J Neurol (1994) 241:448–455

ORIGINAL COMMUNICATION

Stuart Neilson
Ian Robinson
Annick Alperovitch

Rising amyotrophic lateral sclerosis mortality in France 1968–1990: increased life expectancy and inter-disease competition as an explanation

Received: 20 May 1993
Received in revised form: 3 November 1993
Accepted: 8 November 1993

S. Neilson (✉) · I. Robinson
The John Bevan MND Research Unit,
Department of Human Sciences,
Brunel, The University of West London,
Uxbridge, Middlesex, UB8 3PH, UK

A. Alperovitch
INSERM U.360,
16 Avenue Paul-Vaillant-Couturier,
F-94807 Villejuif Cedex, France

Abstract Gompertzian analysis is a statistical technique which has been successfully applied to the analysis of amyotrophic lateral sclerosis (ALS) mortality in England and Wales, Japan and the United States. This paper analyses the consistent trend of rising ALS mortality in France over the years 1968–1990, a period during which crude mortality rose from 400 deaths in 1968 to 950 deaths in 1990. The findings indicate that age-specific mortality rates have risen at ages older than 54 years for men and 53 years for women and decreased slightly at younger ages. The evolving ALS mortality pattern is attributable to changing inter-disease competition resulting from the increased life expectancy of the French population, rather than to changing environmental aetiopathogenic factors or to substantial artefact effects.

Key words Amyotrophic lateral sclerosis · Survival · Mortality Gompertzian analysis · France

Introduction

Despite intensive epidemiological research and laboratory-based studies, amyotrophic lateral sclerosis (ALS) remains as significant a challenge to medicine [29] as when it was first described [5]. Recent studies in a wide range of countries [2, 11, 14, 20, 45], including France [6, 7], have pointed to a worldwide trend of rising ALS incidence and mortality.

The search for the causes of this worldwide trend has centred on either particular and changing environmental factors [1, 3, 10, 16, 17, 21] or on the possibility of the trend being an artefact of increased recognition of existing cases of the disease at diagnosis or death [40]. Although it appears plausible that increased knowledge of ALS amongst both physicians and patients has contributed in some measure to the increased recognition of cases of the disease, the uniformity of the rise in patterns of ALS mortality in many advanced industrialised societies – with very different health care systems, neurological services and patient organisations – suggests that such an explanation is problematic and, in the light of present research into ALS, is largely speculative [8, 15, 44].

Detailed research attention has been paid to exogenous environmental factors as causes for the rising world trends in ALS mortality. Intensive analysis of many factors [15, 44] has identified some weak but statistically significant associations in single countries or in regions within countries, but no factor has yet been identified which could consistently account for the worldwide uniformity of the rising rates. In particular, a large number of environmental variables associated with advanced industrialised societies have been considered as potential aetiological agents in relation to ALS, some on the basis of their known neurotoxicity, but at present it appears that their role must be considered at best unproven. Thus the conclusion of investigators tends to be that there are unknown exogenous factor(s) to which the populations of industrialised countries have (relatively) recently become subject, but to which the populations of other, largely developing countries and some minority populations in developed countries appear to have some resistance [4, 30]. This conclusion has led to an even more intensive and continuing search for exogenous ALS risk factors which has proved so far largely unproductive.

Recently it has become clear that general theories of ageing and mortality may be of considerable utility in un-

covering the most plausible reasons for the worldwide trends in ALS deaths. It has become commonplace to observe that changing patterns of mortality have been associated with demographic change. In many industrialised countries mortality from infectious diseases has been replaced – at a later age – by mortality from chronic cardiovascular and respiratory conditions, amongst others. Mortality at these later ages is undoubtedly "caused" in two senses, first through the action of specific endogenous and/or exogenous factors on individuals, but second through changing demographic structure (especially increased life expectancy through the reduction in general mortality) which results in a larger proportion of the population living to the ages at which most mortality from cardiovascular and respiratory diseases occurs. In a number of countries the beginning of a further trend is apparent with falling cardiovascular mortality, and rising mortality from neurological diseases at even older ages as the life expectancy of populations rises through the critical years at which mortality from certain neurological diseases is already most prevalent. It thus appears that population life expectancies, and what has been described as "competition" between diseases is a critical variable in determining patterns of mortality, whatever the aetiologies of specific diseases for individual patients. In the case of ALS, it is a disease whose expression, in the form of both onset and mortality, mainly occurs in the upper band of current life expectancies in industrialised countries [4].

