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Controlled population-based comparative study of USA and international adult [55-74] neurological deaths 1989-2014

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Objectives: A population-based controlled study to determine whether adult (55-74 years) neurological disease deaths are continuing to rise and are there significant differences between America and the twenty developed countries 1989-91 and 2012-14.

Method: Total Neurological Deaths (TND) rates contrasted against control Cancer and Circulatory Disease Deaths (CDD) extrapolated from WHO data. Confidence intervals compare USA and the other countries over the period. The Over-75's TND and population increases are examined as a context for the 55-74 outcomes.

Results: Male neurological deaths rose >10% in eleven countries, the other countries average rose 20% the USA 43% over the period. Female neurological deaths rose >10% in ten counties, averaging 14%, the USA up 68%. USA male and female neurological deaths increased significantly more than twelve and seventeen countries, respectively. USA over-75s population increased by 49%, other countries 56%. Other countries TND up 187% the USA rose fourfold. Male and female cancer and CDD fell in every country averaging 26% and 21%, respectively, and 64% and 67% for CDD. Male neurological rates rose significantly more than Cancer and CCD in every country; Female neurological deaths rose significantly more than cancer in 17 countries and every country for CDD. There was no significant correlation between increases in neurological deaths and decreases in control mortalities.

Conclusions: There are substantial increases in neurological deaths in most countries, significantly so in America. Rises in the 55-74 and over-75's rates are not primarily due to demographic changes and are a matter of concern warranting further investigation.

KEYWORDS
comparison, international, mortality, neurological, USA

1 | INTRODUCTION

From neurological studies covering the later part of the 20th century, evidence is growing of increases in a range of neurological morbidity and mortality especially related to Alzheimer's and Amyotrophic Lateral Sclerosis (ALS), known as Motor Neurone Disease (MND) in Europe.[1-4] The accumulation of evidence has continued to build in this century.[5-8] The first international comparison of the changing neurological mortality was between 1979-1981 and 1995-1997 in twenty-one developed countries found that the dementias were starting a decade earlier in a number of nations.[5,7] This was followed-up in a second international study taking the results to 2010. The latter analysis used the later baseline years of 1989-91, which confirmed the earlier onset of neurological morbidity and that neurological deaths continued to increase in the majority of the countries reviewed.[1-12] Rises in USA the over-75s neurological deaths were considerable as the USA had significantly greater increases than fourteen of the other twenty nations, with threefold rises in American men and a fivefold

increase in women in just 21 years.[8] Furthermore, there is a new interest in neurological diseases in Latin America and Asia, with a rising incidence than previously, although the rates remain lower than those found in developed countries,[2,12,13] suggesting this is increasingly a worldwide phenomenon.

The rises in neurological mortality have been questioned as an artefact, for example, due to improved diagnosis of ALS[14] and the effect of changing demographics giving rise to the "Gompertzian hypothesis." This states that the neurological increases are a consequence of people living longer and therefore developing age-related diseases that they had not lived long enough to develop previously.[15-17] However, the diagnostic issue has limited impact as it is mortality rates that are measured not separate diagnostic categories, and at this point, there is little evidence of diagnostic uncertainty as the primary cause of death is categorized as being due to a neurological condition.[1,5-8] Moreover, the Gompertzian position appears to have ignored the marked changes between the sexes and in different countries.[1,5-11] Crucially, the Gompertzian hypothesis does not account for the substantial rise in early onset dementia reported in many Western countries.[12,13,18-22]

To reduce a primarily Gompertzian explanation, this population-based study focuses upon people aged 55-74 years, below life expectancies in the developed world and utilizes the latest WHO data, updated December 2016 to take the analysis up to 2014.[23] Consequently, studying the adults aged 55-74 over a relatively short time means any Gompertzian influence will be minimal. However, to place the results on adults aged 55-74 in a wider context, the over-75s rates and matching population increases are also examined to explore any possible strengths of the Gompertzian influence.

