001	0.60 (0.52-0.68)	<0.0001
	124-136	0.47 (0.42-0.52)	<0.0001	0.50 (0.43-0.57)	<0.0001	0.44 (0.37-0.51)	<0.0001
	>136	0.36 (0.32-0.41)	<0.0001	0.37 (0.32-0.43)	<0.0001	0.35 (0.29-0.43)	<0.0001

HR (95% CI) and p-values were computed using a Cox proportional hazards model with age as the time axis.

The region of residence, sex, and year of first visit were forced in the overall model.

Table 5. Baseline Predictors of Survival: Multivariable Models ALSFRS-R dataset

Covariate	Coding	All France		Paris region		Rest of France	
		HR (95 % CI)	p-value	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Region of residence	Paris region vs rest of France	0.96 (0.86-1.07)	0.4543	--	--	--	--
Year of first visit	≤2003	1.06 (0.93-1.21)	0.4058	1.05 (0.88-1.26)	0.5734	1.01 (0.82-1.24)	0.9350
	2004-2005	1.00 (ref)	--	1.00 (ref)	--	1.00 (ref)	--
	2006-2007	0.98 (0.86-1.12)	0.7389	0.97 (0.82-1.16)	0.7643	0.94 (0.76-1.18)	0.2550
	>2007	0.54 (0.45-0.65)	<0.0001	0.58 (0.46-0.74)	<0.0001	0.44 (0.31-0.61)	<0.0001
Sex	Men vs women	1.04 (0.94-1.16)	0.4362	1.08 (0.94-1.25)	0.2602	1.02 (0.86-1.21)	0.8008
Site of onset	Limb vs bulbar	0.68 (0.61-0.77)	<0.0001	0.69 (0.60-0.81)	<0.0001	0.67 (0.55-0.81)	<0.0001
Time to first visit (months)	≤7.0	1.00 (ref)	--	1.00 (ref)	--	1.00 (ref)	--
	7.1-10.6	0.95 (0.82-1.09)	0.4493	0.94 (0.79-1.12)	0.4980	1.00 (0.80-1.28)	0.9665
	10.7-17.0	0.80 (0.70-0.93)	0.0032	0.78 (0.64-0.94)	0.0093	0.86 (0.68-1.09)	0.2224
	>17.0	0.56 (0.48-0.66)	<0.0001	0.54 (0.44-0.67)	<0.0001	0.60 (0.45-0.74)	<0.0001
ALSFRS-R Score	≤35	1.00 (ref)	--	1.00 (ref)	--	1.00 (ref)	--
	36-39	0.69 (0.60-0.80)	<0.0001	0.73 (0.61-0.88)	0.0008	0.62 (0.50-0.78)	<0.0001
	40-42	0.46 (0.40-0.53)	<0.0001	0.46 (0.38-0.56)	<0.0001	0.45 (0.35-0.56)	<0.0001
	>42	0.33 (0.28-0.39)	<0.0001	0.34 (0.28-0.42)	<0.0001	0.32 (0.24-0.42)	<0.0001

HR (95% CI) and p-values were computed using a Cox proportional hazards model with age as the time axis.

The region of residence, sex, and year of first visit were forced in the overall model.

Figure 1 Kaplan-Meier Survival Curve by Region of Residence (Paris region, solid line; rest of France, dotted line).

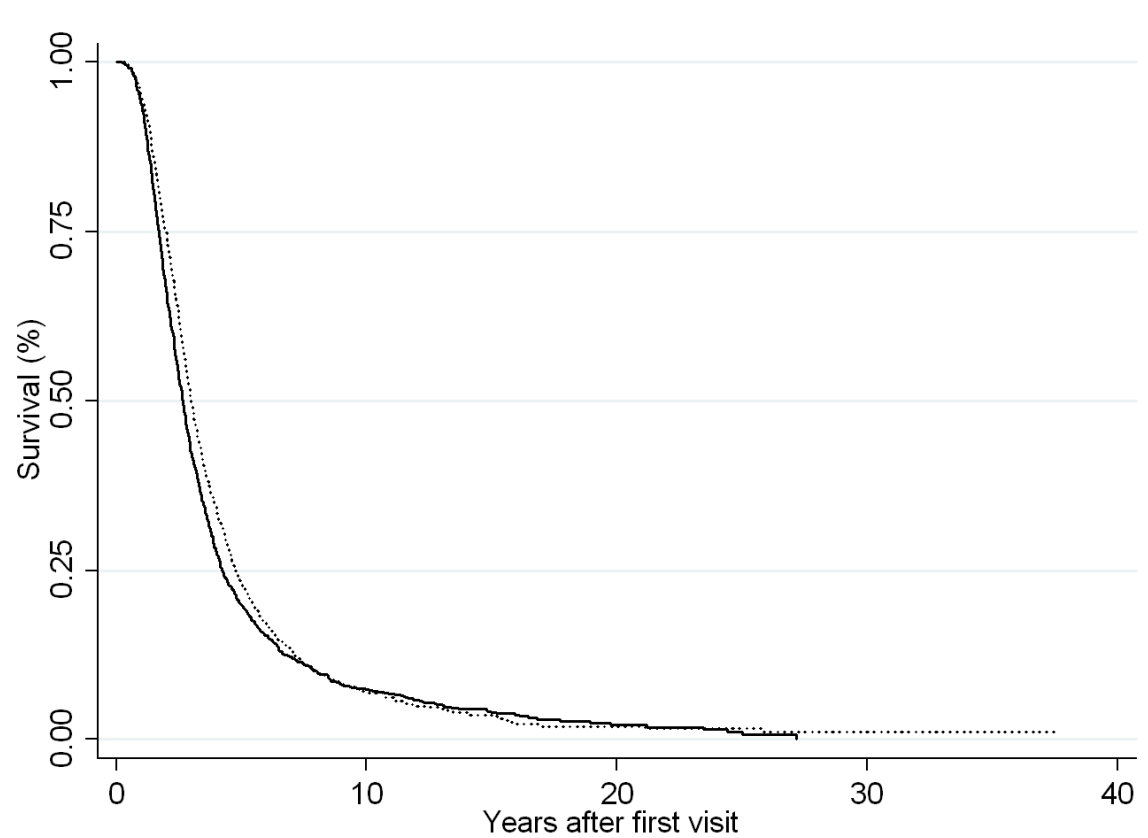
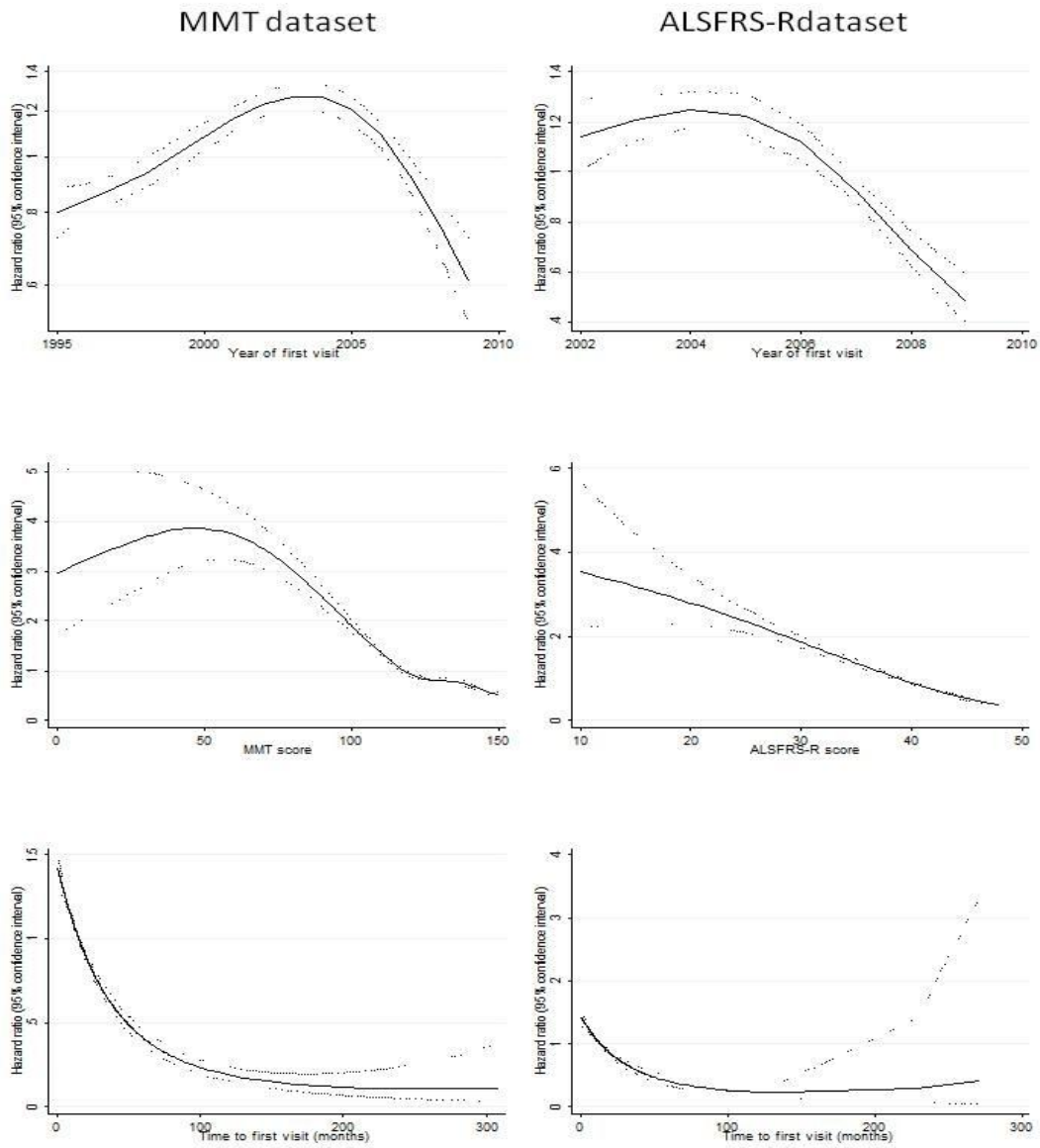