The majority of studies use conventional epidemiological techniques to analyse changing mortality patterns which, despite great statistical sophistication, fail to account for life expectancy and changing "competition" between causes of death. The analysis of survival distributions with increasing failure (mortality) rates has proved to be of particular importance in relation to the investigation of trends in mortality in later life. Amongst the models used for this kind of analysis the exponential, the Weibull, the Gompertz, and the Gompertz-Makeham have been the most useful. One of the most promising of these models of mortality and ageing for the analysis of rising ALS in France, which specifically takes into account life expectancy and inter-disease competition, is based on the observations of Gompertz [9], a nineteenth century English actuary. He noted that the relationship between age and mortality was an exponential one. In recent years his arguments have been used to develop further theoretical approaches to understanding patterns of general mortality, and to investigate the changing characteristics of mortality from individual diseases [18, 39]. The technique has proved appropriate to the analysis of adult mortality [33], stroke [36] and Parkinson's disease [35] mortality in the United States. Application of the Gompertzian relationship to the rising trend of mortality from ALS in the United States, and to a similar trend in England and Wales both nationally [25, 26] and regionally [23], has demonstrated its explanatory power [27]. These analyses have shown that the rises in mortality from ALS in recent decades in both these countries are almost entirely associated with the increased life expectancies of the general population over that time, rather than being associated with either changing environmental or artefact effects. Furthermore, mortality appears from these studies to be confined to a defined subpopulation of similar size in each country and region.

An analysis of ALS mortality in France from 1968 to 1990 provides an additional comparative means of testing the general hypothesis that rising mortality from the disease is strongly related to population life expectancy, and results from changing inter-disease competition, rather than having its origin in environmental aetiopathogenesis, or in artefact effects. In addition, such an analysis complements recent thorough investigations of French ALS mortality using more traditional epidemiological techniques [7].

Materials and methods

In France, the Institut National de la Santé et de la Récherche Medical (INSERM) is responsible for collecting and recording all death certificates. The data provided by INSERM include certificates where ALS was coded as the underlying cause of death under the rubric of the International Classification of Diseases (ICD-7 356.1 [42], ICD-8 348.0 [43] and ICD-9 335.2 [41] for the 23 years from 1968 to 1990. Deaths were categorised by sex and by age in the 5-year age-groups 0–4, etc., up to 85 years and over. Population data were supplied in the same age and sex categories for the years 1968, 1975 and 1990. Linear interpolation was used to calculate population distributions for the intervening years. In Fance unclassified causes remain a significant proportion, of the order of 5%, of all deaths [13] and it cannot be determined what proportion of these might be attributable to ALS [7]. However, ALS mortality records, despite significant problems of diagnosis [22], have been shown to encompass the majority of previously diagnosed cases of the disease [12, 32].

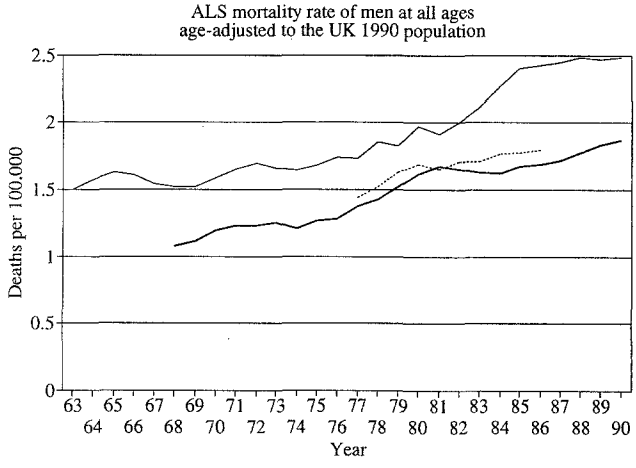

Fig. 1 Amyotrophic lateral sclerosis (ALS) mortality rate for men at all ages in France, 1968–1990; age-adjusted to the 1990 UK population. —— France; —— England and Wales; ----- United States

Table 1 Age-specific amyotrophic lateral sclerosis (ALS) mortality rates in France in 1968 and in 1990

Age (years)	Men		Women	
	1968	1990	1968	1990
0– 4	0.06	0.00	0.00	0.07
5– 9	0.00	0.00	0.00	0.00
10–14	0.05	0.00	0.00	0.00
15–19	0.09	0.05	0.00	0.00
20–24	0.00	0.09	0.00	0.05
25–29	0.00	0.23	0.07	0.05
30–34	0.13	0.09	0.00	0.05
35–39	0.35	0.19	0.06	0.09
40–44	0.24	0.45	0.12	0.14
45–49	0.91	1.00	0.70	0.55
50–54	1.89	2.44	1.59	1.67
55–59	2.51	2.93	1.91	2.59
60–64	2.56	4.88	2.04	3.18
65–69	4.24	9.10	2.45	5.29
70–74	4.81	7.28	2.66	4.68
75–79	3.97	11.32	1.95	8.17
80–84	3.17	10.59	0.75	4.69
85+	2.98	8.96	1.43	5.17
0–54	0.25	0.35	0.17	0.20
55+	3.35	6.82	2.05	4.57
All ages	0.91	1.80	0.68	1.53

The age-adjusted mortality rate was calculated for the period using the population of England and Wales in 1990 as a reference, and is shown for men in Fig. 1. As can be seen from comparable curves for England and Wales (1963–1990) [25] and for the United States (1977–1986) [34], there is a similar trend of increasing ALS mortality in all three countries. The trend for women is broadly similar, with rates about one-quarter lower than for men. The age-specific mortality rates for both men and women in 1968 and 1990 are given in Table 1.