Two control mortalities are juxtaposed against neurological death rates, Cancer Mortality and Circulatory Disease Deaths (CDD) because they are considered age related. It should be noted, however, that this analysis is not designed to postulate about possible aetiologies, but only to determine whether there continues to be substantial increases in neurological deaths over the past two decades and whether there are any significant differences in the US rates and the other nations.

There are four working null hypotheses; in each country between 1989-91 and 2012-14 that there will be no statistically significant differences between:

1. Total Neurological Deaths and Cancer Mortality;
2. Total Neurological Deaths and CDD,
3. between USA neurological death rates and the other twenty developed countries, and
4. no statistical association between rises in neurological deaths and falls in the control mortalities of Cancer and CDD.

2 | MATERIALS AND METHOD

This population-based study of the latest WHO mortality data, updated December 2016, examines mortality rates per million (pm) of population of people aged 55-74 years by sex. The categories are based upon the 10th edition of the International Classification of Diseases ensuring as uniform a categorization as possible.[23] The WHO classifies neurological mortality under two broad categories, *Nervous Disease Deaths* (G00-G99), which include Parkinson's disease, Motor Neurone Disease, Multiple Sclerosis, Multiple System Atrophy, etc. and *Alzheimer's disease and Other Dementias* (F01-F03 G30-31).[23] The two rates are combined to calculate a Total Neurological Death (TND) rate for the average baseline years for 1989-91 with the average index years 2012-14.[23] Germany, Portugal and Spain baseline years are 1990-92, and the few countries that have earlier index years, 2010-12 and 2011-13, are noted in the tables. Whilst the focus is upon people aged 55-74, as a context for the 55-74 results, the over-75s TND rates and increases in population are also examined to indicate whether the rises in the elderly TND are primarily related to increased population.

The control mortality categories are Cancer Mortality (CM) (coded C00-D48, WHO, 2015) and the CDD (coded H100-199).[23] Each country is compared against its baseline and index years, and a ratio of change over the period is calculated.

An inherent problem of international comparisons is the reliability of the data as well as how differing health/social policies and health services influence health outcomes. Only country-specific research could resolve this latter problem. The issue of reliability of diagnosis can be significant,[14] but is largely resolved at the point of death in a global category such as "nervous disease deaths".[1,5-8] It is acknowledged that 100% accuracy can never be established, but as the WHO data are collected in a consistent and uniform system in these broad categories this is probably the most reliable and valid international data as yet available.

2.1 | Statistics

Confidence intervals (to ±95% significance) are used to compare changes between the control mortalities and TND over the period and between the USA and the other countries. Spearman's rank order correlation examines any link between increases in neurological mortality any decreases in either Cancer or CDD deaths. Odds ratio calculates proportional differences between ratios of change, from which a ratio of ratios is calculated. An example best explains this. Rises in neurological deaths[5,7,8] had been attributed to rises in population[15-17]. Odds ratio tests this using the ratio of change in the USA elderly population, 1989 and 2014, giving a ratio of 1.49 and divides it into the ratio of change of neurological deaths, 5.13 and the ensuing ratio of ratios is the odds ratio of 3.44.

3 | RESULTS

3.1 | Male (55-74) TND

Table 1 lists adult (55-74) Male Total Neurological Deaths (TND) ranked by the highest frequency ranging from Finland at 1070 per million (pm), USA 690 pm and Belgium 645 pm down to Japan 270 pm, Greece 307 pm and Austria 363 pm.