Figure 2. Multivariable Cox Proportional Hazards Models Including Continuous Variables Modeled as Restricted Cubic Splines.



Reference List

- (1) Logroscino G, Traynor BJ, Hardiman O, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry* 2008 Jan;79:6-11.
- (2) Louwrese ES, Visser CE, Bossuyt PM, Weverling GJ. Amyotrophic lateral sclerosis: mortality risk during the course of the disease and prognostic factors. The Netherlands ALS Consortium. *J Neurol Sci* 1997 Oct;152 Suppl 1:S10-S17.
- (3) del Aguila MA, Longstreth WT, Jr., McGuire V, Koepsell TD, van BG. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology* 2003 Mar 11;60:813-819.
- (4) Testa D, Lovati R, Ferrarini M, Salmoiraghi F, Filippini G. Survival of 793 patients with amyotrophic lateral sclerosis diagnosed over a 28-year period. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2004 Dec;5:208-212.
- (5) Millul A, Beghi E, Logroscino G, Micheli A, Vitelli E, Zardi A. Survival of patients with amyotrophic lateral sclerosis in a population-based registry. *Neuroepidemiology* 2005;25:114-119.
- (6) Czaplinski A, Yen AA, Appel SH. Amyotrophic lateral sclerosis: early predictors of prolonged survival. *J Neurol* 2006 Nov;253:1428-1436.
- (7) Kollewe K, Mauss U, Krampfl K, Petri S, Dengler R, Mohammadi B. ALSFRS-R score and its ratio: a useful predictor for ALS-progression. *J Neurol Sci* 2008 Dec 15;275:69-73.
- (8) Zoccolella S, Beghi E, Palagano G, et al. Predictors of long survival in amyotrophic lateral sclerosis: a population-based study. *J Neurol Sci* 2008 May 15;268:28-32.
- (9) Kaufmann P, Levy G, Thompson JL, et al. The ALSFRS_r predicts survival time in an ALS clinic population. *Neurology* 2005 Jan 11;64:38-43.
- (10) Chio A, Mora G, Leone M, et al. Early symptom progression rate is related to ALS outcome: a prospective population-based study. *Neurology* 2002 Jul 9;59:99-103.
- (11) Paillisse C, Lacomblez L, Dib M, Bensimon G, Garcia-Acosta S, Meininger V. Prognostic factors for survival in amyotrophic lateral sclerosis patients treated with riluzole. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2005 Mar;6:37-44.
- (12) Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. *Neurology* 1999 Sep 22;53:1059-1063.

- (13) **Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. *Neurology* 1998 Jan;50:66-72.**
- (14) **Lopez-Vega JM, Calleja J, Combarros O, Polo JM, Berciano J. Motor neuron disease in Cantabria. *Acta Neurol Scand* 1988 Jan;77:1-5.**
- (15) **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;240:339-346.**
- (16) **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;1:293-299.**
- (17) **great lakes study group. A comparison of muscle strength testing techniques in amyotrophic lateral sclerosis. *Neurology* 2003 Dec 9;61:1503-1507.**
- (18) **Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci* 1999 Oct 31;169:13-21.**
- (19) **Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004 Dec 30;23:3803-3820.**
- (20) **Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology* 1995 Jul;6:356-365.**
- (21) **Royston P, Sauerbrei W. Multivariable modeling with cubic regression splines: a principled approach. *The Stata Journal* 2007;7:45-70.**
- (22) **Gordon PH, Salachas F, Bruneteau G, et al. Improving survival in a large French ALS center cohort. *J Neurol* 2012 Jan 19.**
- (23) **Preux PM, Couratier P, Boutros-Toni F, et al. Survival prediction in sporadic amyotrophic lateral sclerosis. Age and clinical form at onset are independent risk factors. *Neuroepidemiology* 1996;15:153-160.**
- (24) **Zoccolella S, Beghi E, Palagano G, et al. Analysis of survival and prognostic factors in amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry* 2008 Jan;79:33-37.**
- (25) **Tysnes OB, Vollset SE, Aarli JA. Epidemiology of amyotrophic lateral sclerosis in Hordaland county, western Norway. *Acta Neurol Scand* 1991 May;83:280-285.**
- (26) **Gordon PH, Delgado D, Piquard A, et al. The range and clinical impact of cognitive impairment in French patients with ALS: A cross-sectional study of neuropsychological test performance. *Amyotroph Lateral Scler* 2011 May 17.**

- (27) Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. *Brain* 1995 Jun;118 (Pt 3):707-719.
- (28) Thijs V, Peeters E, Theys P, Matthijs G, Robberecht W. Demographic characteristics and prognosis in a Flemish amyotrophic lateral sclerosis population. *Acta Neurol Belg* 2000 Jun;100:84-90.
- (29) Beghi E, Millul A, Logroscino G, Vitelli E, Micheli A. Outcome measures and prognostic indicators in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2008 Jun;9:163-167.
- (30) Ganesalingam J, Stahl D, Wijesekera L, et al. Latent cluster analysis of ALS phenotypes identifies prognostically differing groups. *PLoS One* 2009;4:e7107.
- (31) Czaplinski A, Yen AA, Appel SH. Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. *J Neurol Neurosurg Psychiatry* 2006 Mar;77:390-392.
- (32) McDonald ER, Wiedenfeld SA, Hillel A, Carpenter CL, Walter RA. Survival in amyotrophic lateral sclerosis. The role of psychological factors. *Arch Neurol* 1994 Jan;51:17-23.
- (33) Olney RK, Murphy J, Forsheew D, et al. The effects of executive and behavioral dysfunction on the course of ALS. *Neurology* 2005 Dec 13;65:1774-1777.
- (34) Chio A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler* 2009 Oct;10:310-323.
- (35) Pinto AC, Evangelista T, Carvalho M, Alves MA, Sales Luis ML. Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. *J Neurol Sci* 1995 May;129 Suppl:19-26.

SUMMARY

5. SUMMARY

This work examined mortality and survival of ALS in France using three studies. The first study analyzed the change in mortality rate from 1968 to 2007 using data obtained from two French national data sources, the Centre d'épidémiologie sur les causes médicales de décès (CépiDc; www.cepidec.vesinet.inserm.fr), which provided data on causes of death, and the Institut National de la Statistique et des Etudes Economiques (INSEE; www.insee.fr), which provided French population statistics. The mortality of MND has increased with time in many studies from different countries, but the reasons for the changes are debated.(73-77) We obtained data on gender, region, date of birth and date of death for 37,624 people aged 40 to 89 years, and examined the change in mortality rate over time along with possible reasons for change. We used Age-period-cohort modeling to assess whether the effect of age, period of death, or cohort of birth best explained changes in mortality.

APC models are statistical tools that can be used to examine temporal variation in disease rates, and were first developed to analyze the causes leading to changing cancer incidence. Without modeling, identifying potential causes behind trends can be difficult. APC models were preceded by techniques that standardize rates, for example using age-standardization, which allowed comparison of vital rates between populations. Indirect standardization was then adapted to estimation of parameters in APC analyses, which use log-linear models to describe variations in rates in terms of either the calendar period or the cohort/generation. The model can be written so that the parameters have a simple interpretation of relative risk in comparison to one period or cohort as a reference. Models are built in sequence, describing age, drift, period, cohort, and the combination of age-period-cohort. The best model for the data, and therefore the best explanation for a changing rate, is chosen based on a goodness-of-fit approach. APC modeling provides a rigorous statistical approach to investigations of the influence of each contributing variable.(173, 174)

The data from this first project showed that the mortality rate for MND in France increased significantly during 1968-2007, that the change was more marked in women, and that, in APC models, the change was more consistent with a cohort effect than a period effect. One interpretation of this cohort effect is that environmental risks for ALS have increased with time and underlie the increasing mortality of MND seen in the study. The more substantial

increase in women implies that changing environmental risks have influenced women to a greater extent than men.