In a Gompertz model the mortality rate R_x rises by equal proportions in equal intervals of age x, being determined by an initial rate R_0 at age zero and the rate of exponential increase α as shown in Eq. 1. It should be noted that the mortality rate at birth in the Gompertz model is an extrapolation from the age range analysed and does not represent the actual mortality rate at age zero. Taking logarithms of both sides transforms Eq. 1 into the computationally simpler relationship expressed by Eq. 2 in Appendix I.

$$R_x = R_0 10^{\alpha x} \quad (1)$$

Age-specific mortality rates were calculated for all age and sex groups for each year of the study. The mortality rate curve for men is shown for some selected years (1970, 1980 and 1990) in Fig. 2. The curve for women is similar, with rates of approximately half those for men. The procedures set out in Appendix 1 were used to fit a linear model to the logarithm of the mortality rate and test whether adult ALS mortality rates in France conform to the Gompertz model.

The Strehler-Mildvan modification of the Gompertz model [39] provides the possibility of a more comprehensive analysis of the factors influencing ALS mortality. They propose a negative linear relationship between the rate of exponential increase in mortality (α) and the logarithm of the extrapolated mortality rate at age

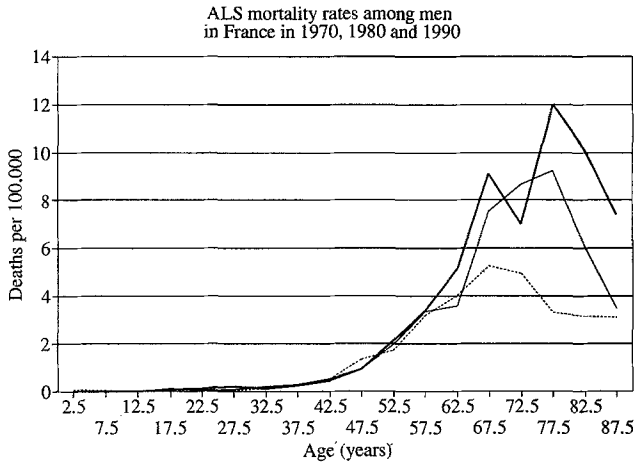

Fig. 2 ALS mortality rate for men in France, selected years. ----- 1970; —— 1980; —— 1980

zero (R_0). This implies that a high initial mortality rate will be accompanied by a low rate of increase with age, and that mortality rate curves, even when drawn from populations with differing life expectancies, will intersect at an age point determined by the rate of ageing *(B)*. Mortality rates at this age point will therefore be static and independent of variations in life expectancy. This relationship was tested by linear regression of the (α, log R_0) pairs calculated from ALS mortality rates in each year studied (see Eq. 3 in Appendix II). This modification of the Gompertz model allows the identification of an aetiopathogenic factor *(K)*, which can be considered to be the sum of all environmental causative influences upon ALS mortality, and which affects mortality rates at all ages by the same proportion. This is in contrast to the competitive effects of changing life expectancy, which decrease early mortality and shift the age distribution of deaths to later ages. Thus, in an unchanging causative environment and with a constant rate of ageing, mortality rates at all ages are determined solely by R_0, as demonstrated (by substitution of Eq. 3 into Eq. 2) in Eq. 4 of Appendix II.

In our previous studies we have proposed that ALS is restricted to an inherently susceptible subpopulation [25] and that increasing mortality rates amongst older age-groups were due to increasing survival of susceptible individuals, effectively increasing the heterogeneity of the elderly human population [31]. We further suggested a means of determining the subpopulation size [24] using the methods given in Appendix III. In the United States [34] and in England and Wales [25, 26] the estimated subpopulation sizes were consistent, both across time and between countries. Environmental causative influences upon ALS mortality (summarised by K) were also found to be essentially constant over considerable periods of time, whilst the extrapolated initial mortality rate (R_0) continuously declined.

Results

The logarithm of the mortality rate over the age range 30–64 years showed a strong linear correlation with age for both men ($0.936 < r^2 < 0.995$) and women ($0.942 < r^2 < 0.986$) for all years studied. The high squared correlation coefficient indicates that the linearised Gompertz model explains more than 93% of the age-specific variation in mortality rates within this age range. For both sexes the

Table 2 Full results of linear regression of ALS mortality rates (ages 30–64) in France, 1968–1990

