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Changing patterns of adult (45–74 years) neurological deaths in the major Western world countries 1979–1997

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Neurological; Deaths; International comparisons

Summary *Objectives*. To compare changes in 'adult' (45–74 years) 'all-cause deaths' (ACDs) with all neurological death categories by age and gender in the 10 major Western countries between the 1970s (1979–1981) and the 1990s (1995–1997).

Method. World Health Organization standardized mortality data for age and gender (1979/97) were used to examine changes in adult mortality rates per million based upon ICD-9 categories for ACDs, 'neurological deaths' and the special neurological categories of 'other neurological deaths' (ONDs) and 'mental disorder deaths' (MDDs), which include the dementias. Ratios of ratios were calculated to demonstrate how each individual country's pattern changed over the period by age and gender, resolving the problem of cross-national comparisons. Rates of change across the endpoints and between age groups (45–54, 55–64, 65–74 and 75+ years) were examined using analysis of variance, stepwise regression analysis and cross-tabulation analyses.

Results. Meningitis deaths fell substantially, but there was little change in multiple sclerosis or epilepsy deaths. OND rates for the 1990s increased compared with the 1970s rates for males and female, in actual terms and relative to ACDs for almost all countries. Many of the relative rates of increase were substantially higher than 20%. There were significant statistical differences with respect to relative rates of ONDs between the 1970s and the 1990s data, even when the 75+ years age group was excluded. Significant differences were also found between age groups, but only in the 1990s data. MDD rates showed similar trends. Analyses of actual rates of increase in these causes of death showed that males outnumber females in all ages below 74 years. The extent of this difference remained constant across the endpoints. However, in those aged 75 years and over, females outnumbered males at both endpoints, but this disparity widened significantly in the 1990s data.

Conclusions. The 1990s data indicate substantial increases compared with the 1970s data for ONDs (especially amongst 65–74 year olds), and rises in MDDs in 55–64 year olds in five countries, including England and Wales and Germany, and in 65–74 year olds in most countries, suggesting earlier onsets of the underlying conditions. Further country-specific research is required to explain the emerging morbidity and mortality.

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Introduction

Neurological disease affects 2% of the general population in England and Wales, and appears to have increased in recent years.[1] The annual incidence rates of epilepsy, meningitis and multiple sclerosis are approximately 500, 150 and 30 per million (pm), respectively.[2] Both the World Health Organization (WHO) and the Office for National Statistics (ONS) report mortality rates for these diseases [International Classification of Disease 9 (ICD-9)-categories 220, 223 and 225] which are relatively rare.[3,4] For example, 1997 mortality rates in England and Wales were 18 pm for epilepsy, 4 pm for meningitis and 15 pm for multiple sclerosis.[4]

The majority of neurological deaths are actually subsumed in two special categories, namely 'mental disorder deaths' (MDDs) (ICD-9, categories 290–319) and 'other diseases of the nervous system and sense organs deaths', abbreviated here to other neurological deaths (ONDs) (ICD-9, categories 221, 222, 224, 229, 23, 24).

The OND category also includes deaths due to a wide range of disparate conditions including Parkinson's disease, motor neurone disease, hereditary neuromuscular conditions, and degenerative diseases, reflecting the range and complexity of the neurological disorders. Parkinson's disease has the greatest prevalence in the OND category, with one to two cases per 1000 aged 50 years and over, rising to 1–2% in elderly individuals.[8] Whilst 80% of Parkinson's disease cases remain idiopathic, there is a genetic predisposition;[9] 15% of cases are secondary, including a possible association with what Lishman calls 'environmental toxins'.[10,11] About one-quarter of patients either die or are severely disabled within five years, as are two-thirds of patients after 10 years.[6] There would have been benefits in being able to compare changes within these portmanteau categories, but the data are not yet available in an international standardized format. Nonetheless, ONDs represent the sixth highest mortality in England and Wales, with current rates of 186 pm for men and 191 pm for women,[4] so this is an area relevant for public health study.

