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## Original Research

# Changing patterns of neurological mortality in the 10 major developed countries – 1979–2010

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## SUMMARY

**Objectives:** To examine whether there is a continued increase in neurological deaths in the major developed countries over the period 1979–2010.

**Study design:** Analyzes changing patterns of neurological deaths and Total Mortality of people aged 55–74 years by sex.

**Methods:** Baseline WHO 3-year average mortality for 1979–81 were compared with changes in 2008–10, for Total Mortality and the neurological categories Nervous Disease, and Alzheimer & other Dementias deaths in rates per million. To control for different diagnostic practice, the focus is upon Total Neurological Deaths in relation to Total Mortality and Odds ratios are calculated. UK Motor Neuron Disease, Parkinson's disease and variant CJD are explored as possible constituent categories of Nervous Disease for other countries.

**Results:** Total Mortality fell substantially in every country, conversely, Nervous Disease and Alzheimer's rose in seven and six countries respectively. Total Neurological Deaths for males and females increased significantly in Australia, Canada, England & Wales, Italy, the Netherlands and especially the USA.

Unlike motor neurone disease, variant CJD' deaths in England and Wales did not contribute substantially to the overall neurological increases found.

Odds ratios indicated that neurological deaths differentially increased significantly in every country compared to Total Mortality.

**Conclusions:** These results pose a major public health problem, as the epigenetic contribution to these changes, rather than longevity, have serious implications indicating earlier onset of neurological morbidity pressurizing families, health and social care services, with resource implications especially for Australia, Canada, Italy, Netherlands, Spain, the UK and the USA.

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## Introduction

Neurological disease affects 2% of the general population in England and Wales and has increased in recent years.<sup>1</sup> Until recently neurological deaths were mainly included within two global categories, namely ‘*mental disorder deaths*’, which are deaths due to the dementias, and ‘*other diseases of the nervous system and sense organs deaths*’. This latter category included such disparate conditions as Parkinson’s disease, motor neurone disease, hereditary neuromuscular conditions, prion disorders, degenerative diseases, as well as Creutzfeldt Jacob’s Disease and variant CJD.<sup>2</sup> In 2012 however, the WHO has narrowed ‘other diseases of the nervous system’ down to Nervous Disease Deaths, which is the former category but minus deaths related to sensory organs and the WHO produced data specifically for Alzheimer & other Dementia deaths for the whole period between 1979 and 2010,<sup>3</sup> enabling the analysis of the other Nervous Disease deaths separately from the analysis of Alzheimer and other Dementia deaths. Thus the new categories are far more precise than the earlier global categories reported in 2004 and 2008, which reported data up to 2006,<sup>4</sup> whereas the new configuration for most countries and for Total Neurological Disease deaths contains data up to 2010.<sup>3</sup>

Most neurological disorders have a complex aetiology. Only a very few are exclusively genetically determined and an aetiological model of genetic vulnerability that interacts with environmental factors seems best to explain clusters of disease.<sup>5–7</sup> Studies examining Alzheimer type mortality rates, found that population density was a surrogate marker for environmental exposure;<sup>8,9</sup> whilst a similar link found was in relation to cancer deaths<sup>10</sup> and there are reports of increasing dementia rates in some countries,<sup>1,6,11,12</sup> as well as ‘*early onset dementias*’,<sup>13–15</sup> as well as increasing younger aged motor neurone disease patients.<sup>16</sup>

A previous examination of neurological deaths between 1979 and 1997 in ten major developed countries found evidence for notable rises in neurological mortality, indicating that these conditions may have been starting earlier.<sup>17</sup> The 2012 WHO Mortality database now permits a later and much more accurate analysis of these trends up to 2010.<sup>3</sup> This study has two *a priori* working null hypotheses, namely that between 1979–81 and 2008–10:

1. there would be no significant differences between Total Mortality and the combined Nervous Disease and Alzheimer’s & other Dementia deaths in the ten major developed countries; and
2. there would be no evidence of increases in the two categories of neurological deaths over the period.

## Method

WHO format standardized mortality data were utilized to examine changes between baseline years (1979–81) and index years (2008–10) to be contrasted with Total Mortality, i.e. ‘All Causes of Death’ as a quasi ‘control’ group to compare the two neurological mortalities, Nervous Disease deaths and the separately reported Alzheimer’s & other Dementia deaths over the intervening years.<sup>3</sup>

The period covers Editions Nine and Ten of the International Classification of Disease Editions and in terms of Total Mortality there are no changes between these Editions nor were there any related to neurological deaths.<sup>2</sup> The World Health Organisation produce international mortality rates approximately every 4 years and the earlier study was based upon WHO data published in 2004 and reported data up to 1997 and in 2008 they produced data up to 2006, using the same mortality configurations as in 2004.<sup>4</sup> In 2012 the WHO re-configured the reporting of neurological mortality and moved from the more global groupings of Other Neurological Disease and Mental Disorder Deaths,<sup>4</sup> to a much more narrower and precise categorization of Neurological disorders deaths namely, Nervous Diseases and Alzheimer & other Dementia deaths.<sup>3</sup> Nervous Disease deaths on the WHO website are all neurological deaths but by subtracting the *specific* category Alzheimer’s and Other Dementia deaths, actual rates of other Nervous Diseases deaths can be separately calculated. These consist of all the other neurological disease deaths, ranging from inflammatory disease of the nervous system, including multiple sclerosis, to motor neurone disease, Parkinson’s disease, systemic atrophies, extra-pyramidal and movement disorders, demyelinating diseases, polyneuropathies, episodic and paroxysmal disorders, etc.<sup>3</sup> This means that this analysis is far more precise than the earlier more global data, hence this study draws upon the data from the new formulation from 1979 up to 2010,<sup>3</sup> which strengthens the current results.