	Men				Women			
	Log R_0	α	r^2	log K	Log R_0	α	r^2	log K
1968	–2.45	0.05	0.94	1.71	–3.43	0.06	0.94	0.89
1969	–2.49	0.05	0.96	1.83	–3.16	0.06	0.94	0.83
1970	–2.46	0.05	0.97	1.98	–3.04	0.06	0.98	0.83
1971	–2.65	0.05	0.98	1.99	–3.16	0.06	0.94	0.80
1972	–2.58	0.05	0.97	1.91	–3.30	0.06	0.98	0.89
1973	–2.73	0.06	0.96	1.89	–3.27	0.06	0.97	0.96
1974	–2.63	0.05	0.97	1.74	–3.31	0.06	0.98	1.02
1975	–2.70	0.05	0.99	1.73	–3.34	0.06	0.96	0.99
1976	–2.51	0.05	0.99	1.68	–2.99	0.06	0.98	0.98
1977	–2.55	0.05	0.98	1.81	–3.00	0.06	0.96	0.94
1978	–2.49	0.05	0.97	1.84	–3.14	0.06	0.95	0.93
1979	–2.33	0.05	0.97	1.88	–4.02	0.07	0.95	0.84
1980	–2.24	0.05	0.98	1.92	–4.02	0.07	0.95	0.84
1981	–2.28	0.05	0.99	2.02	–3.56	0.07	0.96	0.92
1982	–2.34	0.05	0.99	2.04	–2.86	0.05	0.95	1.04
1983	–2.40	0.05	0.99	2.04	–2.64	0.05	0.94	1.17
1984	–2.70	0.06	0.98	1.97	–2.84	0.06	0.98	1.18
1985	–3.29	0.07	0.97	1.90	–3.18	0.06	0.99	1.20
1986	–3.34	0.07	0.99	1.80	–4.00	0.08	0.95	1.13
1987	–3.18	0.06	0.99	1.86	–3.96	0.08	0.94	1.14
1988	–2.99	0.06	0.99	1.98	–3.96	0.08	0.94	1.14
1989	–2.93	0.06	0.99	2.11	–4.07	0.08	0.96	1.06
1990	–2.85	0.06	0.99	2.10	–4.00	0.08	0.95	1.04
Min.	–3.34	0.05	0.94	1.68	–4.07	0.05	0.94	0.80
Max.	–2.24	0.07	0.99	2.11	–2.64	0.08	0.99	1.20

extrapolated initial rate of mortality (*log* R_0) has declined since 1968, whilst the rate of exponential increase in mortality (α) has increased. The full regression results and values of *log* R_0 and α of Eq. 2 are given in Table 2. The standard errors of both parameters lay between 3% and 11% for men (mean 6%) and between 5% and 12% for women (mean 9%) which, with 7 data points and 5 degrees of freedom, leads to confidence intervals of ± 15.4% and ±23.1% respectively.

A negative linear relationship between the extrapolated initial mortality rate and the rate of exponential increase with age was determined by linear regression of the (α, *log* R_0) pairs for all years, with a squared correlation coefficient of $r^2 = 0.99$ in both sexes. This established a common fixed intersect point in the mortality rate curves for each year and indicated a static aetiopathogenic effect. The logarithm of the mortality rate for the range 30–64 years was therefore defined by Eq. 4 of Appendix II, where R_0 is a variable determined by the competitive effects of increasing life expectancy and where B and K are relatively constant:

$$\log {}^{m}R_x = \log {}^{m}R_0 + 0.01846\,(\log(1.90) - \log {}^{m}R_0)\,x \quad (r^2 = 0.99)$$

$$\log {}^{w}R_x = \log {}^{w}R_0 + 0.01891\,(\log(0.98) - \log {}^{w}R_0)\,x \quad (r^2 = 0.99)$$

The rate of ageing was therefore in the region of 1.8% per annum in both sexes. This determines a set of mortality curves that pass through a fixed point at age $1/B$ and mortality rate K. Thus ALS mortality rates for all years were determined by a set of curves passing through a rate of 1.9 per 100,000 men at an age of 54.2 years and a rate of 0.98 per 100,000 women at an age of 52.9 years.

According to Gompertzian analysis, mortality rates at all ages up to 54.2 years for men and 52.9 years for women have declined over time, whilst those at older ages have risen. This can be examined graphically in Fig. 3, which shows mortality rates in 5-year age groups for men. There is a barely discernible fall in mortality rates below the age of 55 years and an unequivocal increase in mortality rates above the age of 55 years. In addition, the mean age at death has increased from 60.3 to 63.6 years after age adjustment to the 1990 United Kingdom population distribution. A rigorous test was applied to these trends by fitting a linear model to the age-specific mortality rates against time and calculating the rate of change in each group over the period as a percentage of the mean (1968 to 1990) mortality rate, shown in Table 3. There have been declines in the mortality rates in most age groups younger than 55 years, although the 95% confidence intervals reported in Table 3 indicate that these declines are not statistically significant.

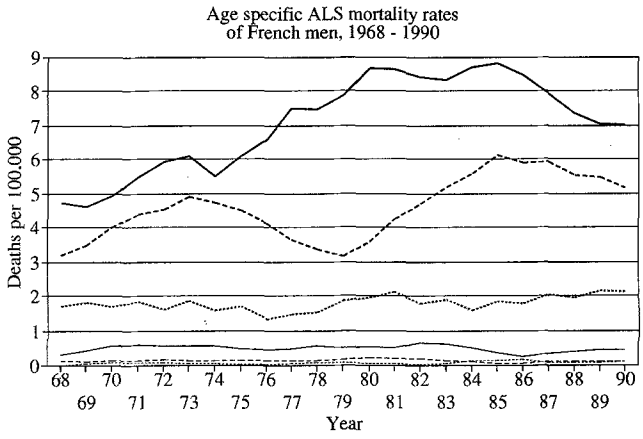

Fig. 3 Age-specific ALS mortality rates for men in France, 1968–1990. ····· 20–24; ----- 30–34; —— 40–44; ····· 50–54; ----- 60–64; —— 70–74