MDDs consist mainly of senile and presenile conditions, as well as deaths due to long-term 'substance' abuse, Wilson's disease, Huntington's chorea, and dementia of the Alzheimer's type[5,6] (full list in Appendix A). These conditions are very much age related, with usual onset after 50 years of age. It is estimated that 2% of people between 65–70 years of age are showing signs of Alzheimer's, as are 20% of people aged 80 years and over.[5] The primary dementias have a genetic-associated aetiology, as 50% of first-degree relatives develop Alzheimer's by the age of 90 years,[7] with death occurring between five and eight years after diagnosis, although some patients live for 20 or more years.[5,6] Whilst there are more than 80 different conditions associated with the 'mental disorders', many very rare, they fall into the following categories of primary cerebral degeneration, prion disorders, inherited metabolic disorders, neoplasms, infections, cerebral degeneration, and metabolic and toxic causes, although 50% appear to have a genetic link.[5] People with dementia have a mortality rate 3.5 times that of the general population rate (GPR),[6] and as more people live longer, this may pose an increasing public health problem.

Interest is growing in genetic, environmental and social factors in the aetiology of some neurological diseases, particularly Parkinson's disease and motor neurone disease.[12–16] An analysis of childhood mortality data suggested that variations in paediatric neurological disease relate partly to socio-economic status, which is also likely to be true for adults.[17–19]

There are considerable differences amongst the neurological diseases, and aggregated data can only give a broad indicator of general changes. Nonetheless, based upon a methodology used in earlier international comparative studies, which maximized standardized WHO data,[20–24] it is possible to examine international mortality rates that can identify temporal trends, first by comparing a nation's pattern of mortality against itself, and then by contrasting any national change against any change found in other countries. Such an approach has resolved many of the problems inherent in cross-national comparisons.[25] This hypothesis-stimulating study explores the assumption that over the period between 1979 and 1997 there would be no change in:

- patterns of all-cause deaths (ACDs) by age or gender;
- WHO-reported (ICD-9) neurological death rates due to meningitis, multiple sclerosis and epilepsy by age and gender;
- patterns of OND rates by age and gender;
- MDD rates by age and gender.

Methodology

Mortality data

The latest standardized mortality data in the WHO format was utilized, taking the ICD-9 for 1979–1997, uniformly collated at source by the WHO based upon annual populations by gender within each of the decade age bands.[4] The 1970s baseline data are 3-year average rates per million population for the population of each age band for 1979–1981 to compare changes in the late 1990s, 3-year average rates for 1995–1997 by age and gender. To maintain the uniformity necessary in international comparisons, we ignored the later ICD-10 data which are available in some countries.

All-cause deaths

ACDs are the baseline against which to explore any patterns of change in ONDs and MDDs by comparing them against ACDs to determine whether these neurological deaths varied from general trends in overall mortality between the endpoints (1970s: 1979–1981 vs 1990s: 1995–1997).[4] This was done by comparing ONDs and MDDs (rates per million) against ACDs (as a proportion) at each endpoint, and examining the extent of change between the endpoints (ratio of ratios). This demonstrates the degree of any convergence or divergence between ONDs, MDDs and ACDs by age and gender over the period, an approach that was found useful in a series of international comparative studies in oncology, public health, child homicide and suicide.[20–24] It is recognized, however, that the main drivers that are likely to reduce ACDs are unlikely to affect neurological deaths; for example, improved treatment for diabetes.[17]

Neurological deaths

Deaths from meningitis, multiple sclerosis and epilepsy over the period were reviewed as a context in which to compare the two largest neurological mortality categories of OND and MDD.

In view of the fact that the vast majority of conditions in the OND category are age related, i.e. often starting after 50 years of age,[6,27] we have focused mainly on the age bands of 45–54 years to 65–74 years. We have included the age group of 75 + years for comprehensiveness, for both ONDs and MDDs.[4] However, it is recognized that as life expectancy lengthens, any increases in neurological disease and deaths could be due to a reduction in other causes of death.[15].

International comparisons

There are inherent problems in international comparisons due to national variations in data recording.[28] Our chosen approach, utilizing WHO standardized data, resolved these difficulties by essentially comparing a country against itself over time, before comparing national data.[25] To determine the proportional changes in each country, ratios of change were calculated from the baseline and index periods. This was repeated for the average 3-year rates for each country, and ratios of change were then used to make comparisons between countries.