TABLE 1 Changes in Total Neurological Deaths (TND) rates per million (pm) by gender (55-74) & ratio of change 1989-91 *v* 2012-14 ranked by highest male rates

Country and years	TND Male 1989	TND Male 2014	Ratio of change	TND Female 1989	TND Female 2014	Ratio of change
1. Finland 2012-14	657	1070	1.63	604	924	1.53
2. USA 2012-14	**481**	**690**	**1.43**	**367**	**618**	**1.68**
3. Belgium 2011-13	658	645	0.98	562	472	0.84
4. UK 2011-13	579	629	1.09	525	564	1.07
5. Sweden 2012-14	377	604	1.18	510	540	1.03
6. Norway 2012-14	525	602	1.15	539	554	1.03
7. Denmark 2012-14	346	565	1.63	377	509	1.35
8. Netherlands 2012-14	520	564	1.08	354	487	1.38
9. Ireland 2011-13	523	538	1.03	428	488	1.14
10. Spain 2012-14	378	527	1.39	356	400	1.12
11. France 2011-13	525	517	0.98	401	375	0.94
12. Germany 2012-14	403	516	1.28	339	392	1.16
13. Switzerland 2011-13	530	510	0.96	466	471	1.01
14. Australia 2012-14	451	510	1.13	365	427	1.17
15. Canada 2010-12	523	493	0.94	430	414	0.96
16. Italy 2010-12	456	479	1.05	367	374	1.02
17. Portugal 2012-14	271	467	1.72	204	399	1.96
18. N. Zealand 2010-12	446	462	0.99	402	414	1.03
19. Austria 2012-14	349	363	1.04	314	334	1.06
20. Greece 2011-13	186	307	1.65	165	252	1.53
21. Japan 2012-14	206	270	1.32	173	176	1.02
Rest (-US) Average	445	532	1.20	394	448	1.14
Rest average:USA ratio	1:1.08	1:1.30	1:1.19	1:0.93	1:1.38	1:1.47

The values for USA are highlighted in bold.

Neurological deaths rose by >10% in eleven countries—Portugal 72% Greece 65%, Denmark and Finland 63%, the USA 43%, Spain 39%, Japan 32%, Germany 28%, Sweden 18%, Norway 15% and Australia, 13%. There were falls >5 in Belgium, Canada, France and New Zealand. In the earlier 1989-91 period, the USA was the 10th highest of the twenty-one countries but is now second highest.

3.2 | Female (55-74) TND

The highest rates were Finland 924 pm, USA 618 pm and the UK 564 pm, the lowest being Japan 176 pm, Greece 252 pm and Austria 334 pm.

Ten countries female rates rose by more than >10% in Portugal 96%, the USA 68%, Greece and Finland 53%, Netherlands 38%, Denmark 35%, Spain 12%, Australia 17%, Germany 16% and Ireland 14%. There were falls in Belgium of 16%, France 6% and Canada 4%. At the base-line years, USA female rates were 11th highest but are now second.

Male and female current rates were significantly correlated (Rho=+0.7714, $P<.001$).

Over the period, there were only few changes between the gender, male and female 1989-91 rates correlated (Rho=+0.8263) and in 2012-14 (Rho=+0.8429, $P<.001$).

3.3 | Over-75s TND as context 1989-2014

Table 2 lists over-75s rates of both sexes and population increases. The highest was Finland at 20 562 pm followed by the USA at 17 207, the Netherlands at 13 145 pm the lowest being Greece 1382, Canada 1746 pm and Japan 2479 pm. Previously the USA had been 9th highest of 21 countries. There was a positive correlation between increases in the 55-74 and over-75s (Rho=+0.8760, $P<.001$) indicating consistency across the countries under review.

The USA had substantially the biggest rise, up fourfold, whilst the elderly American population increased by just 49%, yielding an odds

TABLE 2 Both sexes over-75's Total Neurological Death (TND) rates per million 1989-2014 ratio of change and total population to TND odds ratios (Doubled in BOLD). Ranked by highest TND