Table 3 Annual percentage change in age-specific ALS mortality rates in France between 1968 and 1990

Age (years)	Men	95% CI	Women	95% CI
0– 4	–13.19	(–25.40, –0.99)	4.79	(–10.65, 20.23)
5– 9	–10.02	(–21.11, 1.08)	–21.97	(–43.23, –0.71)
10–14	–5.97	(–18.67, 6.73)	–15.01	(–29.46, –0.57)
15–19	2.97	(–1.31, 7.25)	–4.12	(–22.86, 14.62)
20–24	4.97	(–1.22, 11.17)	–1.56	(–10.91, 7.79)
25–29	5.84	(–0.22, 11.89)	–4.44	(–10.27, 1.39)
30–34	–1.88	(–5.39, 1.62)	–2.05	(–9.41, 5.31)
35–39	–0.36	(–3.85, 3.13)	–0.38	(–5.20, 4.44)
40–44	–0.75	(–2.82, 1.32)	2.77	(–0.10, 5.63)
45–49	–1.36	(–3.33, 0.60)	0.29	(–1.96, 2.54)
50–54	0.92	(–0.52, 2.36)	1.71	(0.06, 3.36)
55–59	0.15	(–1.10, 1.36)	1.89	(0.60, 3.18)
60–64	2.09	(0.87, 3.30)	1.60	(0.30, 2.89)
65–69	2.97	(2.00, 3.94)	1.85	(0.72, 2.98)
70–74	2.25	(1.19, 3.30)	1.38	(–0.07, 2.84)
75–79	5.35	(4.09, 6.62)	5.63	(4.78, 6.48)
80–84	5.45	(3.96, 6.93)	5.28	(3.81, 6.75)
85+	5.89	(3.38, 8.39)	5.54	(3.42, 7.67)
0–54	0.38	(–0.60, 1.35)	1.11	(0.15, 2.08)
55+	2.80	(2.48, 3.11)	2.76	(2.33, 3.18)
All ages	2.72	(2.36, 3.08)	3.08	(2.77, 3.40)

For mortality at ages older than approximately 65 years it is apparent from Fig. 2 that the Gompertz model is no longer an adequate description. Actual mortality rates fall sharply from the calculated exponential curve until, at age 85 years, the mortality rate approaches zero. It has been suggested that this decline in rates is attributable to the existence of a susceptible subpopulation to which ALS death are exclusive [25, 27, 34]. As a result of the higher mortality within this subpopulation (due to the burden of ALS in addition to all other causes), its size will constitute an ever-decreasing proportion of the total population. The observed mortality rate will consequently decline from the expected rate and will reach zero at the age at which no members of the subpopulation remain alive. Based on the assumption that ALS mortality rates follow the Gompertz model within the subpopulation and the assumption that general mortality within the subpopulation is equal to that for the whole French population, it is possible to provide a best first estimate of the size of the susceptible subpopulation. The procedure is described in Appendix III.

The size of the subpopulation susceptible to ALS in France was estimated from the averaged age-specific mortality rates over the entire period at 170 per 100,000 persons born, with a 95% confidence interval (CI) of 124–217 per 100,000. Separate estimates were made for each sex at 220 per 100,000 men (95% CI: 133, 307) and 139 per 100,000 women (95% CI: 85, 193), indicating that susceptibility is significantly higher in men. This compares well with estimates derived from other populations using similar calculations [28]. The susceptible subpopulations were estimated in England and Wales at 199 per 100,000 persons (263 per 100,000 men and 155 per 100,000 women), in Japan at 118 per 100,000 persons (168 per 100,000 men and 81 per 100,000 women) and in the United States at 198 per 100,000 persons (245 per 100,000 men and 153 per 100,000 women). Given the wide range and low levels of confidence implied by the variance, these values should be interpreted as best first estimates only, and probably as a lower bound if a false-negative diagnosis or death certification is considered more likely than a false-positive.

Discussion

On the basis of longitudinal Gompertzian analysis, ALS mortality rates in France were defined by a common fixed intersect point. The mortality rate at this point has remained static over 23 years whilst mortality rates at younger ages have fallen slightly and mortality rates at all higher ages have risen substantially. The broad pattern is similar in both sexes, with marginal differences in the intersect point.

The decline in mortality from ALS among the youngest groups shows the same pattern of long term reduction as that observed in the United States [34] and in England and Wales [25, 27], indicative of an environment increasingly conducive to ALS survival. In the more conductive milieu characterised by higher population life expectancy, early mortality is reduced and the susceptible subpopulation increasingly survives to higher ages. The greater population heterogeneity at older ages results in higher observed rates of ALS mortality. The rise in ALS mortality is a real rise, consequent upon the changing competitiveness of ALS as a cause of death at higher ages.