The baseline period was taken from the publication of ICD-9 for the 1979 data onwards, and the latest 3 years for which data were available, mainly 1995–1997. In a few countries, this was slightly earlier and is noted in the text. The average 3-year death rate in the general population was calculated for each age band by gender based upon the populations in the 10-year age bands. Changes over time were determined by comparing baseline and index year rates, from which a ratio of change was calculated. All Western world countries with populations in excess of 16 million were examined.

Gender differences

To explore gender difference within a country, both rates and the actual number of ONDs and MDDs are shown, and a series of cross-tabulation analyses were undertaken to compare male and female deaths between the two periods.

General data observations: defining substantial change

Only changes in national mortality rates of $\pm 10\%$ may have clinical significance.[29] To err on the side of caution, as in previous studies,[20–24] we define 'substantial' as being when a ratio lies outside 0.80–1.20 (i.e. is equivalent to a change of 20% or more), which is very marked in terms of standard mortality ratios, to which the ratio of ratios is related.[26]

Statistical analyses

In addition, we have reported on those rates that show significant differences ($P < 0.05$), using

analysis of variance (ANOVA), between the various age groups, and particularly between the study endpoints (1970s vs 1990s). It was also important to consider whether any apparent changes may be the artefactual result of changes in diagnostic techniques[30,31] in complex neuropsychiatric conditions.[32–34] Age and time effects were included, and a stepwise regression analysis examined the contribution of age and year to overall variance. However, time was treated as an independent variable, so it was not reduced to binary, which permits analysis of the contribution of time to the amount of variance. Yates' continuity correlation was used to examine this. Spearman rank order correlations were used to determine stability over time between the countries reviewed.

Results

Epilepsy, meningitis and multiple sclerosis deaths

There were no findings of real note with regard to deaths from meningitis, epilepsy or multiple sclerosis.

With regard to meningitis deaths, whilst male GPR in the late 1990s ranged from 2 pm in Canada to 5 pm in England and Wales, The Netherlands and Spain, they were virtually half the level they had been in the 1970s.

Male deaths from epilepsy in the general population in the 1990s ranged from 6 pm in Japan, to 20 pm in the USA and Germany, to 24 pm in France. Most rates were between 8 and 14 pm, and there was little difference from the 1970s rates.

In every country, male meningitis and epilepsy death rates were higher than female rates.

Conversely, with regard to multiple sclerosis deaths, all female death rates were higher than for males. These ranged from 1 pm in Japan, to 14 pm in Canada, Germany and The Netherlands, and 17 pm in England and Wales, but the majority ranged between 5 and 10 pm

Hence, meningitis deaths fell over the period 1979–1997, but there was little change of note in epilepsy and multiple sclerosis deaths.

Other neurological diseases

General observations

Table 1 demonstrates that the GPR for males, with respect to ONDs (rates per million), increased in the 1990s compared with the 1970s in every country except France. The biggest increases were in Canada (2.18) and the USA (2.06), and the lowest were in The Netherlands (1.18) and England and Wales (1.41). For many countries, there was a reduction in relative OND rates in the 45–54-years age group. The remaining age groups presented increased rates across all countries, albeit with wide variation. The rate of change (ratio of ratios) showed an increase in all countries, ranging from 1.04 in France to 2.34 in Canada.

These general trends were largely repeated for females; the GPR for ONDs (1990s vs 1970s) showed increases ranging from 1.53 in England and Wales to 3.54 in Canada, with only France presenting a reduction in relative OND rates. Age-related trends were also similar. The rate of change (ratio of ratios) again showed an increase in all countries, ranging from 1.09 in France to 3.20 in Canada, with similar age trends to males.

When considering individual age groups, the largest increase was seen in the oldest age group (75 + years), with generally lower rates for younger age groups. These will be examined statistically later.

It was noteworthy, however, that in Australia, Canada, England and Wales, Germany, Italy, Spain and the USA, there were rises in the 65–74-year age band for both genders.