There is however one less positive change in the new system. Previously the adult age bands were in decades such as for the 55–64 and 65–74 years, who were reported separately but are now merged into a 55–74-year old age grouping.<sup>3</sup> This means an important earlier finding in which there was an increase in neurological deaths in the 55–64-year age band cannot be replicated directly. To offset this, in addition to analysing the latest data for the 55–74-year olds, the combined neurological mortality rates for the 55–64- and 65–74-year ages, from the earlier WHO configuration, were also analysed up to 2006.<sup>4</sup> This allowed us to replicate whether the increased mortality found in the earlier study<sup>17</sup> has continued on up to 2010.

Baseline data are the 3-year average rates per million of population by gender for all countries for 1979–81, except Germany, whose baseline data is for 1980–82 based upon an average of the former East and West Germany deaths. A few countries’ was data earlier than 2008–10 and these are indicated in the tables e.g. Australia latest data was up to 2004–06.

Baseline 1979–81 rates are compared to the index 3-year average rates for 2008–10 or for the latest years available<sup>3</sup> to determine any substantial level of change over the period. A ratio of change is calculated, which is the current mortality rate divided by the baseline rate. A clinical substantial change is considered when a ratio lies outside 0.90–1.10 (i.e. equivalent to a change of 10% or more), which is marked in terms of standard mortality ratios, to which Odds ratios are related.<sup>18</sup> Ratios of change are calculated for changes in both Total Mortality and for Total Neurological Deaths. The ratios of change were used to calculate the Odds ratios to determine the extent to which Total Mortality varied in relation to Total Neurological Deaths over the period by dividing the ratio of

change for the neurological deaths by the ratio of changes for general mortality.

A simple example best illustrates the process. The UK male 55–74-year old Total Mortality Rate fell over the period giving a ratio of change of 0.45, whilst Total Neurological Deaths rose giving a ratio of 1.32. Dividing the ratios of change of 1.32 by 0.45 yields an Odds ratio of 2.93:1, indicating that compared to ordinary deaths neurological deaths rose very substantially over the period.

The Total Mortality rates are the context in which to contrast any changes over the period between general mortality and Total Neurological Disease deaths, which includes both Nervous Disease and Alzheimer's & other Dementia deaths in people aged between 55 and 74 years, an age which is below the life-expectancy of most Western countries.<sup>19</sup>

The original 10 major developed countries, were chosen on the basis of their relatively larger populations, the smallest being the Netherlands at 16.6 million, ranging through Australia 20.4 million, UK 60.9 million and Germany 81.8million, to the US at 301.6 million. Of the other 10 smaller Western countries only Greece, Belgium and Portugal have populations in excess of 10 million, with five countries populations being fewer than 6 million, which are smaller than many American states.<sup>3</sup> However, it was decided to take advantage of the new configuration, and whilst the focus remains upon the 10 major developed countries, data for the ten smaller Western states were also analyzed. It is acknowledged that amongst the 10 major countries reviewed; Australia, Canada, France, Germany, Italy, Japan, Netherlands, Spain, the UK and the USA, all have different types of healthcare systems; the USA being markedly different from the others in terms of the source of GDP expenditure on health mainly coming from 'private' sources.<sup>19</sup> Indeed recent comparative research into cancer and general mortality outcomes for these 10 countries highlighted that there were markedly different outcomes, which appeared to reflect structural factors in patterns of health service provision.<sup>20,21</sup>

Some studies have suggested that apparent changes in neurological deaths may be due to recording or changes or improvements in diagnosis<sup>22–24</sup> whilst conversely, some argued that there is an under-reporting of neurological deaths.<sup>1,5,23</sup> To resolve this possible dilemma arising from possible diagnostic changes, whilst each neurological category is presented separately, the core comparative analysis will be between Total Mortality and Total Neurological Disease deaths, which include the separately calculated Nervous Disease and the Alzheimer's and other Dementia deaths to determine are there any substantial changes over the period.

#### Component diseases in Nervous Disease deaths

There are many constituent conditions in the Nervous Disease category, many relatively very rare and the WHO does not report these separately. However, motor neurone disease and Parkinson's disease rates, which are included in Nervous Diseases have shown an upward trend and that it may be that a 'substantial percentage of neurological deaths are missed',<sup>24</sup> suggesting any changes found here might be an underestimate as these two sub-categories are a major constituent

of Nervous Diseases. Another minority constituent would be all forms of Creutzfeldt-Jakob Disease, which attracted considerable interest in Britain a decade or more ago, so CJD, motor neurone and Parkinson's disease data are extrapolated,<sup>25,26</sup> to determine whether these conditions might have contributed to the changes in the UK. The measurement of these three constituent disorders in the UK might serve as a surrogate indicator for the other countries possible constituent Nervous Disease deaths. All age rates for Creutzfeldt-Jacob's Disease had to be used<sup>25</sup> as there was no matching of the WHO age bands so the eventual rates may be a slight overestimate.

#### Statistical analysis

Ratios of change in the death rates between the baseline and index years are produced, from which Odds ratios are calculated to demonstrate the degree to which Total Neurological Deaths and Total Mortality may have varied between 1979 and 2010. Spearman rank order correlations (Rho) are used to explore linkages between rates and ratio of change between the sexes and between total increases in the 2004–06 and 2008–10 outcomes.