Country	Population 1989	Ratio of change	TND	Ratio of change	Odds ratio
1. Finland 1989 2014	0.281 0.459	1.63	7204 20 562	2.85	1:1.75
2. USA 1989 2014	**13.103 19.477**	**1.49**	**3355 17 207**	**5.13**	**1:3.44**
3. Netherlands 1989 2014	0.814 1.221	1.50	3420 13 145	3.84	**1:2.56**
4. Sweden 1995 2014	0.683 0.816	1.20	3322 12 956	3.90	**1:3.25**
5. UK 1989 2013	3.987 5.036	1.26	4767 12 780	2.68	**1:2.13**
6. Switzerland 1989 2013	0.471 0.647	1.37	7344 12 521	1.71	1:1.25
7. Norway 1989 2014	0.299 0.354	1.18	3297 11 261	3.43	**1:2.90**
8. Spain 1989 2014	2.142 4.271	1.99	3290 11 221	3.41	1:1.71
9. France 1989 2013	3.931 5.785	1.47	4227 11 066	2.62	1:1.78
10. Australia 1989 2014	0.744 1.496	1.98	4488 11 064	2.47	1:1.25
11. Denmark 1994 2014	0.362 0.411	1.14	2279 10 685	4.69	**1:4.11**
12. Belgium 1989 2014	0.659 0.969	1.47	8101 10 337	1.28	1:0.87
13. Ireland 1989 2013	0.159 0.235	1.48	3329 9835	2.95	1:1.99
14. N. Zealand 1989 2012	0.152 0.263	1.73	3265 9222	2.82	1:1.63
15. Italy 1989 2012	3.678 6.139	1.67	2493 7105	2.81	1:1.68
16. Germany 1990 2014	5.549 8.178	1.47	1977 5919	2.99	**1:2.03**
17. Austria 1989 2014	0.527 0.693	1.31	1640 5540	3.38	**1:2.58**
18. Portugal 1989 2014	0.527 1.006	1.91	899 5537	6.16	**1:3.23**
19. Japan 1989 2014	5.974 15.521	2.60	759 2479	3.27	1:1.26
20. Canada 1989 2012	1.296 2.297	1.77	484 1746	3.61	**1:2.04**
21. Greece 1989 2013	0.608 1.112	1.83	1080 1382	1.28	1:0.70
Rest average (-US)		1.56	3383 9718	2.87	1:1.84

ratio of 1:3.44. The average population rise in the other countries was 56% with TND rising on average 187%, yielding an odds ratio of 1:1.84. Except Belgium and Greece, every country's population to TND odds ratio rose substantially (1:1.25) ten doubling over the period.

3.4 | USA *v* other countries

Table 3 presents USA male rates compared with each of the other twenty countries using confidence intervals (±95%) shaded areas showing significant differences. The USA had significantly greater

TABLE 3 Confidence intervals comparing other countries v USA neurological death rates 1989-2014.

	Male			Female		
Country	OR	Lower	Upper	OR	Lower	Upper
Australia	1:1.27	1:1.07	1:1.51	1:1.44	1:1.19	1:1.74
Austria	1:1.38	1:1.14	1:1.66	1:1.58	1:1.29	1:1.94
Belgium	1:1.46	1:1.25	1:1.72	1:2.01	1:1.68	1:2.4
Canada	1:1.52	1:1.28	1:1.8	1:1.75	1:1.45	1:2.11
Denmark	1:0.88	1:0.74	1:1.05	1:1.25	1:1.04	1:1.5
Finland	1:0.88	1:0.76	1:1.03	1:1.10	1:0.93	1:1.3
France	1:1.46	1:1.23	1:1.72	1:1.80	1:1.49	1:2.18
Germany	1:1.12	1:0.94	1:1.33	1:1.46	1:1.20	1:1.77
Greece	1:0.87	1:0.70	1:1.08	1:1.10	1:0.87	1:1.39
Ireland	1:1.39	1:1.18	1:1.65	1:1.48	1:1.23	1:1.77
Italy	1:1.37	1:1.15	1:1.62	1:1.65	1:1.36	1:2.01
Japan	1:1.09	1:0.88	1:1.36	1:1.66	1:1.29	1:2.12
Netherlands	1:1.32	1:1.12	1:1.56	1:1.22	1:1.01	1:1.48
New Zealand	1:1.38	1:1.16	1:1.65	1:1.64	1:1.35	1:1.97
Norway	1:1.25	1:1.06	1:1.48	1:1.64	1:1.37	1:1.95
Portugal	1:0.83	1:0.69	1:1.01	1:0.86	1:0.70	1:1.06
Spain	1:1.03	1:0.86	1:1.23	1:1.50	1:1.24	1:1.82
Sweden	1:0.90	1:0.75	1:1.07	1:1.59	1:1.33	1:1.9
Switzerland	1:1.49	1:1.26	1:1.76	1:1.67	1:1.39	1:2
UK	1:1.32	1:1.12	1:1.55	1:1.57	1:1.32	1:1.87
USA	1:10	1:0.85	1:1.18	1:10	1:0.83	1:1.2