Mortality is used as a surrogate for incidence of ALS and MND for several reasons. The disease is rapidly progressive so most patients die within several years of onset – mortality rates should equate to incidence rates - and the disease is rare so that conducting population based studies that are large enough and have adequate power to detect small differences over time may be too large and expensive to be practical. The use of existing mortality data is less expensive and simpler to compile, making information available for analyses that might not otherwise be possible.

The calculation of mortality rates from data on death certificates, a standard approach and the one used in this study, is considered an adequate reflection of incidence when the data are of high enough quality.(72) The mortality data in this study meet quality criteria as outlined in one review,(72) except that, in France, mortality and incidence rates have never been examined together; it is not known for certain how accurately death certificate data for MND reflect incidence rates in France, and whether the accuracy could vary by region.

While there are no direct comparisons of mortality and incidence rates in France, indirect reasoning suggests that the correspondence between death certificate reporting and incidence is quite high in France. A comparison to incidence data from the Limousin region of France during 1994-1995 showed that the mortality rate in France (3.00/100,000) was similar to the incidence rate (3.2/100,000) at the center (180). The incidence rate (2.16/100,000) in 6 European registries in 1998-1999 (57) was also comparable to the mortality rate (2.2/100,000) in our study during the same period.

The findings in this study are consistent with those from other studies. Different countries with different medical systems have examined mortality rates from ALS and shown that mortality has increased with time, particularly in women. A previous study examined mortality data in France from 1968-1982, finding that rates were higher among men for all years, and that mortality significantly increased with time.(76) In that study, the increases were greater in those above age 55 and in women, and were similar across regions. An investigation conducted in the United States for the years 1969-1998 showed that the

mortality rate increased by 46% across the study period, leveling off during the most recent decade.(75) The rates stabilized after 1988 in men especially, but continued to rise in women. The rates were lower among American minority populations, and a regional gradient was observed with higher rates in the northwest compared to the southeast. The investigators speculated that improved care and better diagnosis could account for some of the increase in rates over time, but they also found that the number of neurologist per region, a surrogate for specialty care and the ability to diagnose rare neurological conditions, did not correlate with geographic trends in mortality. The North East had the highest concentration of neurologists but the lowest mortality rate from MND, and conversely, the North Mountain region had the lowest concentration of neurologists and one of the highest rates of MND; access to neurological care was not a major determinant of the variation in mortality due to MND.

Not only did the current study confirm and extend the results of the previous studies, but we examined statistically, for the first time, potential reasons for the changing rates in MND with a form of Poisson regression known as APC modeling. This technique discriminates the effects of age, birth cohort and period of death using goodness of fit of different models that explain the three factors. We found that the model representing variation due to birth cohort fit the data better than other models, providing statistical evidence that changing environmental exposures contribute to varying mortality rates. APC models cannot distinguish, however, between age-dependent period effects (i.e., a period effect that is restricted to certain age groups) and cohort effects with certainty. Improved disease identification over time for the elderly and women would lead to an interaction between age and period, manifesting as a cohort effect (173). Our secondary sensitivity analyses examined these possibilities independently.

The issues generally considered most problematic when using mortality as a surrogate for incidence are age and gender bias in recording the diagnosis. In most societies, including industrialized nations, younger patients and men may be more likely than the elderly and women to have an illness recognized, diagnosed, and documented correctly.(181) These discrepancies may reflect bias on the part of health care personnel or differences in health-seeking behavior on the part of the patient. Gender and age bias may be especially true for rare, difficult to diagnose neurodegenerative diseases like MND.(182) For example, register based studies of Parkinson disease indicate higher prevalence in men and declining rates in

the very elderly. By comparison, community-based studies, in which all cases are detected with interview, show prevalence increases to the oldest ages and nearly equal occurrence between genders.(183) At least for Parkinson disease, when great effort is taken to identify every case in a community, age and gender bias disappear. When data are taken from existing sources, and the diagnosis improves over time in certain groups, changing rates could be a reflection of changes in ascertainment bias. The first examination of mortality rates and changes in SMRs with time, including a decreasing ratio of men to women, could be explained by better diagnosis in certain groups or better documentation on death certificates. Either could result from changes to the field of neurology, increases in the number of neurologists, and better recognition of MND. To conduct a more in-depth analysis of whether improving diagnosis over time or in the elderly might contribute to our results, we examined the data APC analyses separately by sex, in those above and below age 70 and also in those who died before and after 1990. The data were best explained by a cohort effect in each of the subgroups; sex, age or time of evaluation did not alter the results. We also did analyses of each of the three time periods corresponding to different ICD codes and obtained similar results. We have no way to directly examine the impact of changing ascertainment bias in our data, but we believe it does not completely explain our findings because the cohort effect was also found in younger patients and patients seen in recent years only.

More rapidly increasing rates in women than men were seen when measuring the rates over time, in examination of relative risk over time in APC analyses (supplementary tables study 1) and in the falling sex ratio from comparisons of SMRs with time. The interpretation of the findings from APC modeling is that the incidence and therefore mortality of ALS and MND are changing and that the changes have been greater in women. The cohort effect seen in our APC analyses suggests that the evolving rates of ALS are a consequence of evolving causative factors and different groups' exposure to them. The changes in environmental exposures are particularly strong for women because the ratio of SMRs for men and women decreased with time.

Greater exposure to environmental risks for women over the past 100 years is plausible. During the Second World War and the subsequent decades, women's role in western societies changed considerably. Women began to leave their standard role as homemakers and enter the workforce in increasing numbers. They began to work in the same professions as men, often

displacing men to other fields. Women began to smoke cigarettes increasingly in the first part of the 20th century, and entered sports and the military. Women acquiring lifestyles and employment similar to men might also expose them increasingly to the same risk factors that have contributed to ALS in men.

Overall, the rate increases were greatest for those born between 1883 and 1920. The rates increased significantly thereafter, but at a slower rate. APC analyses showing the same cohort effect for recent and distant birth cohorts suggests that improved diagnosis and documentation do not entirely explain the differing rates. The rapidly increasing rates prior to 1920 correspond roughly to a period of increasing air and water pollution as well as urbanization that resulted from the Industrial Revolution beginning in the mid-18th century. Coal power was introduced in the 19th century. Deteriorating air and water quality included cholera outbreaks in Europe during the mid-19th Century and critical levels of air pollution in major European cities in the 20th century. It was not until later in the 20th century that standards for clean air and water were enacted. It is possible that societal changes also led to changing risks for ALS that were most marked at the end of the 19th century and the first part of the 20th century.

While as our data suggest that environmental risk factors are responsible for causing at least part of ALS, the strongest causative agents and how they combine to trigger the disease are still unknown. ALS almost certainly has both genetic and environmental etiologies that interact, just as they do in other diseases. Genetic susceptibility to headache, cancer, coronary artery disease, or diabetes is manifest in the setting of behaviors that also contribute to disease, such as diet, occupational exposure and cigarette smoking. The genetic and environmental associations with ALS have proved particularly resistant to discovery. Genome wide screens are being conducted, but effect sizes are small and risk genes have not yet been identified with certainty. Similarly, very few environmental risk factors have been discovered. Cigarette smoking is perhaps the most widely accepted risk factor, but the relative risk of acquiring ALS in those who smoke cigarettes is in the range of 1.5.(102) By comparison, the risk of dying of lung cancer in smokers is more than ten times that of non-smokers.(184) Part of the difficulty in uncovering environmental risk factors for ALS, as supported by the findings in this study, are that risks may occur over the lifetime of the individual, perhaps extending as far back as birth or in utero. Causes dating decades in the past may be unknown,

difficult to measure or long since forgotten, and the feature of changes in risk over a lifetime may be very difficult to measure.

This study showed that the mortality from MND is increasing, independent of the aging of the population, and that this increase is best explained by birth cohort, providing an indication that environmental influences are one explanation for the changing mortality rates seen in MND across the world. Future studies could examine whether changes in mortality rates are associated with varying levels of environmental exposures, and apply APC analyses to data from other countries. Overall, these data suggest that the search for strong environmental contributions to MND should continue. Varying designs, including ecological studies, case-control studies, and eventually large population-based prospective cohort studies could examine different environmental risk factors.

Next, beginning in 2010, we analyzed data from the clinical database at the Salpêtrière Hospital to better describe survival in this population and to examine whether survival rates are also changing in France. We focused on survival rates across time to determine whether survival rates have changed at the center, and separately on clinical predictors of survival at first presentation to the center. These data represent one of the largest center-based populations reported to date.