## Results

*Nervous Disease Deaths (minus Alzheimer's) 1979–2010:* Table 1 shows the rates per million (rpm) of Nervous Disease deaths by sex in the 10 developed countries between 1979–81 and 2008–10.

*Males:* Currently France has the highest male rate at 262 pm, followed by the UK at 242 pm and Germany at 239 pm, down to lows of 130 pm in Japan, 154 pm in Spain and 172 pm in the Netherlands, overall average being 203 pm.

Ratios of change increased substantially in seven countries over the period, ranging from Japan at 1.60 to the three highest, Germany 3.85, Australia up 2.18, the UK 1.85 and the USA up 1.66, with an overall average of 203 pm, equivalent to a rise of 41% over the period. Conversely, there were notable falls in Italy 0.86 and the Netherlands 0.88.

*Females:* Highest female deaths were in Canada 173 pm, the UK 169 pm and Germany at 157 pm, the lowest being in Japan at 78 pm, Spain 104 pm and the Netherlands at 109 pm, with an overall average of 137 pm.

Ratios of change rose substantially for six countries the highest being Australia 2.72, Canada 1.88 and the UK 1.71, the USA 1.61 and notably, albeit from a low base rate, Japan up 1.53, then overall average was 137 pm which was equivalent to an increase of 32% over the period. However, there were falls in the Netherlands 0.84 and Italy 0.87.

There were significant positive correlations between the sexes in regard to rates over the period (Rho = +0.802,  $P < 0.005$ ) and ranked ratios of change (Rho = +0.564,  $P < 0.05$ ).

*Alzheimer's & Other Dementia deaths:* Table 2 shows the changing pattern of Alzheimer type deaths over the period by sex.

*Males:* The highest mortality rate was again found in the USA currently at 186 pm, followed by Spain at 178 pm and Canada 150 pm, down to lows of 43 pm in Japan, 106 pm in

**Table 1 – Nervous diseases (minus Alzheimer's) deaths by sex rates per million [rpm].<sup>a</sup>**

Country, latest comparative years. Rank of ratios of change	Total Nervous Disease deaths males	Total Nervous Disease deaths females
1] Germany		
1980–82	62	99
2008–10	239	157
Ratio of change	<b>3.85</b>	<b>1.42</b>
2] Australia		
1979–81	85	50
2004–06	188	136
Ratio of change	<b>2.18</b>	<b>2.72</b>
3] UK		
1979–81	131	99
2008–10	242	169
Ratio of change	<b>1.85</b>	<b>1.71</b>
4] Canada		
1979–81	145	92
2002–04	210	173
Ratio of change	<b>1.49</b>	<b>1.88</b>
5] USA		
1979–81	134	97
2005–07	223	156
Ratio of change	<b>1.66</b>	<b>1.61</b>
6] Spain		
1979–81	71	98
2006–08	154	104
Ratio of change	<b>2.17</b>	<b>1.06</b>
7] Japan		
1979–81	81	51
2007–09	130	78
Ratio of change	<b>1.60</b>	<b>1.53</b>
8] France		
1979–81	295	165
2006–08	262	154
Ratio of change	0.90	0.93
9] Italy		
1979–81	243	157
2006–08	208	136
Ratio of change	0.86	0.87
10] Netherlands		
1979–81	196	130
2008–10	172	109
Ratio of change	0.88	0.84
<b>Average</b>		
1979–81	144	104
2008–10	203	137
<b>Ratio of change</b>	<b>1.41</b>	<b>1.32</b>

Ranked by highest increases in ratios of change.  
Male vs Female rates  $Rho = +0.8024$ ,  $P < 0.005$ .  
Male vs Female Ranked increases  $Rho = +0.5636$ ,  $P < 0.05$ .  
a Clinically significant results in **BOLD**.

Australia and 109 pm in Germany. There was an overall average of 130 pm. Over the period Male ratios of change increased significantly in five countries and there were notable increases in Spain 2.70 and Italy 2.12 more than doubling and the USA at 1.65.

Conversely there were notable falls in Japan, Germany and Australia with ratios of change down 0.53–0.67.

**Females:** Again the USA had the highest rate at 187 pm, Spain 160 pm and the UK 146 pm, with lows in Japan 30 pm,

**Table 2 – Alzheimer's & other dementia deaths of 55–74-year olds rates per million [rpm].<sup>a</sup>**

Country & years 1979–81 vs latest comparative years	Males rpm	Females rpm
1] Spain		
1979–81	66	53
2006–08	178	160
Ratio of change	<b>2.70</b>	<b>3.02</b>
2] Italy		
1979–81	58	44
2006–08	123	113
Ratio of change	<b>2.12</b>	<b>2.57</b>
3] USA		
1979–81	113	82
2005–07	186	187
Ratio of change	<b>1.65</b>	<b>2.27</b>
4] Netherlands		
1979–81	114	94
2008–10	125	140
Ratio of change	<b>1.10</b>	<b>1.49</b>
5] Canada		
1979–81	135	104
2002–04	150	144
Ratio of change	<b>1.11</b>	<b>1.38</b>
6] UK		
1979–81	137	114
2008–10	138	146
Ratio of change	1.01	<b>1.28</b>
7] France		
1979–81	154	128
2006–08	140	122
Ratio of change	0.91	0.95
8] Germany		
1980–82	191	74
2008–10	109	88
Ratio of change	0.57	<b>1.19</b>
9] Australia		
1979–81	159	120
2004–06	106	101
Ratio of change	0.67	0.84
10] Japan		
1979–81	81	54
2007–09	43	30
Ratio of change	0.53	0.56
<b>Average</b>		
1979–81	128	<b>86</b>
2008–10	130	<b>123</b>
<b>Ratio of change</b>	1.02	<b>1.43</b>

Ranked by highest increases in ratios of change.  
Male and Female rates  $Rho = +0.9578$ ,  $P < 0.001$ .  
Male vs Female Ranked increases  $Rho = +0.9515$ ,  $P < 0.001$ .  
a Clinically significant results in **BOLD**.