Grey areas statistically significant (±95%).

rises than twelve other countries, and no country had bigger increases than the USA.

USA female rates rose significantly more than seventeen other countries, whilst no other country had bigger increases than the USA.

3.5 | Control mortalities

3.5.1 | Males: Cancer

Table 4 present changes in Cancer and CDD over the period, ranked by the highest CDD.

In respect to cancer deaths, the current Western average (minus the USA) was 5511 pm, representing a fall over the period of 26%. The highest rate was France at 6322 pm, the lowest Switzerland 3956 pm, with the USA being fifth lowest at 4908 pm, representing a fall of 41% over the period.

There was a significant *negative* correlation between decreases in cancer mortality with increases in neurological death (Rho=−0.4521, $P<.025$).

3.5.2 | Male CDD

The initial Western average rate was 9118 pm falling to 3321 pm, an equivalent fall of 64%. The highest CDD was Finland 5056 pm, the lowest France 2354 pm, the USA was third highest at 4509 pm but equivalent to a fall of 58%.

There was a slight none significant negative correlation between decreases in CDD and rises in neurological deaths (Rho=−0.2050 n.sig).

3.5.3 | Females: Cancer

Table 4 shows female cancer rates, the Western average being 3514 pm, representing a fall of 21%. The highest was Denmark 4849 pm the lowest Japan at 2706 pm. The USA at 3048 pm was the fifth lowest, equivalent to a fall of 46% over the period.

There was no significant correlation between decreases in female cancer and increases in neurological deaths (Rho=−0.1312 n.sig).

3.5.4 | Female CDD

The Western average was 1432 pm, representing a fall of 67% over the period, the highest was the USA 3879 pm, although equivalent to a 46% reduction over the period, the lowest was France 852 pm.

There was no significant correlation between decreases in CDD and rises in neurological deaths (Rho=−0.2618 n.sig).

TABLE 4 Males and female cancer and CDD rates per million ranked by highest male CDD

Country and years	Male rank	Male cancer	% of Change	Male CDD	% of Change	Female rank	Female cancer	% of Change	Female CDD	% of Change
1. Finland 1989 Finland 2014	1	6844 4731	−31	13 289 5056	−62	7	3954 3274	−17	5836 1256	−88
2. Greece 1989 Greece 2013	2	6281 6245	−1	7922 4882	−38	1	3073 2924	−5	4833 2886	−40
3. USA 1989 **USA 2014**	**3**	**8313** **4908**	**−41**	**10 652** **4509**	**−58**	**2**	**5654** **3048**	**−46**	**8526** **3879**	**−55**
4. Germany 1989 Germany 2014	4	7293 6047	−17	9856 4370	−56	3	4399 3862	−12	4598 1892	−59
5. Austria 1989 Austria 2014	5	7574 5824	−23	9987 4005	−60	4	4490 3865	−14	4776 1711	−64
6. Ireland 1989 Ireland 2013	6	8114 5481	−32	13 873 3763	−73	9	5591 4147	−26	6450 1550	−76
7. UK 1989 UK 2013	7	8492 5636	−34	12 329 3647	−70	6	5831 4190	−28	6198 1631	−74
8. Sweden 1989 Sweden 2014	8	6132 4424	−28	10 546 3546	−66	8	4520 3508	−28	3391 1094	−68
9. N, Zealand 89. Zealand 2012	9	7698 5028	−35	10 918 3375	−69	5	5774 3988	−31	5674 1590	−72
10. Belgium 1989 Belgium 2013	10	8484 6096	−28	7494 3276	−56	10	4195 3760	−10	3581 1526	−57
11. Italy 1989 Italy 2012	11	8901 6107	−31	6942 3224	−54	11	4099 3541	−14	3352 1528	−54
12. Portugal 89 Portugal 2014	13	6287 6145	−2	9240 3180	−66	12	3374 2837	−16	5250 1448	−72
13. Denmark 89 Denmark 2014	12	8824 6198	−30	9501 2990	−69	13	6729 4849	−28	4435 1342	−70
14. Canada 89 Canada 2012	14	7845 4971	−37	8128 2979	−63	15	4986 3883	−22	3655 1317	−64
15. Spain 1989 Span 2014	16	6343 6176	−3	6218 2827	−55	19	3207 2742	−14	3212 1365	−58
16. Japan 1989 Japan 2014	17	6524 5595	−14	4570 2797	−39	18	3020 2706	−10	2607 1094	−58
17. Norway 1989 Norway 2014	18	6910 4659	−33	11 937 2783	−77	16	4793 3778	−21	4852 1156	−76
18. Australia 89 Australia 2014	19	7231 4648	−36	8954 2351	−74	17	4453 3195	−28	4461 1001	−78