Survival is still an outcome of great importance to patients, their doctors and researchers in this rapidly progressive and almost universally fatal condition. Measuring time to death is a robust endpoint used in clinical trials(54, 185), although other endpoints are being developed;(186) and predicting survival time is still an important means of prognostication for patients. Assessing clinical predictors of survival could elucidate homogeneous subgroups for enrollment in trials as well as studies of genetic and environmental contributors.

We divided the clinical database from the Salpêtrière into several sub-databases to facilitate analyses and to minimize variation due to uncontrolled factors. First, we analyzed data from 2002, the year multi-disciplinary care was standardized across France and the year the center began to use the revised ALS Functional Rating Scale, until 2009; and second, we examined data from 1995, the date multidisciplinary care and riluzole therapy were instituted, until 2009

to provide an overall view of change and to analyze predictors of survival in the largest sample.

In the first analyses of this second component of the research, we found that survival improved at the center after 2006. Other clinical variables also changed, but survival improved even when these factors were controlled for in Cox proportional hazards models. Survival improved in univariate models, in multivariate models and in splines analysis, showing a steady survival pattern until 2006, then improvement. These data suggest that, despite the bleak results of clinical trials over the past 18 years, steady improvements in clinical care have likely impacted survival.

In recent years, meaningful contributions to patient care have come from the regulatory approval of riluzole, the advent of multidisciplinary clinics and possibly from nutritional support.(27, 43) These approaches were in place by 2002, however, and the data, therefore, indicate most strongly that improving and aggressive respiratory support with non-invasive ventilation, the one intervention that did change after that date, could improve outcome. The center developed a more concerted approach to respiratory care, and as a consequence, the number of patients receiving NIV increased beginning in 2004. That year patients at the center began to be referred to a pulmonologist for prescription of NIV once any clinical or laboratory parameter suggested respiratory muscle impairment. The proportion of patients receiving NIV increased from 16% in 2004 to 51% in 2008.

While this is the first study showing that NIV use can affect outcome at an entire center, several other studies show that respiratory care can extend survival in ALS,(50, 187), and several studies have reported improved survival with time, showing possibly that the natural history of the disease is changing due, at least in part, to continually evolving practices of clinical care.

In a center based study, the rate of functional decline and survival both improved in patients seen after 1999 compared to patients seen in 1984-1999 (159). That study used Kaplan-Meier and Cox proportional hazards analyses to examine outcome in 1041 patients seen over 20 years. The Survival time increased approximately one year and Appel Functional Rating Scale deteriorated more slowly in contemporary patients. As in our study, clinical variables also

changed with time, but the improved survival persisted after these factors were controlled for in the analyses. Riluzole, gastrostomy or NIV use had no effect in that study. The authors proposed that the course of ALS may have improved with time or that unmeasured clinical factors could have impacted outcome without being included in analyses. An analysis of patients enrolled in the placebo arm of clinical trials conducted between 1999-2005 also showed improved survival over time (188). Trial patients have different features than ALS patients generally, however.

The strengths of this study include the large number of patients who were included in the analyses, minimal amounts of missing data, and use of standard predictors of outcome as covariates. The weaknesses are that the data derive from a single center and are not necessarily generalizable to all French patients with ALS – patients who attend centers and participate in trials tend to be younger, healthier and more likely to be men (182) - and that parameters of respiratory care could not be included in the analyses. Large center-based studies are still of value because most patients are cared for in centers. In addition, the data from this study showed remarkable consistency not only between regions and across time, but also with findings from other center- as well as population-based studies. There were large numbers of missing values for vital capacity that varied according to time, and use of NIV was not recorded directly in the database. Direct measures of respiratory function and treatment were not available for use as covariates. Inclusion of NIV use in the database may have been of limited importance because of our focus on baseline predictors in these analyses instead of treatments instituted across time, but it would have allowed us, as we did for gastrostomy placement, to perform secondary analyses to determine if NIV was a significant predictor of survival. Similarly, inclusion of FVC at baseline could have allowed us to control for an important respiratory predictor of survival. It is possible, as patients came to the clinic earlier in their course, that FVC improved with time and was one explanation for improving survival rates at the center. The link between use of NIV and survival rate resulted from descriptive statistics showing concurrent increases. Other variables that changed during the study were controlled for in the analyses, and the period of the study was chosen because other treatments were stable, including multi-disciplinary care, as well as riluzole, tracheostomy and gastrostomy use.

In this large center-based cohort, survival improved significantly after 2006, possibly due to increased use of NIV. Longer observation of these patients is needed to determine whether the improved survival pattern persists with time. Studies that examine the impact of NIV on survival in population-based studies are needed to determine whether the improvement is being seen in patients with ALS generally.

Finally, in order to better characterize the population at the Salpêtrière Hospital, we examined predictors of survival for the entire period, encompassing nearly 4000 patients, as well as for the period 2002-2009. We used Kaplan-Meier and univariate as well as multi-variate Cox proportional hazard methods to describe the clinical features that best predict outcome. Multivariate splines models depicted the data graphically. At this large French ALS center, we found that the strongest predictors of better survival rate were limb-onset symptoms, younger age, better motor function as measured by manual strength testing or the ALSFRS-R score, and greater interval between symptom onset and first visit to the center. Those who took longer than 18 months to reach the center had a significantly better outcome. Conversely, older age, bulbar-onset, shorter delay to first visit and poor motor function at first visit predicted shorter survival rates. The findings were consistent across time and region of residence. Survival improved after 2006 in analyses from both the longer and shorter time period.

Our findings are consistent with other studies that have examined predictors of survival. Other reports have shown that older age at onset; bulbar-onset symptoms; a shorter interval from onset of symptoms to diagnosis; (141-147) poor strength, motor function (132, 145) or breathing capacity ; (145, 148, 149) and weight loss (44, 150) as well as female sex (142, 151, 152) are associated with shorter survival. A cluster analysis of multiple variables indicated that the strongest predictors in one sample were site-of-onset and interval from onset to first evaluation (159).

Just one of our analyses suggested that being overweight as measured by body mass index was associated with worse survival, but the association was no longer significant in multivariate analyses. We did not find a significant association between malnutrition at first visit and survival. Other studies have suggested that changes in nutritional status, particularly drop in weight from normal (189), or change prior to enrollment in a trial (44) predict worse

survival; each of these studies also showed no association of baseline BMI and survival. We had no way to measure changes in weight prior to first visit in the current study. Comparison of our data to other studies that assess nutritional status and survival suggest that change in BMI may be a more important predictor of survival than absolute BMI alone.

The strengths of this study include the large sample size of nearly 4000 consecutively evaluated patients seen over 15 years and the low proportion of missing data for survival analyses. The study may not represent the French ALS population as a whole, and the evolving patient characteristics make it impossible to determine with certainty whether the markedly improved survival during recent years represents a truly improved rate or whether the change is due partly or entirely to the evolving makeup of the sample.

There are biases that limit comparison with population samples, but since care is delivered via specialist centers like the one in Paris, it is important to understand the natural history, including changes in outcomes, associated with changes in management over time.

In this sample, the patients' characteristics varied depending on where they resided and when they developed ALS. Patients originating from outside of Paris were more likely to be men, have younger age, have limb-onset symptoms, take longer to reach the center, weigh more, and be weaker; features that reflect which patients can travel long distances and the longer time needed to reach the center. It is likely that the patients who came to the center from outside Paris were not representative of the population of ALS patients in France as a whole or even those patients seen at centers in the provinces. However, even this uniquely self-selected group had predictors of survival with hazard ratios very similar to those patients who resided in Paris, even in the most recent years. As time passed, patients coming to the center became older, more likely to reside in Paris, stronger, and present earlier in the disease course. But these changing characteristics by region and time period did not translate into significant differences in survival rate or predictors of survival. No unique phenotypes became apparent, but the strongest predictors persisted no matter where the patients originated or in what time period.

Future studies could assess change in variables over time to examine whether different interventions and clinical features impact survival rate. Studies with radiographic or clinico-

pathologic correlation using autopsy studies might also better define subgroups, but identification of etiologies may be needed to elucidate individual forms of ALS with unique survival patterns.

CONCLUSIONS AND PERSPECTIVE

6. CONCLUSIONS AND PERSPECTIVE

ALS is still a mysterious disease of unknown cause and few truly meaningful treatments. The course is progressive and death occurs for most patients within three years of onset. Some of the cellular events that occur after disease onset are partially understood, but little is known about the underlying causes and when they might take effect or interact. Triggers may act in distant youth or even before birth. Care is now multidisciplinary and includes respiratory support, supplemental feeding and riluzole, all of which may impact survival. Symptomatic medications can be tried but have not been shown to improve survival. Better characterization of the disease could provide clues in the ongoing search for causes and stronger treatments.

The current work analyzed mortality and survival rates in France using several approaches. We first examined mortality rates in all of France from 1968-2007 using a statistical tool known as Age-period-cohort modeling, finding that mortality due to ALS has increased with time in France, more quickly in women than men, and that a cohort effect, usually due to environmental factors, best explains the change. An alternative explanation for the findings is that the diagnosis of ALS and its certification on death certificates has improved with time, particularly in elderly women.