Germany 88 pm and 101 pm in Australia, averaging in the ten countries 123 pm.

Over the period seven countries had clinically substantial rises in their ratio of change. Ratios of change more than doubled in three countries with substantial increases in Spain 3.70, Italy 2.57 and 2.27 in the USA, other notable increases were the Netherlands 1.49, Canada 1.38 and the UK 1.28. There were falls of 0.56 in Japan and 0.84 in Australia.

**Table 3a – Total mortality vs total neurological deaths by sex rates per million [rpm] and ratios of change.<sup>a,b</sup>**

Country, latest years & combined rank	Total Mortality Deaths males	Total Mortality Deaths females	Total Neurological Deaths males	Total Neurological Deaths females
1] USA				
1979–81	26981	14370	247	179
2005–07	16288	10635	409	343
Ratio of change	0.60	0.74 <sup>b</sup>	1.66	1.92 <sup>b</sup>
2] Spain				
1979–81	22469	11746	217	151
2006–08	14571	6164	332	264
Ratio of change	0.65	0.52	1.53	1.75 <sup>b</sup>
3] Canada				
1979–81	24799	12696	276	196
2002–04	14278	8845	360	317
Ratio of change	0.58	0.69 <sup>b</sup>	1.30	1.62 <sup>b</sup>
4] UK				
1979–81	31146	17153	288	213
2008–10	14005	9131	380	315
Ratio of change	0.45	0.53 <sup>b</sup>	1.32	1.48 <sup>b</sup>
4] Germany				
1988–90	25734	17926	253	173
2008–10	16360	7191	348	245
Ratio of change	0.64	0.40	1.38	1.42 <sup>b</sup>
6] Australia				
1979–81	26087	13286	244	170
2004–06	12061	7092	291	237
Ratio of change	0.46	0.53 <sup>b</sup>	1.20	1.39 <sup>b</sup>
7] Italy				
1979–81	27257	13669	301	201
2006–08	13522	7044	331	249
Ratio of change	0.50	0.52 <sup>b</sup>	1.10	1.24 <sup>b</sup>
8] Japan				
1979–81	20066	11018	162	105
10] 2007–09	12700	5501	173	108
Ratio of change	0.63	0.50	1.07	1.03
9] Netherlands				
1979–81	25615	12092	310	224
2008–10	13017	8375	297	249
Ratio of change	0.51	0.69 <sup>b</sup>	0.96	1.11 <sup>b</sup>
10] France				
1979–81	26049	11948	445	293
4] 2006–08	14776	6651	402	276
Ratio of change	0.57	0.56	0.90	0.91 <sup>b</sup>
<b>Average</b>				
1979–81	25620	13591	275	101
2008–10	14158	6195	332	260
Ratio of change	0.55	0.46	1.21	1.29 <sup>b</sup>

a Clinically significant increases in **BOLD**.

b Countries with female increased ratios higher than males.

There were very strong positive correlations in regard to the gender for both rates ( $Rho = +0.958$ ,  $P < 0.001$ ) and ranked ratios of change ( $Rho = +0.952$ ,  $P < 0.001$ ).

### Total Mortality rates contrasted with Total Neurological Deaths

**Total Mortality:** Table 3a juxtaposes Total Mortality deaths (i.e. all deaths by all causes, by gender in columns 2 and 3) with Total Neurological Deaths (combined Nervous Disease and Alzheimer type deaths) and the ratios of change over the period.

**Males:** German Males had the highest Totally Mortality rates at 16360 pm, the USA 16288 pm and France 14776 pm to the lowest three countries Australia at 12061 pm, Japan 12700 pm and the Netherlands at 13017 pm, an overall average of 14158 pm, representing an overall reduction of 45%.

Every country's male rates fell substantially, with the biggest reductions being in the UK falling 55%, in Australia by 54% and by 49% in the Netherlands, whilst the smallest declines were in Germany, 36%, Japan 37% and the USA 40%.

**Females:** US females had the highest female Total Mortality rate at 10635 pm, followed by the UK 9131 pm and Canada 8845 pm, the lowest being Japan 5501 pm, Spain 6164 pm and

**Table 3b – Total Mortality & Total Neurological Disease Deaths odds ratio 1979–2010. Ranked by highest average odd ratios.**

Country & rank of odds ratios	Male Total Mortality: neurological deaths odds ratios	Females Total Mortality: neurological deaths odds ratios	Average odds ratios
1=] UK	2.93	2.79	2.86
1=] Germany	2.16	3.55	2.86
1=] Spain	2.35	3.37	2.86
4] USA	2.77	2.59	2.68
5] Australia	2.61	2.62	2.62
6] Canada	2.24	2.35	2.30
7] Italy	2.20	2.38	2.29
8] Japan	1.70	2.06	1.88
9] Netherlands	1.88	1.61	1.75
10] France	1.58	1.62	1.60
<b>Average</b>	<b>2.24</b>	<b>2.49</b>	<b>2.37</b>

Male vs Female ranking odds ratios  $Rho = +0.6121$ ,  $P < 0.005$ .

France 6651 pm, with an overall average of 6195, representing a reduction of 54% over the period.