(Continues)

TABLE 4 (Continued)

Country and years	Male rank	Male cancer	% of Change	Male CDD	% of Change	Female rank	Female cancer	% of Change	Female CDD	% of Change
19. Switzerland89	20	6536	−39	5772	−56	20	3850	−15	2393	−56
Switzerland 2013		3956		2557			3284		1061	
20. Netherland 89	15	8543	−30	9169	−73	14	4717	−5	3786	−65
Netherlands 2014		5922		2452			4486		1337	
21. France 1989	21	8024	−21	5617	−58	21	3535	−11	2033	−58
France 2013		6322		2354			3136		852	
Rest (-US) Average		7444	−26	9118	−64		4430	−21	4369	−67
2014		5511		3321			3514		1432	

The values for USA are highlighted in bold.

3.5.5 | Comparing control to neurological deaths

Table 5 provides the confidence interval results comparing male cancer to neurological and CDD to neurological deaths over the period.

Every country's neurological deaths worsened significantly in comparison with the control deaths.

This pattern was found for Female cancer and CDD neurological seventeen and nineteen countries, respectively.

3.5.6 | Rates are statistics—numbers people

Mortality rates are "statistics," whereas actual numbers of people can give a better feel to the practice reality of these increases.

In 1979, there were 28 261 American TND deaths of which 11 033 were in the 55-74 age band. By 1989, these had risen to 65 656 and 16 677, respectively. By 2014, there were 405 187 TND deaths of which 44 825 people aged 55-74 had died of a neurological condition. Thus, over 25 years, albeit within a growing elderly population, there were an "extra" 339 31 people dying from a neurological condition, of which an "extra" 28 148 were under 74 years old. Such numbers of people dying in such a relatively short time is an indication of the extent of the likely pressure on families and services.

4 | CONCLUSIONS

4.1 | Limitations to the study

Death rates depend upon the reliability of diagnosis, which some believe have resulted in higher specific diagnosis of ALS.[14] However, as the measures are in the broad category of neurological diseases, this is less of a problem [1.5-8]. The claims that increases in neurological morbidity are due to the Gompertzian effect[15-17] is largely questionable, as the 55-74 age band is below current Western life expectancy.[23] Moreover, the fourfold rise in the American over-75s TND rates, emerged from just a 49% increase of the elderly population counters a primarily Gompertzian explanation.