We also examined survival rates at the Salpêtrière Hospital using two separate databases, 1995-2009 and 2002-2009, and found that survival has improved with time, possibly due to more aggressive use of non-invasive ventilation. The improving survival rates began in 2006, the year that NIV began to be prescribed for patients in increasing numbers. The changing survival pattern was seen using Kaplan-Meier statistics, univariate as well as multivariate Cox proportional hazards models, and graphically using splines analysis.

Finally, we analyzed clinical predictors of survival at the Paris hospital. Clinical variables at baseline were first assessed using univariate Cox models and then entered into multivariate models using a backward stepwise approach. Certain clinical phenotypes such as younger age, limb onset, and longer time to first visit predicted better outcome.

Future studies could examine mortality rates in other countries using APC analyses and correlate mortality in France with ecological findings to examine whether specific

environmental exposures influence mortality rate. Improved understanding of the relationship between mortality rate using diagnoses recorded on death certificates and incidence rates in population-based studies is needed in France; in order to detect change in incidence, future population-based studies should have adequate power by examining a large enough population over long enough periods.

Examination of survival rates in population-based studies along with measures of respiratory support could determine whether survival is improving in ALS patients generally and whether use of NIV explains the change. Radiographic, pathologic and prospective studies could better define unique ALS phenotypes for in-depth examination of causes in homogeneous subgroups. Rigorous studies in minority populations could also produce unique genetic or environmental associations.

Better characterization of the disease, including changing patterns over time and clinical phenotypes, along with gene analysis and environmental risk assessment, especially over the lifetime of the patient, could all help define causes and lead to improved treatments for this incurable disease.

7. BIBLIOGRAPHY

Reference List

- (1) Gubbay SS, Kahana E, Zilber N, Cooper G, Pintov S, Leibowitz Y. Amyotrophic lateral sclerosis. A study of its presentation and prognosis. *J Neurol* 1985;232:295-300.
- (2) Ravits J, Paul P, Jorg C. Focality of upper and lower motor neuron degeneration at the clinical onset of ALS. *Neurology* 2007 May 8;68:1571-1575.
- (3) Gordon PH, Cheng B, Katz IB, et al. The natural history of primary lateral sclerosis. *Neurology* 2006 Mar 14;66:647-653.
- (4) Lomen-Hoerth C, Murphy J, Langmore S, Kramer JH, Olney RK, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 2003 Apr 8;60:1094-1097.
- (5) Gordon PH, Delgadillo D, Piquard A, et al. The range and clinical impact of cognitive impairment in French patients with ALS: A cross-sectional study of neuropsychological test performance. *Amyotroph Lateral Scler* 2011 May 17.
- (6) Gordon PH, Goetz RR, Rabkin JG, et al. A prospective cohort study of neuropsychological test performance in ALS. *Amyotroph Lateral Scler* 2010 May 3;11:312-320.
- (7) Olney RK, Murphy J, Forshew D, et al. The effects of executive and behavioral dysfunction on the course of ALS. *Neurology* 2005 Dec 13;65:1774-1777.
- (8) Gordon PH. Amyotrophic lateral sclerosis: pathophysiology, diagnosis and management. *CNS Drugs* 2011 Jan 1;25:1-15.
- (9) Rabkin JG, Albert SM, Del Bene ML, et al. Prevalence of depressive disorders and change over time in late-stage ALS. *Neurology* 2005 Jul 12;65:62-67.
- (10) Judt T. Night. New York: Random House, 2010:15-35.
- (11) Gordon PH, Corcia P, Lacomblez L, et al. Defining survival as an outcome measure in amyotrophic lateral sclerosis. *Arch Neurol* 2009 Jun;66:758-761.
- (12) Gautier G, Verschueren A, Monnier A, Attarian S, Salort-Campana E, Pouget J. ALS with respiratory onset: clinical features and effects of non-invasive ventilation on the prognosis. *Amyotroph Lateral Scler* 2010 Aug;11:379-382.
- (13) Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology* 2009 Sep 8;73:805-811.
- (14) 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;1:293-299.

- (15) Carvalho MD, Swash M. Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis. *Amyotroph Lateral Scler* 2009 Feb;10:53-57.
- (16) Shefner JM. Statistical motor unit number estimation and ALS trials: the effect of motor unit instability. *Suppl Clin Neurophysiol* 2009;60:135-141.
- (17) Mitsumoto H, Ulug AM, Pullman SL, et al. Quantitative objective markers for upper and lower motor neuron dysfunction in ALS. *Neurology* 2007 Apr 24;68:1402-1410.
- (18) Le FN, Maisonobe T, Piquard A, et al. Does primary lateral sclerosis exist? A study of 20 patients and a review of the literature. *Brain* 2001 Oct;124:1989-1999.
- (19) Rowland LP. Primary lateral sclerosis, hereditary spastic paraplegia, and mutations in the alsin gene: historical background for the first International Conference. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2005 Jun;6:67-76.
- (20) Fink JK. The hereditary spastic paraplegias: nine genes and counting. *Arch Neurol* 2003 Aug;60:1045-1049.
- (21) Gordon PH, Cheng B, Katz IB, Mitsumoto H, Rowland LP. Clinical features that distinguish PLS, upper motor neuron-dominant ALS, and typical ALS. *Neurology* 2009 Jun 2;72:1948-1952.
- (22) Pringle CE, Hudson AJ, Munoz DG, Kiernan JA, Brown WF, Ebers GC. Primary lateral sclerosis. Clinical features, neuropathology and diagnostic criteria. *Brain* 1992 Apr;115 (Pt 2):495-520.
- (23) Singer MA, Statland JM, Wolfe GI, Barohn RJ. Primary lateral sclerosis. *Muscle Nerve* 2007 Mar;35:291-302.
- (24) Gordon P. History of ALS. In: Mitsumoto H, Przedborski S, Gordon P, eds. *Amyotrophic Lateral Sclerosis*. New York: Taylor & Francis Group, 2006:1-16.
- (25) Rowland LP. Progressive muscular atrophy and other lower motor neuron syndromes of adults. *Muscle Nerve* 2010 Feb;41:161-165.
- (26) Kim WK, Liu X, Sandner J, et al. Study of 962 patients indicates progressive muscular atrophy is a form of ALS. *Neurology* 2009 Nov 17;73:1686-1692.
- (27) Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996-2000. *J Neurol Neurosurg Psychiatry* 2003 Sep;74:1258-1261.
- (28) Andersen PM, Borasio GD, Dengler R, et al. EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. *Eur J Neurol* 2005 Dec;12:921-938.
- (29) Miller RG, Rosenberg JA, Gelinas DF, et al. Practice parameter: The care of the patient with amyotrophic lateral sclerosis (An evidence-based review). *Muscle Nerve* 1999 Aug;22:1104-1118.
- (30) Rowland LP. Dr. Rowland's six levels of hope. *ALSD33ALA-On-Line ALS Digest #332* 1997.

- (31) ForsheW DA, Bromberg MB. A survey of clinicians' practice in the symptomatic treatment of ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003 Dec;4:258-263.
- (32) Bellingham MC. A review of the neural mechanisms of action and clinical efficiency of riluzole in treating amyotrophic lateral sclerosis: what have we learned in the last decade? *CNS Neurosci Ther* 2011 Feb;17:4-31.
- (33) Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med* 1994 Mar 3;330:585-591.
- (34) Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet* 1996 May 25;347:1425-1431.
- (35) Practice advisory on the treatment of amyotrophic lateral sclerosis with riluzole: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1997 Sep;49:657-659.
- (36) Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2007;CD001447.
- (37) Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2012;3:CD001447.
- (38) Lacomblez L, Bensimon G, Leigh PN, et al. Long-term safety of riluzole in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2002 Mar;3:23-29.
- (39) Miller RG, Bouchard JP, Duquette P, et al. Clinical trials of riluzole in patients with ALS. ALS/Riluzole Study Group-II. *Neurology* 1996 Oct;47:S86-S90.
- (40) Walley T. Neuropsychotherapeutics in the UK: what has been the impact of NICE on prescribing? *CNS Drugs* 2004;18:1-12.
- (41) Gordon PH, Mitsumoto H. Chapter 20 Symptomatic therapy and palliative aspects of clinical care. *Handb Clin Neurol* 2007;82:389-424.
- (42) Haute Autorité de Santé. Prise en charge de personnes atteintes de sclérose latérale amyotrophique; conférence de consensus. 2006.
- (43) Limousin N, Blasco H, Corcia P, et al. Malnutrition at the time of diagnosis is associated with a shorter disease duration in ALS. *J Neurol Sci* 2010 Oct 15;297:36-39.
- (44) Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. *Neurology* 1998 Jan;50:66-72.
- (45) Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009 Oct 13;73:1218-1226.