Every country's female rate fell substantially, the biggest fall being in Japan 50%, and Italy and Spain by 48%, the smallest reductions being in the USA 26%, and Canada and the Netherlands by 31%.

It should be noted that women's ratios of change were higher than males in six countries.

### Total Neurological Death rates

Columns 4 and 5 of Table 3a gives the combined rates followed by ratios of change, which were used to calculate Odds ratios between changes in Total Mortality and Neurological Deaths.

It should be noted that in nine of the ten countries female Nervous Disease death ratio of change was higher than their male ratios.

There was no significant correlation between the sexes in regards to Total Mortality but there was a strong positive correlation between the rates of neurological deaths between the gender ( $Rho = +0.876$ ,  $P < 0.001$ ). There was a positive correlation between ratios of change between both Total deaths and the Total Neurological Deaths ( $Rho = +0.8758$ ,  $P < 0.005$ ).

### Odds ratios of Total Mortality: neurological deaths

Table 3b shows the examination of the Odds ratios that indicate the degree to which neurological deaths have worsened compared to Total Mortality in each of the major developed countries over 20 and more years.

**Males:** The male Total Mortality: neurological Odds ratios were quite dramatic led by the UK at 1:2.93, the USA 1:2.77 and Australia 1: 2.61, with a further four countries having Odds ratios more than 1:2.0. Even less substantial Odds ratios, such as found in Japan (1:1.70) and France (1: 1.58) indicate that neurological deaths have worsened, relative to total mortality in the countries under review.

**Females:** Female Odds ratios showed an even greater divergence between Total Deaths and Neurological mortality than Male, led by Germany 1:3.55, Spain 1:3.37 and the UK at

1:2.79, with five other countries having ratios of more than 1:2.0 and the remaining countries having neurological mortality worsening compared to Total deaths.

When combing the Male and Female Odds ratios, the UK, Germany and Spain were equal first 1:2.86 followed by the USA 1:2.68, with relative lows for France 1:1.60, the Netherlands 1:1.75 and Japan 1:1.88.

### Smaller Western Countries Total Mortality & Total Neurological Deaths

Table 4a shows that the outcomes found in the major developed countries are mirrored in these 10 smaller nations. They all experienced substantial falls in Total Mortality whilst the majority, eight, had increases in their Total Neurological Deaths. These ranged from male rate of 748 pm in Finland to 223 pm in Austria, with an overall average of 381 pm. In regard to females the range went from 484 pm in Finland down to 135 pm in Greece, averaging 256 pm. It should be noted that women's ratio of change was higher than their males in six countries.

### Smaller Western Countries Total Mortality: Neurological Deaths Odds ratios

Table 4b lists the Total Mortality to total Neurological Odds ratios over the period. Similar to the major countries, seven countries had Odds ratios of greater than 1.90:1 for both sexes.

The results from these smaller countries add to the validity of the findings from the major developed countries.

### Previous configuration of neurological deaths in 55–64- and 65–74-year olds

Table 5 is based upon the previous configuration of combined Other Neurological Disease deaths and Mental Disorder deaths from 1979 up to 2004–06 period, where the current 55–74-year old formulation was split between 55–64- and 65–74-year olds in rates per million (rpm).

The point to note is that amongst the 55–64-year olds clinical significant increases were found in this younger age

**Table 4a – Minor Western Countries Total Neurological Deaths 1979–2010. Ranked by biggest increase in both sexes.**

Country, latest years & combined rank	Total Mortality male	Total Mortality female	Total Neurological Deaths male	Total Neurological Deaths female	Total Deaths: Neurological Deaths Odds ratio male–female
1] Portugal					
1980–82	29748	15878	228	102	
2008–10	16021	7599	370	216	
Ratio of change	<b>0.54</b>	<b>0.48</b>	<b>1.62</b>	<b>2.12*</b>	<b>2.79–4.42</b>
2] Finland					
1987–89	30300	10798	422	238	
2008–2010	17093	7291	748	484	
Ratio of change	<b>0.56</b>	<b>0.68</b>	<b>1.75</b>	<b>2.04</b>	<b>3.12–3.00</b>
3] New Zealand					
1979–81	29264	16556	238	243	
2006–08	12004	8370	331	279	
Ratio of change	<b>0.41</b>	<b>0.51</b>	<b>1.39</b>	<b>1.15</b>	<b>3.39–2.25</b>
4] Belgium					
1979–81	30803	15556	342	228	
1997–99	16392	8739	427	336	
Ratio of change	<b>0.53</b>	<b>0.56</b>	<b>1.25</b>	<b>1.47*</b>	<b>2.36–2.63</b>
5] Sweden					
1987–89	20529	10958	172	206	
2008–10	11971	7153	312	233	
Ratio of change	<b>0.58</b>	<b>0.65</b>	<b>1.82</b>	<b>1.13</b>	<b>3.14–1.74</b>
6] Austria					
1979–81	20137	15289	195	170	
2008–10	15144	7718	223	203	
Ratio of change	<b>0.75</b>	<b>0.49</b>	<b>1.14</b>	<b>1.19*</b>	<b>1.52–2.43</b>
7] Ireland					
1979–81	32363	14591	400	256	
2007–09	18668	8591	471	262	
Ratio of change	<b>0.58</b>	<b>0.59</b>	<b>1.18</b>	<b>1.04</b>	<b>2.03–1.76</b>
8] Denmark					
1994–96	24297	15292	316	145	
10] 2004–06	16566	11512	353	179	
Ratio of change	<b>0.68</b>	<b>0.75</b>	<b>1.12</b>	<b>1.23*</b>	<b>1.65–1.64</b>
9] Greece					
1979–81	21933	10543	279	174	
2007–09	11408	6893	251	135	
Ratio of change	<b>0.52</b>	<b>0.65</b>	<b>0.90</b>	<b>0.78</b>	<b>1.73–1.20</b>
10] Switzerland					
1995–97	19380	9577	396	206	
4] 2005–07	11907	7153	328	233	
Ratio of change	<b>0.61</b>	<b>0.75</b>	<b>0.83</b>	<b>1.13*</b>	<b>1.36–1.51</b>
<b>Average</b>					
1979–81	25875	13504	299	197	
2008–10	14717	8102	352	256	
Ratio of change	<b>0.57</b>	<b>0.60</b>	<b>1.18</b>	<b>1.30*</b>	<b>2.07–2.17</b>