The causative environmental contribution to ALS mortality (summarised by the aetiopathogenic factor log K) shows no significant within-country change over time, indicating an unchanging causative environment. It can therefore be concluded that the real increase in mortality from ALS does not arise from an increase in exposure to causative agents. However, the value of K does differ between countries and this warrants further investigation. The measured value of K is exponentially dependent on the rate of ageing (B in Eq. 3), and therefore small linear errors in the measurement of B lead to much larger exponential errors in the measurement of K. Using a common value of $B = 0.182$ for all three countries leads to much greater consistency in the measurement of log K for both men (1.84–2.35 in France, 2.43–3.30 in England and Wales and 2.23–2.37 in the United States) and women (1.05–1.63 in France, 1.46–2.16 in England and Wales and 1.44–1.63 in the United States) and it is probable that most of the difference results from measurement error.

There may be inter-country aetiopathogenic factors of environmental origin which are constant over time, and which affect men and women differently. In all the countries studied (France, England and Wales, Japan and the United States) male mortality is more affected by such factors shown in the Gompertzian analysis than female mortality. This inter-sex difference may imply either a differential response to a common source and magnitude of exposure, or that the nature and magnitude of the exposure may itself be different, perhaps through occupational patterns. The relatively constant relationship between male and female mortality in the countries studied, whatever the overall level of ALS mortality, suggests that the former explanation is more probable. However, if this is indeed the case, it appears that such factors do not increase the size of the susceptible population itself, but may lower the age at which the disease is normally expressed, and perhaps also accelerate the course of the disease once its onset has occurred. It should be noted that in France, England and Wales and the United States the aetiopathogenic factor (K) is still of relatively low significance in comparison with the competitive effects of life expectancy (R_0).

The generally lower common fixed intersect point for ALS mortality for both men and women in France, together with the lower value of K, may also be partly the result of consistent biases in death certification processes. It has been noted [13] that the residual category of unclassified deaths is relatively high in France and could (in principle) include significant numbers of ALS death. However, for such a factor to result in the constant value of K, the biases in death certification would have to be of similar order over many years, with little variation, or more particularly little improvement in the rate of certification. Durrleman and Alperovitch [7] indicated that the classification (and therefore reduction in numbers) of this residual category is improving, and this may in itself be enough to disqualify this factor from affecting the value of K that has been observed.

The calculation of the size of the susceptible subpopulation indicates that 0.2–0.4% of men and 0.1–0.2% of women are susceptible to ALS. The values calculated for all countries studied fall within this range and it can therefore be considered to be a reasonable guide to the true size of the underlying population. As there are, at present, no means of clinically identifying an individual with susceptibility to ALS, there are no means of gaining independent confirmation of prevalence. The identification of the existence of susceptibility does not, of course, mean the identification of the nature of that susceptibility. The recent discovery of a gene for familial ALS [38] and the identification of its function in coding for the superoxide dismutase enzyme [37] may point to the possibility of genetic involvement in sporadic ALS, although the basis of the sporadic form may prove more complex. The pattern of ALS mortality implies strongly that susceptibility is either genetic or is acquired very young (and certainly prior to the age of 20 years). The consistency of ALS mortality patterns over time and in all the countries studied would appear to confirm a consistent aetiological process.

Conclusions

The use of a technique evaluating ALS mortality in France in the context of population survival (the Gompertz relationship) has demonstrated, in common with previous analyses of mortality from the disease in England and Wales and the United States, that increasing rates over the period from 1968–1990 are largely explicable in terms of increased life expectancy of the population and decreased mortality from other conditions at an earlier age.

Whilst, intriguingly, the level of mortality from ALS in France appears to be lower both for men and women than in England and Wales or the United States, the reasons for this lower level appear unclear and require further study. Nonetheless, the pattern of mortality from ALS in France indicates that deaths are limited to a susceptible subpopulation many more of whose members are now living to an age at which ALS is expressed. The distinctive mortality curve for ALS which shows a sharp decline beyond the age of 75 years is similar in France to that in England and Wales, Japan and the United States, and demonstrates that the susceptible subpopulation is substantially depleted beyond that age both by increased mortality from the disease, and mortality from other unrelated causes. The size of the susceptible subpopulation has been estimated at 160 per 100,000 persons, which is of similar order to that in England and Wales, Japan and the United States, allowing for appropriate margins of error.

In France, as in other countries [15, 19], there is little evidence of any cohort effect in the mortality data as

would be the case if a discrete and recent environmental factor had any major aetiological role, nor is there any substantial evidence that the rise in mortality can be accounted for by artefact effects such as the increasing recognition of the disease at diagnosis or death. It appears that susceptibility to the disease is acquired early in life and that the increasing expression of ALS reflected in the mortality statistics is primarily the result of increased life expectancy in France and decreasing competition from mortality from other diseases at earlier ages.

Acknowledgement We are grateful to the Centre for the Study of Health, Brunel University, for financial support of this research.