- (46) Mitsumoto H, Davidson M, Moore D, et al. Percutaneous endoscopic gastrostomy (PEG) in patients with ALS and bulbar dysfunction. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003 Sep;4:177-185.
- (47) bdelnour-Mallet M, Verschueren A, Guy N, et al. Safety of home parenteral nutrition in patients with amyotrophic lateral sclerosis: a French national survey. *Amyotroph Lateral Scler* 2011 May;12:178-184.
- (48) Morgan RK, McNally S, Alexander M, Conroy R, Hardiman O, Costello RW. Use of Sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 2005 Feb 1;171:269-274.
- (49) Heckmatt JZ, Loh L, Dubowitz V. Night-time nasal ventilation in neuromuscular disease. *Lancet* 1990 Mar 10;335:579-582.
- (50) Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol* 2006 Feb;5:140-147.
- (51) Newsom-Davis IC, Lyall RA, Leigh PN, Moxham J, Goldstein LH. The effect of non-invasive positive pressure ventilation (NIPPV) on cognitive function in amyotrophic lateral sclerosis (ALS): a prospective study. *J Neurol Neurosurg Psychiatry* 2001 Oct;71:482-487.
- (52) Gordon PH, Salachas F, Bruneteau G, et al. Improving survival in a large French ALS center cohort. *J Neurol* 2012 Jan 19.
- (53) Lechtzin N, Wiener CM, Clawson L, et al. Use of noninvasive ventilation in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2004 Mar;5:9-15.
- (54) Gordon PH, Corcia P, Lacomblez L, et al. Defining survival as an outcome measure in amyotrophic lateral sclerosis. *Arch Neurol* 2009 Jun;66:758-761.
- (55) Bradley MD, Orrell RW, Clarke J, et al. Outcome of ventilatory support for acute respiratory failure in motor neurone disease. *J Neurol Neurosurg Psychiatry* 2002 Jun;72:752-756.
- (56) Oliver D. Opioid medication in the palliative care of motor neurone disease. *Palliat Med* 1998 Mar;12:113-115.
- (57) Logroscino G, Traynor BJ, Hardiman O, et al. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry* 2010 Apr;81:385-390.
- (58) Rothstein JD. Current hypotheses for the underlying biology of amyotrophic lateral sclerosis. *Ann Neurol* 2009 Jan;65 Suppl 1:S3-S9.
- (59) Gordon PH, Meininger V. How can we improve clinical trials in amyotrophic lateral sclerosis? *Nat Rev Neurol* 2011 Nov;7:650-654.
- (60) Annegers JF, Appel S, Lee JR, Perkins P. Incidence and prevalence of amyotrophic lateral sclerosis in Harris County, Texas, 1985-1988. *Arch Neurol* 1991 Jun;48:589-593.

- (61) Beghi E, Millul A, Micheli A, Vitelli E, Logroscino G. Incidence of ALS in Lombardy, Italy. *Neurology* 2007 Jan 9;68:141-145.
- (62) Marin B, Gil J, Preux PM, Funalot B, Couratier P. Incidence of amyotrophic lateral sclerosis in the Limousin region of France, 1997-2007. *Amyotroph Lateral Scler* 2009 Aug;10:216-220.
- (63) Alonso A, Logroscino G, Jick SS, Hernan MA. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. *Eur J Neurol* 2009 Jun;16:745-751.
- (64) Chio A, Mora G, Calvo A, Mazzini L, Bottacchi E, Mutani R. Epidemiology of ALS in Italy: a 10-year prospective population-based study. *Neurology* 2009 Feb 24;72:725-731.
- (65) Fang F, Valdimarsdottir U, Bellocco R, et al. Amyotrophic lateral sclerosis in Sweden, 1991-2005. *Arch Neurol* 2009 Apr;66:515-519.
- (66) Cronin S, Hardiman O, Traynor BJ. Ethnic variation in the incidence of ALS: a systematic review. *Neurology* 2007 Mar 27;68:1002-1007.
- (67) Murphy M, Quinn S, Young J, Parkin P, Taylor B. Increasing incidence of ALS in Canterbury, New Zealand: a 22-year study. *Neurology* 2008 Dec 2;71:1889-1895.
- (68) Sorenson EJ, Stalker AP, Kurland LT, Windebank AJ. Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925 to 1998. *Neurology* 2002 Jul 23;59:280-282.
- (69) Mandrioli J, Faglioni P, Merelli E, Sola P. The epidemiology of ALS in Modena, Italy. *Neurology* 2003 Feb 25;60:683-689.
- (70) O'Toole O, Traynor BJ, Brennan P, et al. Epidemiology and clinical features of amyotrophic lateral sclerosis in Ireland between 1995 and 2004. *J Neurol Neurosurg Psychiatry* 2008 Jan;79:30-32.
- (71) Chio A, Magnani C, Oddenino E, Tolardo G, Schiffer D. Accuracy of death certificate diagnosis of amyotrophic lateral sclerosis. *J Epidemiol Community Health* 1992 Oct;46:517-518.
- (72) Marin B, Couratier P, Preux PM, Logroscino G. Can mortality data be used to estimate amyotrophic lateral sclerosis incidence? *Neuroepidemiology* 2011;36:29-38.
- (73) Seljeseth YM, Vollset SE, Tysnes OB. Increasing mortality from amyotrophic lateral sclerosis in Norway? *Neurology* 2000 Nov 14;55:1262-1266.
- (74) Maasilta P, Jokelainen M, Loytonen M, Sabel CE, Gatrell AC. Mortality from amyotrophic lateral sclerosis in Finland, 1986-1995. *Acta Neurol Scand* 2001 Oct;104:232-235.
- (75) Noonan CW, White MC, Thurman D, Wong LY. Temporal and geographic variation in United States motor neuron disease mortality, 1969-1998. *Neurology* 2005 Apr 12;64:1215-1221.
- (76) Durrleman S, Alperovitch A. Increasing trend of ALS in France and elsewhere: are the changes real? *Neurology* 1989 Jun;39:768-773.
- (77) Dean G, Elian M. Motor neuron disease and multiple sclerosis mortality in Australia, New Zealand and South Africa compared with England and Wales. *J Neurol Neurosurg Psychiatry* 1993 Jun;56:633-637.

- (78) Chio A, Magnani C, Schiffer D. Amyotrophic lateral sclerosis mortality in Italy, 1958 to 1987: a cross-sectional and cohort study. *Neurology* 1993 May;43:927-930.
- (79) Al-Chalabi A, Fang F, Hanby MF, et al. An estimate of amyotrophic lateral sclerosis heritability using twin data. *J Neurol Neurosurg Psychiatry* 2010 Dec;81:1324-1326.
- (80) Chio A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler* 2009 Oct;10:310-323.
- (81) Majoor-Krakauer D, Ottman R, Johnson WG, Rowland LP. Familial aggregation of amyotrophic lateral sclerosis, dementia, and Parkinson's disease: evidence of shared genetic susceptibility. *Neurology* 1994 Oct;44:1872-1877.
- (82) Fallis BA, Hardiman O. Aggregation of neurodegenerative disease in ALS kindreds. *Amyotroph Lateral Scler* 2009 Apr;10:95-98.
- (83) Chio A, Schymick JC, Restagno G, et al. A two-stage genome-wide association study of sporadic amyotrophic lateral sclerosis. *Hum Mol Genet* 2009 Apr 15;18:1524-1532.
- (84) Cronin S, Tomik B, Bradley DG, Slowik A, Hardiman O. Screening for replication of genome-wide SNP associations in sporadic ALS. *Eur J Hum Genet* 2009 Feb;17:213-218.
- (85) Fernandez-Santiago R, Sharma M, Berg D, et al. No evidence of association of FLJ10986 and ITPR2 with ALS in a large German cohort. *Neurobiol Aging* 2011 Mar;32:551-554.
- (86) Shatunov A, Mok K, Newhouse S, et al. Chromosome 9p21 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study. *Lancet Neurol* 2010 Oct;9:986-994.
- (87) van Es MA, van Vught PW, Veldink JH, et al. Analysis of FGGY as a risk factor for sporadic amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2009 Oct;10:441-447.
- (88) Diekstra FP, Saris CG, van RW, et al. Mapping of gene expression reveals CYP27A1 as a susceptibility gene for sporadic ALS. *PLoS One* 2012;7:e35333.
- (89) Dunckley T, Huentelman MJ, Craig DW, et al. Whole-genome analysis of sporadic amyotrophic lateral sclerosis. *N Engl J Med* 2007 Aug 23;357:775-788.
- (90) van Es MA, van Vught PW, Blauw HM, et al. ITPR2 as a susceptibility gene in sporadic amyotrophic lateral sclerosis: a genome-wide association study. *Lancet Neurol* 2007 Oct;6:869-877.
- (91) van Es MA, van Vught PW, Blauw HM, et al. Genetic variation in DPP6 is associated with susceptibility to amyotrophic lateral sclerosis. *Nat Genet* 2008 Jan;40:29-31.
- (92) Simpson CL, Lemmens R, Miskiewicz K, et al. Variants of the elongator protein 3 (ELP3) gene are associated with motor neuron degeneration. *Hum Mol Genet* 2009 Feb 1;18:472-481.
- (93) Andersen PM, Al-Chalabi A. Clinical genetics of amyotrophic lateral sclerosis: what do we really know? *Nat Rev Neurol* 2011 Nov;7:603-615.