Clinically significant increases in **BOLD**.

band in Males in the Netherlands, up the equivalent of 51%, up 31% in the UK, a rise of 24% in USA and 15% in Spain.

In respect to the younger females, there were increases in the USA of 95%, by 37% in Spain, 29% in Italy, 24% in the UK and by 17% and 12% respectively in the Netherlands and Canada.

In both the 55–64- and 65–74-year age bands, women's rates rose more than men's in nine of the ten countries.

Correlating the ranked ratios of change between the 2004–06 and 2008–10 for both sexes there was an overall significant correlation between the two periods ( $P < 0.05$ ), indicating there is a continuation of the increases noted in the earlier period.

Some constituents of Nervous Disease Deaths: i] *Cruzfeldt Jakob's Disease (CJD) and Variant CJD (VCJD)*, ii] *Motor Neurone and Parkinson's Disease deaths in England & Wales*. i] Extrapolating CJD

mortality for England & Wales, no separate gender or age bands were given, hence the data is for all CJD deaths in England for people aged from 20 to 75+ years. Variant CJD was not reported until after 1994 when in 1995–97 VCJD averaged 0.14 per million in with a total incidence of 1.07 pm, rising to a peak in 2001–03 of 0.3 pm for VCJD in a total incidence of 1.62 pm.

By 2004–06 VCJD fell to 0.09 pm and total CJD to 1.32 pm, indicating that at least in England and Wales, these prion type deaths did not contribute greatly to an increase in Nervous Disease deaths in the UK.

*Motor Neurone Disease (MND) and Parkinson's Disease (PD) deaths (Table 6)*: MND 55–74-year old males rose to 111 pm a ratio of change of 1.56 and women's 1.65 up to 81 pm. The remaining elderly group aged 75+ are shown with increases up to

**Table 4b – Total Mortality & Total Neurological Disease Deaths Odds ratio 1979–2010. Ranked by highest average odd ratios.**

Country & rank of Odds ratios	Male Total Mortality: neurological deaths Odds ratios	Females Total Mortality: neurological deaths Odds ratios	Average Odds Ratios
1] Portugal	2.79	4.42	3.61
2] Finland	3.12	3.00	3.06
3] New Zealand	3.39	2.25	2.82
4] Belgium	2.36	2.63	2.50
5] Sweden	3.14	1.74	2.44
6] Austria	1.52	2.43	1.98
7] Ireland	2.03	1.76	1.90
8] Denmark	1.65	1.64	1.65
9] Greece	1.73	1.20	1.47
10] Switzerland	1.36	1.51	1.44
Average	2.31	2.26	2.29

378 pm for men indicative that MND might well have contributed to the overall rises in UK Nervous Disease deaths.

Amongst the 55–74-year old age band for men and 167 pm for women rises equivalent of 294% and 255% over the period.

In regard to PD, there was no change for males aged 55–74 a fall for women, equivalent to 23% but older males rose 213% and females up 172% over the period.

## Discussion

It seems reasonable to reject the working null hypotheses because there were substantial differences between Total Mortality and Total Neurological Disease deaths over the period. The previous finding of an increasing and relatively earlier onset of such deaths between 1979 and 1997 and up to 2004–06<sup>17</sup> was shown to be continuing and the 2010 results appear to conform these trends, which have serious public health implications.

### What the study adds

The original study<sup>17</sup> was the first-ever comparative international analysis of changing patterns of neurological disease deaths in the ten major developed countries between 1979 and 1997. This study, by taking the review up to 2010, confirms the increase in actual neurological deaths of people aged 55–74-years in the majority of countries; an observation which is given further validity from finding similar results in eight of the ten smaller (<11.3 millions) countries (population less than 11.3 million). It shows that relative to the reductions in cancer deaths for the same age bands, which have been associated with major increases in funding specifically to cancer services in the West,<sup>18,21</sup> there does not appear to have been the same priority given to neurological diseases, leading to a reduced death rate. The new configuration that identified Alzheimer and other Dementia separately has confirmed clinical studies of increased Alzheimer deaths.<sup>13–15</sup> At an international level, it has also shown that there have been substantial rises in the other neurological deaths i.e. the Nervous Disease deaths minus the Alzheimer's, raising serious public health questions in all the nations reviewed.

### Study limitations

The main limitation is that the current results based upon the 2012 WHO re-configuration cannot be compared directly with the earlier 2004 and 2008 versions, albeit the Nervous Disease and Alzheimer's and Other Dementias data which are far more precise than the previous formulations. Another limitation was that by merging the 55–64 year-old age bands into the wider 55–74-year age bands, it is less easy to highlight the rises in the relatively younger 55–64 years group.

A minor limitation was that under the old configuration the data covered by two Editions of the ICD, meant that the previously used Mental Disorder deaths had varied slightly between editions. This new version is based entirely upon the 10th ICD edition<sup>2</sup> and covers the whole period under review and resolves this satisfactorily. Furthermore, expanding the analysis to twenty Western countries, gives further weight to the overall outcomes.