References

1. Bharucha NE, Schoenberg BS, Raven RH, Pickle LW, Byar DP, Mason TJ (1983) Geographic distribution of motor neuron disease and correlation with possible etiological factors. Neurology 33:911–915
2. Buckley J, Warlow C, Smith P, Hilton-Jones D, Irvine S, Tew JR (1983) Motor neuron disease in England and Wales, 1959–1979. J Neurol Neurosurg Psychiatry 46:197–205
3. Campbell AMG, Williams ER, Barltrop D (1970) Motor neuron disease and exposure to lead. J Neurol Neurosurg Psychiatry 33:877–885
4. Chancellor AM, Warlow CP, Carstairs V, Elton RA, Swingler RJ (1992) Affluence, age and motor neurone disease. J Epidemiol Community Health 46:172–173
5. Charcot JM (1874) De la sclerose laterale amyotrophique. Prog Med 2: 325–327, 342, 453–455
6. Chazot F, Vallat JM, Hugon J, Lubeau M, Dumas M (1986) ALS in Limousin (Limoges area, France). Neuroepidemiology 5:39–46
7. Durrleman S, Alperovitch A (1989) Increasing trend of ALS in France and elsewhere: are the changes real? Neurology 39:768–773
8. Flaten TP (1989) Rising mortality from Motoneuron Disease. Lancet 335: 1018–1019
9. Gompertz B (1825) On the nature of the function expressive of the law of human mortality. Phil Trans R Soc Lond 115:513–585
10. Gunnarson L-G, Lindberg G (1989) Amyotrophic lateral sclerosis in Sweden 1970–83 and solvent exposure. Lancet 335:958
11. Hern JEC, Knight R, Davidson D, Forster A, Roberts R, Swingler RJ, Ashworth B, Chancellor AM, Cull RE, Fraser H, Jellinek EH, Holloway SM, McInnes A, Pentland B, Sandercock PAG, Warlow CP, Will R, Ballantyne JP, Behan PO, Bone I, Draper I, Durward F, Jamal G, Kennedy P, Metcalfe R, Thomas M, Weir AI, Fisher LR (1992) The scottish motor-neuron disease register: a prospective study of adult onset motor-neuron disease in Scotland. J Neurol Neurosurg Psychiatry 55:536–541
12. Hoffman PM, Brody JA (1971) The reliability of death certificate reporting for amyotrophic lateral scerlosis. J Chron Dis 24:5–8
13. INSERM (1980) Statistiques des causes de décés; résultats en France, I, 1976. Institut National de la Santé et de la Recherche Médicale, Paris
14. Juergens SM, Kurland LT, Okazaki H, Mulder DW (1980) ALS in Rochester, Minnesota 1925–77. Neurology 30: 463–470
15. Kurtzke JF (1982) Epidemiology of amyotrophic lateral sclerosis. In: Rowland LP (ed) Human motor neuron diseases. Raven Press, New York, pp 281–302
16. Kurtzke JF (1991) Risk factors in amyotrophic lateral sclerosis. Adv Neurol 56:245–270
17. Kurtzke JF, Beebe GW (1980) Amyotrophic lateral sclerosis. 1. A case-controlled comparison based on ALS deaths. Neurology 30:453–462
18. Lestienne R (1988) On the thermodynamical and biological interpretation of the Gompertzian mortality rate distribution. Mech Ageing Dev 42:197–214
19. Li TM, Swash M, Alberman E (1985) Morbidity and mortality in motor neuron disease: comparison with multiple sclerosis and Parkinson's disease: age and sex specific rates and cohort analyses. J Neurol Neurosurg Psychiatry 48: 320–327
20. Lilienfeld DE, Chan E, Ehland J, Godbold J, Landrigan PJ, Marsh G, Perl DP (1989) Rising mortality from motoneuron disease in the USA, 1962–1984. Lancet 335:710–712
21. Martyn CN (1990) Poliovirus and motor neuron disease. J Neurol 237: 336–338
22. Mulder DW, Rosebaum RA, Layton DD (1972) Late progression of poliomyelitis or forme fruste amyotrophic lateral sclerosis? Mayo Clin Proc 47: 756–771
23. Neilson S, Robinson I (1993) Cross sectional Gompertzian analysis: the development of a 'Gompertz mortality ratio' (GMR) and its applicability. Mech Ageing Dev 68:137–149
24. Neilson S, Robinson I (1993) Reinterpreting mortality statistics: some uses of Gompertzian analysis in epidemiological research. Clin Epidemiol 46: 1063–1069
25. Neilson S, Robinson I, Hunter M (1992) Longitudinal Gompertzian analysis of ALS mortality in England and Wales, 1963–1990: estimates of susceptibility in the general population. Mech Ageing Dev 64:201–216
26. Neilson S, Robinson I, Hunter M (1993) Static and dynamic models of interdisease competition: past and projected mortality from amyotrophic lateral sclerosis and multiple sclerosis. Mech Ageing Dev 66:223–241
27. Neilson S, Robinson I, Clifford Rose F, Hunter M (1993) Rising mortality from motor neurone disease – an explanation. Acta Neurol Scand 87: 184–191
28. Neilson S, Robinson I, Kondo K (1993) A new analysis of mortality from motor neurone disease in Japan, 1950–1990: rise and fall in the postwar years. J Neurol Sci 117:46–53
29. Norris FH (1992) Motor-neuron disease. BMJ 304:459–460
30. Olivares L, San Esteban E, Alter M (1972) Mexican "resistance" to amyotrophic lateral sclerosis. Arch Neurol 27:397–402
31. Olshansky SJ (1993) The aging of the human species. Sci Am 268(4):46–52
32. O'Malley F, Dean G, Elian M (1987) Multiple sclerosis and motor neurone disease: survival and how certified after death. J Epidemiol Community Health 41:14–17
33. Riggs JE (1990) Longitudinal Gompertzian analysis of adult mortality in the United States, 1900–1986. Mech Ageing Dev 54:235–247
34. Riggs JE (1990) Longitudinal Gompertzian analysis of amyotrophic lateral sclerosis mortality in the United States, 1977–1986 – evidence for an inherently susceptible subset. Mech Ageing Dev 55:207–220