Finally, aggregated international studies cannot account for any particular country's substantial changes, which will require country-specific research possibly requiring a geo-epidemiology approach which involves detailed mapping of cases right down to houses in street locations.[24]

4.2 | Main findings

We can reject all four null hypotheses as neurological deaths rose significantly more than the control deaths in every country and for both sexes. Furthermore, whilst no other country had greater rises in their neurological deaths than the USA, American male and female neurological deaths rose significantly more than twelve and seventeen countries, respectively, occurring only just 25 years. Furthermore, there was no positive statistical link between increases in neurological

TABLE 5 Confidence intervals male and female 55-74 cancer *v* Total Neurological Deaths and CDD *v* Total Neurological Deaths 1989-2013

Confidence intervals—Cancer: ND/CDD: TND MALES							Confidence intervals—Cancer: ND/CDD:TND FEMALES					
	Cancer: ND			CDD: ND			Cancer: ND			CDD: ND		
	OR	Lower	Upper	OR	Lower	Upper	OR	Lower	Upper	OR	Lower	Upper
Australia	1:1.76	1:1.54	1:2.01	1:4.31	1:3.76	1:4.93	1:1.63	1:1.41	1:1.89	1:5.21	1:4.46	1:6.09
Austria	1:1.35	1:1.16	1:1.57	1:2.59	1:2.23	1:3.02	1:1.24	1:1.05	1:1.45	1:2.97	1:2.52	1:3.5
Belgium	1:1.36	1:1.22	1:1.53	1:2.24	1:2.20	1:2.52	1:0.94	1:0.82	1:1.07	1:1.97	1:1.72	1:2.26
Canada	1:1.49	1:1.31	1:1.69	1:2.57	1:2.26	1:2.93	1:1.24	1:1.07	1:1.42	1:2.67	1:2.30	1:3.10
Denmark	1.2.32	1:2.03	1:2.67	1:5.19	1:4.51	1:5.97	1:1.87	1:1.3	1:2.15	1:4.46	1:3.85	1:5.17
Finland	1:2.36	1:2.12	1:2.61	1:4.28	1:3.86	1:4.74	1:1.85	1:1.65	1:2.07	1:7.11	1:6.31	1:8.01
France	1:1.25	1:1.10	1:1.42	1:2.35	1:2.06	1:2.68	1:1.05	1:0.91	1:1.22	1:2.23	1:1.90	1:2.62
Germany	1:1.54	1:1.35	1:1.77	1:2.89	1:2.52	1:3.31	1:1.32	1:1.13	1:1.53	1:2.81	1:2.41	1:3.28
Greece	1:1.66	1:1.38	1:1:20	1:2.68	1:2.22	1:3.22	1:1.31	1:1.31	1:1.97	1:2.56	1:2.09	1:3.13
Ireland	1:1.52	1:1.34	1:1.73	1:3.79	1:3.34	1:4.3	1:1.34	1:1.54	1:1.76	1:4.12	1:4.74	1:5.46
Italy	1:1.53	1:1.34	1:1.75	1:2.26	1:1.98	1:2.59	1:1.01	1:1.18	1:1.37	1:1.91	1:2.24	1:2.62
Japan	1:1.53	1:1.27	1:1.84	1:2.14	1:1.78	1:2.58	1:1.14	1:0.91	1:1.41	1:2.42	1:1.94	1:3.03
Netherlands	1:1.56	1:1.38	1:1.77	1:4.06	1:3.57	1:4.61	1:1.45	1:1.25	1:1.67	1:3.90	1:3.35	1:4.53
N. Zealand	1:1.59	1:1.39	1:1.81	1:3.35	1:2.93	1:3.84	1:1.49	1:1.29	1:1.72	1:3.68	1:3.17	1:4.26
Norway	1:1.70	1:1.50	1:1.92	1:4.92	1:4.34	1:5.57	1:1.30	1:1.15	1:1.48	1:4.31	1:3.77	1:4.94
Portugal	1:1.76	1:1.51	1:2.06	1:5.01	1:4.29	1:5.85	1:2.33	1:1.95	1:2.77	1:7.09	1:5.93	1:8.48
Spain	1:1.43	1:1.25	1:1.64	1:3.07	1:2.67	1:3.53	1:3.31	1:1.13	1:1.53	1:2.64	1:2.26	1:3.09
Sweden	1:2.22	1:1.94	1:2.54	1:4.76	1:4.17	1:5.45	1:1.36	1:1.20	1:1.55	1:3.28	1:2.86	1:3.77
Switzerland	1:1.59	1:1.40	1:1.81	1:2.17	1:1.91	1:2.47	1:1.18	1:1.03	1:1.36	1:2.28	1:1.97	1:2.64
UK	1:1.64	1:1.45	1:1.84	1:4.14	1:3.26	1:4.14	1:1.50	1:1.32	1:1.69	1:4.08	1:3.58	1:4.65
USA	1:2.43	1:2.15	1:2.74	1:3.39	1:3.30	1:3.83	1:3.12	1:2.73	1:3.58	1:3.70	1:3.24	1:4.23