A further limitation may arise from the categorization of neurological deaths, where there may have been greater willingness to report such deaths than before,<sup>1,5–7</sup> but by focussing on Total Nervous Disease deaths, which are the combined neurological deaths to include the non-Alzheimer Nervous Disease deaths and the other Nervous Disease mortalities, any such problems are reduced.

Although whilst some studies have found little change in regard to Motor Neurone Disease, attributing any rises to improved categorization,<sup>24,28,29</sup> other research has unequivocally reported an upward trend in Motor Neurone Disease deaths,<sup>1,3,11,12,30</sup> as shown from the Anglo-Welsh data,<sup>25,26</sup> there appears to be unequivocal rises in MND for males up to 65%, which may well be the case in other developed countries. Although others have argued that the problem lies in differentiating between underlying contributory and final cause of death, which is said to be linked to under-reporting neurological mortality.<sup>5,11,24</sup> However, the rise in specific MND mortalities may be due to a greater accuracy in death certification rather than a true rise in MND or the inclusion of MND as a contributory cause in some countries.<sup>24,29,30</sup>

Data for constituent OND sub-categories were only available for England and Wales, which includes the highly publicized 'outbreak' of Variant CJD in Britain<sup>29</sup> yet when transposing the annual numbers of total Variant CJD into rates,<sup>25</sup> at their peak all types of CJD never exceeded 1.62 pm, so did not contribute significantly to an increase in Anglo-Welsh OND deaths. Whilst rises in MND suggest that some of the increases may arise from increases in MND.<sup>1,11,12,16,30,31</sup>

In Parkinson's disease, male 45–74 rates increased, but rates in women fell slightly over the period; though substantial increases occurred in older people (75+), posing questions about underlying mechanisms. Overall, given the focus on Total Neurological Deaths, although the various constituent diseases within the Nervous Disease category may vary between countries, these results show notable rises in seven of the 10 major developed countries over a relative short period and should be a matter of some concern.

One feature that might have influenced the results is the different healthcare system of the countries reviewed. This is a complex issue where for example, against media expectations and analysis of Total Mortality in 20 Western nations



**Table 5 – Earlier Global Configuration: ‘Other Neurological Diseases’ (OND) & ‘Mental Disorder Deaths’ (MDD) by sex for 55–64-year olds & 65–74-year olds 1979–81 vs 2004–06. Countries where female ratios higher than males\*. Ranked by highest increased ratios of change by both sexes in 2004–06.**

Country – years 1979–81 vs 2004–06	OND males 55–64	OND females 55–64	MDD males 65–74	MDD females 65–74
1] USA				
1979–81	271	135	540	291
2003–05	335	263	925	683
Ratio of change	<b>1.24</b>	<b>1.95*</b>	<b>1.71</b>	<b>2.36*</b>
2] Spain				
1979–81	176	90	399	262
2003–05	203	123	787	570
Ratio of change	<b>1.15</b>	<b>1.37*</b>	<b>1.97</b>	<b>2.18*</b>
3] Italy				
1979–81	164	92	429	281
2001–03	169	119	673	754
Ratio of change	1.03	<b>1.29*</b>	<b>1.57</b>	<b>2.68*</b>
4] Netherlands				
1979–81	146	117	515	314
2004–06	220	137	749	601
Ratio of change	<b>1.51</b>	<b>1.17</b>	<b>1.45</b>	<b>1.91*</b>
5] Canada				
1979–81	281	73	641	161
2002–04	256	82	931	317
Ratio of change	0.98	<b>1.12*</b>	<b>1.45</b>	<b>1.97*</b>
6] UK				
1979–81	147	108	454	341
2004–06	192	134	687	495
Ratio of change	<b>1.31</b>	<b>1.24</b>	<b>1.51</b>	<b>1.45</b>
7] Australia				
1979–81	210	119	556	320
2001–03	204	132	706	480
Ratio of change	0.97	<b>1.11*</b>	<b>1.27</b>	<b>1.50*</b>
8] Germany				
1980–82	333	158	596	336
2004–06	366	151	647	325
Ratio of change	<b>1.10</b>	0.96	1.09	0.97
9] France				
1979–81	452	180	1122	615
2003–05	435	190	1010	605
Ratio of change	0.96	<b>1.06*</b>	0.90	<b>0.98*</b>
10] Japan				
1979–81	120	76	314	209
2004–06	105	55	276	163
Ratio of change	0.81	0.72	0.88	0.78
<b>Average</b>				
1979–81	230	115	557	313
2004–06	249	125	739	499
Ratio of change	1.08	<b>1.09*</b>	<b>1.33</b>	<b>1.59*</b>

Ranked by total increases 2006 vs 2010,  $Rho = +0.6152$ ,  $P < 0.05$ . Male 2004–06 vs 2008–10 increase,  $Rho = +0.4546$ ,  $P < 0.1$  trend. Female 2004–06 vs 2008–10  $Rho = +0.6242$ ,  $P < 0.05$ .

Clinically significant increases in BOLD.