35. Riggs JE (1990) Longitudinal Gompertzian analysis of Parkinson's disease mortality in the United States, 1955–1986 – the dramatic increase in overall mortality since 1980 is the natural consequence of deterministic mortality dynamics. Mech Ageing Dev 55: 221–233
36. Riggs JE (1991) The decline of martality due to stroke: a competitive and deterministic perspective. Neurology 41: 1335–1338
37. Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, Donaldson D, Goto J, O'Regan JP, Deng H-X, Rahmani Z, Krizus A, McKenna-Yasek D, Cayabyab A, Gaston SM, Berger R, Tanzi RE, Halperin JJ, Herzfeldt B, Van den Bergh R, Hung W-Y, Bird T, Deng G, Mulder DW, Smith C, Laing NG, Soriano E, Pericak-Vance MA, Haines J, Rouleau GA, Gusella JS, Horvitz HR, Brown R (1993) Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 362:59–62
38. Siddique T, Figlewicz DA, Pericak-Vance MA, Haines JL, Rouleau G, Jeffers AJ, Sapp P, Hung W-Y, Bebout J, McKenna-Yasek D, Deng G, Horvitz HR, Gusella JF, Brown RH, Roses AD (1991) Linkage of a gene causing familial amyotrophic lateral sclerosis to chromosome 21 and evidence of genetic-locus heterogeneity. N Engl J Med 324:1381–1384
39. Strehler BL, Mildvan AS (1960) General theory of mortality and ageing. Science 132:14–21
40. Swash M, Schwartz MS, Li T-M (1989) Trends in mortality from motoneuron disease. Lancet 335:958
41. WHO (1957) The International Classification of Disease, seventh revision. The World Health Organisation, Geneva
42. WHO (1968) The International Classification of Disease, eighth revision. The World Health Organisation, Geneva
43. WHO (1985) The International Classification of Disease, ninth revision. The World Health Organisation, Geneva
44. Williams DB, Windebank AJ (1991) Motor neuron disease (amyotrophic lateral sclerosis). Mayo Clinic Proc 66: 54–82
45. Yoshida S, Mulder DW, Kurland LT, Chu C-P, Okazaki H (1986) Follow-up study on amyotrophic lateral sclerosis in Rochester, Minn., 1925 through 1984. Neuroepidemiology 5:61–70

Appendix I

The relationship between age and mortality given in Eq. 1 can be transformed to the linear relationship shown in Eq. 2 by taking logarithms of both sides. A graph of the logarithm of the mortality rate should then be a straight line of slope α intercepting the Y-axis at $\log R_0$.

$$\log R_x = \log R_0 + \alpha x \quad (2)$$

Simple least-squares regression calculates the parameter values resulting in the smallest squared error in the predicted $\log R_x$ values. The quality of fit can be assessed from the r^2 statistic, which is the proportion of the total variation in $\log R_x$ explained by a linear model based on x. The standard errors of the parameters have a t-distribution with n-2 degrees of freedeom (where n is the number of data points), and can be used to estimate 95% confidence intervals of $\pm t_{0.25} \times \mathrm{SE}$.

Appendix II

The Strehler-Mildvan thermodynamic analogy predicts a negative linear correlation between initial mortality rate and rate of increase given by Eq. 3 which, by substitution into Eq. 2, gives the relationship in Eq. 4:

$$\alpha = B(\log K - \log R_0) \quad (3)$$
$$\log R_x = \log R_0 + B(\log K - \log R_0)\, x \quad (4)$$

Appendix III

The proportion of the susceptible remaining alive at age x (where L_x is the number surviving from L_0 at birth) is given by the survival function in Eq. 5. The observed rate of mortality, $*R_x$, depends on the survival function as shown in Eq. 6.

$$L_x/L_0 = \exp\left[R_0/\alpha\,(1-10^{\alpha x})\right] \quad (5)$$
$$*R_x = S \exp\left[R_0/\alpha\,(1-10^{\alpha x})\right] R_x \quad (6)$$

The integral of the observed rate therefore leads to the value of S, the size of the susceptible subpopulation as a fraction of all individuals at birth.

$$S = \int_0^\infty *R_x\, dx \quad (7)$$

The standard error of S is estimated by the sum of the standard errors of the probability of death q in each age group, thus for n age groups each of width 5 years, the standard error would be given by Eq. 8 and 95% CI can be found from a t-test with n-2 degrees of freedom.

$$\mathrm{SE}(S) = 5 \cdot \Sigma_{i=1}^{n} \sqrt{(q^i\,(1-q^i)/L^i)} \quad (8)$$