Shading indicates significant differences at ±95%.

deaths and decreases in the control mortalities, which would have been expected if the Gompertzian was a strong factor. Moreover, compared with the earlier analyses between 1989 and 2010 where there were notable rises in males in six countries and in four countries for females, by 2014 there had been rises of equivalent to >10% in twelve countries for men and in eleven countries for females. A Gompertzian perspective also ignores rises in early onset dementia (EOD) reported in many countries.[4-13,19,20,22,25] For example, one found 29% of their cohort were aged under 65 years, which 30 years before would have been considered extraordinary.[4-13,19,20,22,25] Another indication of the extent of increased EOD is seen in examining Medline studies related to EOD. The first paper was published June 1967 by June 1987 there were 100 papers, whereas from January to December 2016, there were 299 directly or indirectly related to EOD, clearly whatever the multiple causal explanations, something has changed.

Moreover, the over-75's TND results showed that the increases were essentially far in excess of rises in the over-75's population. Whilst there may be some Gompertzian influences related to demography it does not appear to be the predominant factor, especially in the USA and nine other countries whose elderly population to TND rates produced odds ratios that had more than doubled.

The study adds confirmation that the changes noted at the end of the last century, are continuing, and despite the limitations, provides valid data for future research, whilst raising questions as to what might account for these global changes.

Although this study does not attempt to explain the reasons behind these increases, it is clear that the neurological morbidity is starting earlier and the reported rises are not primarily an artefact. There are confirmed rises of ALS from a number of Western clinical studies[1-13,25] as well as small increases in Asian and Latin American countries.[18,19]

This is not to discount studies that identified genetic and familial patterns[20-22] but others recognize lifestyle and possible interactive environmental contributions.[2,4,6-8,25] Including such factors as occupation, heavy metals, petro-chemicals, organophosphate/pesticides[26-30] and possible influence of electromagnetic field (EMF)[18,25,31] and military service.[32] Although not all studies related to ALS have consistently reported environmental factors,[33] the majority have highlighted environmental factors rather than longevity[4-8,18,25-30] as well as epigenetic changes,[33-35] whist recently, research had linked rises in dementias to proximity to major roads.[30]

This project is not equipped to explain the reasons behind these changes, but in view of the relatively short period, it is indicative that

multi-interactive environmental factors are probably having a greater influence.

Focusing only on the USA in 1989-91, male neurological rates were ninth highest and are now second highest and American females moved from being twelfth to fourth highest. There is an urgent need to explain these remarkable changes.

At a practice level, both families and the medical specialities dealing with the concomitant problems of neurological disease are in danger of being overwhelmed. In particular, is issue of relatively younger neurological patients burden upon their families, complicated by the psychiatric and psychosocial problems associated with neurological disease. Moreover, until the extent of these changes is recognized the present configuration of services will be overwhelmed. Consequently, there is an urgent need for cross-disciplinary research to understand the underlying interactive processes that contribute to rises in neurological morbidity and mortality and for the necessary community-based support that will be needed until or if effective preventative and/or treatments can be introduced.

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CONFLICT OF INTEREST

The authors have no conflict or vested interest in this study.

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