- (94) Dion PA, Daoud H, Rouleau GA. Genetics of motor neuron disorders: new insights into pathogenic mechanisms. *Nat Rev Genet* 2009 Nov;10:769-782.
- (95) Gurney ME, Pu H, Chiu AY, et al. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. *Science* 1994 Jun 17;264:1772-1775.
- (96) Ludolph AC, Bendotti C, Blaugrund E, et al. Guidelines for preclinical animal research in ALS/MND: A consensus meeting. *Amyotroph Lateral Scler* 2010;11:38-45.
- (97) Millicamps S, Salachas F, Cazeneuve C, et al. SOD1, ANG, VAPB, TARDBP, and FUS mutations in familial amyotrophic lateral sclerosis: genotype-phenotype correlations. *J Med Genet* 2010 Aug;47:554-560.
- (98) Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006 Oct 6;314:130-133.
- (99) Sreedharan J, Blair IP, Tripathi VB, et al. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science* 2008 Mar 21;319:1668-1672.
- (100) Strong MJ. The syndromes of frontotemporal dysfunction in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2008 Dec;9:323-338.
- (101) Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001 May 31;344:1688-1700.
- (102) Nelson LM, McGuire V, Longstreth WT, Jr., Matkin C. Population-based case-control study of amyotrophic lateral sclerosis in western Washington State. I. Cigarette smoking and alcohol consumption. *Am J Epidemiol* 2000 Jan 15;151:156-163.
- (103) Horner RD, Kamins KG, Feussner JR, et al. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 2003 Sep 23;61:742-749.
- (104) Gallo V, Bueno-De-Mesquita HB, Vermeulen R, et al. Smoking and risk for amyotrophic lateral sclerosis: analysis of the EPIC cohort. *Ann Neurol* 2009 Apr;65:378-385.
- (105) Weisskopf MG, Ascherio A. Cigarettes and amyotrophic lateral sclerosis: only smoke or also fire? *Ann Neurol* 2009 Apr;65:361-362.
- (106) Sutedja NA, Veldink JH, Fischer K, et al. Lifetime occupation, education, smoking, and risk of ALS. *Neurology* 2007 Oct 9;69:1508-1514.
- (107) Weisskopf MG, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. Prospective study of cigarette smoking and amyotrophic lateral sclerosis. *Am J Epidemiol* 2004 Jul 1;160:26-33.
- (108) Alonso A, Logroscino G, Hernan MA. Smoking and the risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2010 Nov;81:1249-1252.
- (109) Alonso A, Logroscino G, Jick SS, Hernan MA. Association of smoking with amyotrophic lateral sclerosis risk and survival in men and women: a prospective study. *BMC Neurol* 2010;10:6.

- (110) Armon C. Smoking may be considered an established risk factor for sporadic ALS. *Neurology* 2009 Nov 17;73:1693-1698.
- (111) Wang H, O'Reilly EJ, Weisskopf MG, et al. Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of 5 prospective cohorts. *Arch Neurol* 2011 Feb;68:207-213.
- (112) Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity athletics in ALS. *Neurology* 2002 Sep 10;59:773-775.
- (113) Sutedja NA, Veldink JH, Fischer K, et al. Exposure to chemicals and metals and risk of amyotrophic lateral sclerosis: a systematic review. *Amyotroph Lateral Scler* 2009 Oct;10:302-309.
- (114) McGuire V, Longstreth WT, Jr., Nelson LM, et al. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. *Am J Epidemiol* 1997 Jun 15;145:1076-1088.
- (115) Chio A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* 2005 Mar;128:472-476.
- (116) Armon C. Sports and trauma in amyotrophic lateral sclerosis revisited. *J Neurol Sci* 2007 Nov 15;262:45-53.
- (117) Beghi E, Logroscino G, Chio A, et al. Amyotrophic lateral sclerosis, physical exercise, trauma and sports: results of a population-based pilot case-control study. *Amyotroph Lateral Scler* 2010 May 3;11:289-292.
- (118) Chen H, Richard M, Sandler DP, Umbach DM, Kamel F. Head injury and amyotrophic lateral sclerosis. *Am J Epidemiol* 2007 Oct 1;166:810-816.
- (119) Pupillo E, Messina P, Logroscino G, et al. Trauma and amyotrophic lateral sclerosis: a case-control study from a population-based registry. *Eur J Neurol* 2012 Apr 27.
- (120) Cedarbaum JM, Stambler N. Disease status and use of ventilatory support by ALS patients. BDNF Study Group. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2001 Mar;2:19-22.
- (121) A double-blind placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rHCNTF) in amyotrophic lateral sclerosis. ALS CNTF Treatment Study Group. *Neurology* 1996 May;46:1244-1249.
- (122) Miller RG, Moore DH, Gelinas DF, et al. Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 2001 Apr 10;56:843-848.
- (123) Cudkovicz ME, Shefner JM, Schoenfeld DA, et al. A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis. *Neurology* 2003 Aug 26;61:456-464.
- (124) great lakes study group. A comparison of muscle strength testing techniques in amyotrophic lateral sclerosis. *Neurology* 2003 Dec 9;61:1503-1507.
- (125) Sorenson EJ, Windbank AJ, Mandrekar JN, et al. Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. *Neurology* 2008 Nov 25;71:1770-1775.

- (126) Cedarbaum JM, Stambler N. Performance of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFERS) in multicenter clinical trials. *J Neurol Sci* 1997 Oct;152 Suppl 1:S1-S9.
- (127) Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci* 1999 Oct 31;169:13-21.
- (128) Levy G, Kaufmann P, Buchsbaum R, et al. A two-stage design for a phase II clinical trial of coenzyme Q10 in ALS. *Neurology* 2006 Mar 14;66:660-663.
- (129) Scelsa SN, MacGowan DJ, Mitsumoto H, et al. A pilot, double-blind, placebo-controlled trial of indinavir in patients with ALS. *Neurology* 2005 Apr 12;64:1298-1300.
- (130) Gordon PH, Moore DH, Miller RG, et al. Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial. *Lancet Neurol* 2007 Dec;6:1045-1053.
- (131) Meininger V, Drory VE, Leigh PN, Ludolph A, Robberecht W, Silani V. Glatiramer acetate has no impact on disease progression in ALS at 40 mg/day: a double-blind, randomized, multicentre, placebo-controlled trial. *Amyotroph Lateral Scler* 2009 Oct;10:378-383.
- (132) Kaufmann P, Levy G, Thompson JL, et al. The ALSFRS-R predicts survival time in an ALS clinic population. *Neurology* 2005 Jan 11;64:38-43.
- (133) Montes J, Levy G, Albert S, et al. Development and evaluation of a self-administered version of the ALSFRS-R. *Neurology* 2006 Oct 10;67:1294-1296.
- (134) Gordon PH, Cheng B, Salachas F, et al. Progression in ALS is not linear but is curvilinear. *J Neurol* 2010 Oct;257:1713-1717.
- (135) Gordon PH, Cheng B, Montes J, Doorish C, Albert SM, Mitsumoto H. Outcome measures for early phase clinical trials. *Amyotroph Lateral Scler* 2007 Oct;8:270-273.
- (136) Schmidt EP, Drachman DB, Wiener CM, Clawson L, Kimball R, Lechtzin N. Pulmonary predictors of survival in amyotrophic lateral sclerosis: use in clinical trial design. *Muscle Nerve* 2006 Jan;33:127-132.
- (137) A controlled trial of recombinant methionyl human BDNF in ALS: The BDNF Study Group (Phase III). *Neurology* 1999 Apr 22;52:1427-1433.
- (138) Meininger V, Bensimon G, Bradley WR, et al. Efficacy and safety of xaliproden in amyotrophic lateral sclerosis: results of two phase III trials. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2004 Jun;5:107-117.
- (139) Sanjak M, Salachas F, Frija-Orvoen E, et al. Quality control of vital capacity as a primary outcome measure during phase III therapeutic clinical trial in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2010 Aug;11:383-388.
- (140) Logroscino G, Traynor BJ, Hardiman O, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry* 2008 Jan;79:6-11.