\*Source: WHO, 2008.

showed that despite being one of the lowest funded countries for health care, the UK was the second most effective and efficient in reducing deaths under 74 years.<sup>20</sup> Equally, the UK had a similar successful outcome in reducing cancer deaths compared with other countries<sup>21</sup> but were relatively less successful in regard to reducing child mortality, although the NHS relatively achieved more with comparatively far less funding than most other countries.<sup>32</sup> These results reflected differential impacts of not just a nation's GDP health expenditure but how the system were configured. In respect to child mortality, the worst results are for children in the USA, and it was clear that

relative poverty impacted upon the outcomes as the USA had the worst relative poverty in the West. The UK had the third highest relative poverty levels, and relatively poor results of child mortality were also seen for the UK.<sup>32</sup> Such factors need to be considered when comparing the results between countries and whether similar increases in resource allocation and priority given to cancer services<sup>19,21</sup> might equally benefit the neurological field.

Another difficulty is that this study cannot explain particular variations in some of the countries. For example the Alzheimer's deaths rose considerably in Italy and the

**Table 6 – Constituent Disease of Nervous Disease Deaths in the UK as surrogate for other countries. Motor Neurone Disease (MND) and Parkinson's Disease (PD) rates per million\*.**

Mortality	Males 55–74	Females 55–74	Males 75+	Females 75+
Motor neuron				
1979–81	71	49	96	47
2010	111	81	378	167
Ratio of change	1.56	1.65	3.94	3.55
Parkinson's				
1979–81	76	47	505	218
2010	76	30	1579	593
Ratio of change	1.00	0.77	3.13	2.72

\*Source: ONS (2012).

Netherlands but at the same time fell for the Nervous diseases. Another apparent anomaly was France, whose neurological mortality was highest and whilst still second highest amongst males, their overall rates have seen a small decline. Nothing in the study however can explain these apparent inconsistencies and only country-specific research can explain the results.

What is unequivocal is that in contrast to major reductions in general mortality in all 20 countries, Total Neurological Deaths actually rose substantially between 1980 and 2010 in both sexes in 16 of the twenty Western countries.

### Potential explanations

Neurological diseases are considered to be diseases of older people and as people live longer they develop diseases which previously they had not lived long enough to develop, this is called the 'Gompertzian effect'<sup>33,34</sup> – i.e. that as people live longer, they have diseases that previously they would not have lived long enough to develop.<sup>33,34</sup> The question posed therefore is whether these substantial changes, occurring over a relatively short period, are mainly due to the Gompertzian effect? The explanation for example that arises in cancer deaths is mainly due to having proportionately more people living longer. This is not a Gompertzian prediction, for example breast cancers are increasingly occurring in increasingly younger women under 40 years old,<sup>21,35</sup> and the Gompertzian does not account for changes between countries and gender.<sup>10,17,21</sup> Moreover, in respect to cancers, whilst increases in the incidence of new cases of cancer have slowed down over the past decade in many countries, the incidence does still continue to rise, across all age bands and in particular the under 40-year olds – hardly a Gompertzian affect'.<sup>21,26</sup>

Other possible explanations for these changes might be related to improved diagnostic techniques<sup>1,11,13,14</sup> and the re-categorization of deaths, but the new configuration is even more precise than the earlier one and moreover, whilst in the early treatment stage of some of these conditions there may have been early doubts about diagnosis but by the time of death, it would be fairly clear that it was a neurological disease, and the new Nervous Disease death category covers that much better than before.<sup>3</sup> Moreover, looking back 30 or more years the concept of early onset

dementia or the need for the creation of a Young Parkinson's Disease society in Britain would have seemed a tautology.

A major explanation for the increases must be in regard to the major life-style changes in Western countries, especially amongst women and the fact that changes in Total Neurological Deaths were overall worst amongst females in the majority of countries – a factor also found in many countries in regard to cancers in women,<sup>3,24</sup> which suggests the rises in female neurological deaths are indicator of environmental factors.<sup>35–37</sup> Furthermore increasing deaths from Parkinson's Disease and Motor Neurone Disease cannot be attributable to longevity, bearing in mind the relatively short- time period, and cannot explain the 55–64-year old mortality rises up to 2006. Clearly other influences must be operating, though in no way does this deny the importance of hereditary factors<sup>38</sup> but rather strongly points towards an epigenetic explanation, that is negative environmental triggers impacting upon underlying genetic predispositions.<sup>1,6–9,23,35–37</sup>

The nature of any environmental factors are uncertain but there have been major environmental changes; including increased population, economic activity, air and road traffic, and increased home technology involving increased background electro-magnetic fields (mobile phones, micro-wave ovens, computers, etc),<sup>9,13,27,31,35,36</sup> which are unique to these later years. Such an interpretation is strengthened by the fact that since the late 1970's more women are entering the work force,<sup>39</sup> in areas that previously were virtually male, so it is only now that women are increasingly exposed to background electro-magnetic fields, petro-chemical etc as previously only men have been.

More research is needed to assess the potential impact of these environmental changes upon neurological deaths and the wider aspects of human health, especially when considering how, relative to general mortality, neurological deaths have disproportionately increased.

### Implications

Within the context of increased longevity, rising numbers of people with dementia and surviving strokes will add further pressure on already stretched health and social care services. The earlier onset of neurological disorders will have profound implications for patients, families and front-line services. Crucially, relative to other specialities, the present configuration of services may require re-organization, especially for specialist neurological services and for community psycho-social provision, to meet the challenge of more 'disabled' people in the community.

There are lessons to be drawn from reduced cancer mortality over the period. Every Government of the countries under review have made major additional investments in cancer services and research<sup>19,21</sup> and this needs to be done in the field of neurology.

Finally, a new British study showing that age-related cognitive decline was earlier than first thought but acknowledged that some of their findings 'could simply be the correlates of a disease process'<sup>40</sup> and this might be an early indicator of initial stages of neuro-degenerative diseases, which may be another indicator that the dementias are starting earlier.

## Author statements

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