- (141) Louwrese ES, Visser CE, Bossuyt PM, Weverling GJ. Amyotrophic lateral sclerosis: mortality risk during the course of the disease and prognostic factors. The Netherlands ALS Consortium. *J Neurol Sci* 1997 Oct;152 Suppl 1:S10-S17.
- (142) del Aguila MA, Longstreth WT, Jr., McGuire V, Koepsell TD, van BG. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology* 2003 Mar 11;60:813-819.
- (143) Testa D, Lovati R, Ferrarini M, Salmoiraghi F, Filippini G. Survival of 793 patients with amyotrophic lateral sclerosis diagnosed over a 28-year period. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2004 Dec;5:208-212.
- (144) Millul A, Beghi E, Logroscino G, Micheli A, Vitelli E, Zardi A. Survival of patients with amyotrophic lateral sclerosis in a population-based registry. *Neuroepidemiology* 2005;25:114-119.
- (145) Czaplinski A, Yen AA, Appel SH. Amyotrophic lateral sclerosis: early predictors of prolonged survival. *J Neurol* 2006 Nov;253:1428-1436.
- (146) Kollwe K, Mauss U, Krampfl K, Petri S, Dengler R, Mohammadi B. ALSFRS-R score and its ratio: a useful predictor for ALS-progression. *J Neurol Sci* 2008 Dec 15;275:69-73.
- (147) Zoccolella S, Beghi E, Palagano G, et al. Predictors of long survival in amyotrophic lateral sclerosis: a population-based study. *J Neurol Sci* 2008 May 15;268:28-32.
- (148) Chio A, Mora G, Leone M, et al. Early symptom progression rate is related to ALS outcome: a prospective population-based study. *Neurology* 2002 Jul 9;59:99-103.
- (149) Paillisse C, Lacomblez L, Dib M, Bensimon G, Garcia-Acosta S, Meininger V. Prognostic factors for survival in amyotrophic lateral sclerosis patients treated with riluzole. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2005 Mar;6:37-44.
- (150) Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. *Neurology* 1999 Sep 22;53:1059-1063.
- (151) Lopez-Vega JM, Calleja J, Combarros O, Polo JM, Berciano J. Motor neuron disease in Cantabria. *Acta Neurol Scand* 1988 Jan;77:1-5.
- (152) 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;240:339-346.
- (153) Preux PM, Couratier P, Boutros-Toni F, et al. Survival prediction in sporadic amyotrophic lateral sclerosis. Age and clinical form at onset are independent risk factors. *Neuroepidemiology* 1996;15:153-160.
- (154) Zoccolella S, Beghi E, Palagano G, et al. Analysis of survival and prognostic factors in amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry* 2008 Jan;79:33-37.
- (155) Tysnes OB, Vollset SE, Aarli JA. Epidemiology of amyotrophic lateral sclerosis in Hordaland county, western Norway. *Acta Neurol Scand* 1991 May;83:280-285.

- (156) Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. *Brain* 1995 Jun;118 (Pt 3):707-719.
- (157) Thijs V, Peeters E, Theys P, Matthijs G, Robberecht W. Demographic characteristics and prognosis in a Flemish amyotrophic lateral sclerosis population. *Acta Neurol Belg* 2000 Jun;100:84-90.
- (158) Beghi E, Millul A, Logroscino G, Vitelli E, Micheli A. Outcome measures and prognostic indicators in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2008 Jun;9:163-167.
- (159) Ganesalingam J, Stahl D, Wijesekera L, et al. Latent cluster analysis of ALS phenotypes identifies prognostically differing groups. *PLoS One* 2009;4:e7107.
- (160) Czaplinski A, Yen AA, Appel SH. Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. *J Neurol Neurosurg Psychiatry* 2006 Mar;77:390-392.
- (161) Kimura F, Fujimura C, Ishida S, et al. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. *Neurology* 2006 Jan 24;66:265-267.
- (162) Gordon PH, Cheung YK. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. *Neurology* 2006 Oct 10;67:1314-1315.
- (163) McDonald ER, Wiedenfeld SA, Hillel A, Carpenter CL, Walter RA. Survival in amyotrophic lateral sclerosis. The role of psychological factors. *Arch Neurol* 1994 Jan;51:17-23.
- (164) Chio A, Finocchiaro E, Meineri P, Bottacchi E, Schiffer D. Safety and factors related to survival after percutaneous endoscopic gastrostomy in ALS. ALS Percutaneous Endoscopic Gastrostomy Study Group. *Neurology* 1999 Sep 22;53:1123-1125.
- (165) Meininger V, Asselain B, Guillet P, et al. Pentoxifylline in ALS: a double-blind, randomized, multicenter, placebo-controlled trial. *Neurology* 2006 Jan 10;66:88-92.
- (166) Czaplinski A, Yen AA, Simpson EP, Appel SH. Slower disease progression and prolonged survival in contemporary patients with amyotrophic lateral sclerosis: is the natural history of amyotrophic lateral sclerosis changing? *Arch Neurol* 2006 Aug;63:1139-1143.
- (167) Qureshi M, Schoenfeld DA, Paliwal Y, Shui A, Cudkowicz ME. The natural history of ALS is changing: improved survival. *Amyotroph Lateral Scler* 2009 Oct;10:324-331.
- (168) Cheung YK, Gordon PH, Levin B. Selecting promising ALS therapies in clinical trials. *Neurology* 2006 Nov 28;67:1748-1751.
- (169) Aggarwal SP, Zinman L, Simpson E, et al. Safety and efficacy of lithium in combination with riluzole for treatment of amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2010 May;9:481-488.
- (170) Ludolph AC, Bendotti C, Blaugrund E, et al. Guidelines for the preclinical in vivo evaluation of pharmacological active drugs for ALS/MND: report on the 142nd ENMC international workshop. *Amyotroph Lateral Scler* 2007 Aug;8:217-223.

- (171) European Parliament and Council of the European Union. Directive 2001/20/ZC of the European Parliament and the Council of 4 April 2001. *OJ L* 2001;121:34-44.
- (172) Hunter P. Facing the credit crunch. Politics sends mixed messages for science in the wake of the global financial crisis. *EMBO Rep* 2010 Dec;11:924-926.
- (173) Clayton D, Schiffers E. Models for temporal variation in cancer rates. I: Age-period and age-cohort models. *Stat Med* 1987 Jun;6:449-467.
- (174) Clayton D, Schiffers E. Models for temporal variation in cancer rates. II: Age-period-cohort models. *Stat Med* 1987 Jun;6:469-481.
- (175) Goetz CG. Chapter 15: Jean-Martin Charcot and the anatomico-clinical method of neurology. *Handb Clin Neurol* 2010;95:203-212.
- (176) Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004 Dec 30;23:3803-3820.
- (177) Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology* 1995 Jul;6:356-365.
- (178) Royston P, Sauerbrei W. Multivariable modeling with cubic regression splines: a principled approach. *The Stata Journal* 2007;7:45-70.
- (179) Pinto AC, Evangelista T, Carvalho M, Alves MA, Sales Luis ML. Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. *J Neurol Sci* 1995 May;129 Suppl:19-26.
- (180) Preux PM, Druet-Cabanac M, Couratier P, et al. Estimation of the amyotrophic lateral sclerosis incidence by capture-recapture method in the Limousin region of France. *J Clin Epidemiol* 2000 Oct;53:1025-1029.
- (181) Weisz D, Gusmano MK, Rodwin VG. Gender and the treatment of heart disease in older persons in the United States, France, and England: a comparative, population-based view of a clinical phenomenon. *Gen Med* 2004 Aug;1:29-40.
- (182) Ragonese P, Filippini G, Salemi G, et al. Accuracy of death certificates for amyotrophic lateral sclerosis varies significantly from north to south of Italy: implications for mortality studies. *Neuroepidemiology* 2004 Jan;23:73-77.
- (183) de Rijk MC, Breteler MM, Graveland GA, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. *Neurology* 1995 Dec;45:2143-2146.
- (184) Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: a preliminary report. 1954. *BMJ* 2004 Jun 26;328:1529-1533.
- (185) World Federation of Neurology Research Group on Neuromuscular Diseases Subcommittee on Motor Neuron Disease. Airlie House guidelines. Therapeutic trials in amyotrophic lateral sclerosis. Airlie House "Therapeutic Trials in ALS" Workshop Contributors. *J Neurol Sci* 1995 May;129 Suppl:1-10.

- (186) Cudkowicz M, Bozik ME, Ingersoll EW, et al. The effects of dextramipexole (KNS-760704) in individuals with amyotrophic lateral sclerosis. *Nat Med* 2011 Dec;17:1652-1656.
- (187) Aboussouan LS, Khan SU, Banerjee M, Arroliga AC, Mitsumoto H. Objective measures of the efficacy of noninvasive positive-pressure ventilation in amyotrophic lateral sclerosis. *Muscle Nerve* 2001 Mar;24:403-409.
- (188) Gil J, Funalot B, Verschueren A, et al. Causes of death amongst French patients with amyotrophic lateral sclerosis: a prospective study. *Eur J Neurol* 2008 Nov;15:1245-1251.
- (189) Marin B, Desport JC, Kajeu P, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. *J Neurol Neurosurg Psychiatry* 2011 Jun;82:628-634.