Statistical analyses

Univariate ANOVA was conducted for ONDs in respect of effects for age group and year (1990s vs 1990s). Significant main effects were seen for age ($F = 8.833$, df 4200, $P < 0.001$) and year ($F = 103.433$, df 1200, $P < 0.001$), and there was significant interaction between these ($F = 6.138$, df 4200, $P < 0.001$). A stepwise regression analysis demonstrated that year and age significantly contributed 31% of the overall variance ($F = 44.194$, df 2199, $P < 0.001$), with year contributing more ($t = 9.140$, $P < 0.001$) than age ($t = 2.200$, $P = 0.029$).

A series of individual ANOVA tests also highlighted a number of significant differences with respect to endpoint (1990s vs 1970s) and age group (45–54, 55–64, 65–74, 75 + years). OND rates, as a proportion of all deaths, were significantly higher for the 1990s than the 1970s ($F = 81.96$, $P = 0.001$). Appendix B shows a list of ACDs (rates per million). This effect for decade was found for all age groups ($P < 0.001$) and within each country except France (Australia, $F = 16.49$, $P = 0.001$; Canada, $F = 19.98$, $P < 0.001$; England and Wales, $F = 62.57$, $P < 0.001$;

Table 1 OND (rates per million), proportion (%) to ACDs, by age group and gender.

Country/ gender	Time period	OND									
		All ages	%	45–54 years	%	55–64 years	%	65–74 years	%	75 + years	%
Australia											
Males	1970s[a]	74	0.90	46	0.71	118	0.72	337	0.81	1079	0.97
	1990s[b]	135	1.81	34	0.94	100	0.93	420	1.41	2274	2.43
	Ratios	1.82	2.01	0.74	1.32	0.85	1.29	1.25	1.74	2.11	2.51
Females	1970s	61	0.94	32	0.95	84	1.04	208	1.02	639	0.78
	1990s	149	2.42	26	1.19	84	1.43	291	1.82	1866	2.61*
	Ratios	2.44	2.57	0.81	1.25	1.00	1.37	1.40	1.78	2.92	3.35
Canada											
Males	1970s	78	0.96	52	0.80	123	0.76	392	1.03	913	0.87
	1990s	170	2.25	49	1.26	132	1.22	536	1.85	2789	3.03
	Ratios	2.18	2.34	0.94	1.57	1.07	1.60	1.37	1.80	3.05	3.47
Females	1970s	61	1.00	35	1.01	94	1.18	227	1.17	571	0.78
	1990s	216	3.20	36	1.50	109	1.73	380	2.36	2634	3.82*
	Ratios	3.54	3.20	1.03	1.49	1.16	1.47	1.67	2.02	4.61	4.90
England and Wales											
Males	1970s	104	0.85	48	0.75	116	0.63	343	0.73	1008	0.79
	1990s	147	1.39	41	1.02	124	1.51	391	1.13	1626	1.53
	Ratios	1.41	1.64	0.85	1.36	1.07	2.39	1.14	1.55	1.61	1.94
Females	1970s	105	0.91	33	0.84	83	0.86	238	0.97	796	0.86
	1990s	161	1.46*	30	1.13	93	1.31*	281	1.37	1235	1.49*
	Ratios	1.53	1.51	0.91	1.35	1.12	1.52	1.18	1.41	1.55	1.73
France											
Males	1970s	183	1.70	55	0.69	153	0.88	624	1.62	2175	2.02
	1990s	172	1.78	51	0.91	141	1.10	486	1.73	2074	2.18
	Ratios	0.94	1.04	0.93	1.32	0.92	1.26	0.78	1.07	0.95	1.08
Females	1970s	203	2.12	36	1.13	101	1.57	397	2.28	1803	2.22
	1990s	197	2.31	28	1.19	90	1.81	343	2.85	1693	2.29
	Ratios	0.97	1.09	0.78	1.05	0.89	1.15	0.86	1.25	0.94	1.03
Germany											
Males	1970s	95	0.80	51	0.72	136	0.81	370	0.46	795	0.65
	1990s	144	1.42	44	0.80	110	0.83	425	1.26	2073	1.85
	Ratios	1.52	1.77	0.86	1.12	0.81	1.02	1.15	2.74	2.61	2.84
Females	1970s	93	0.81	35	0.98	90	1.12	256	1.08	542	0.59
	1990s	172	1.54*	26	0.94	76	1.25	289	1.62	1367	1.50*
	Ratios	1.85	1.90	0.74	0.96	0.84	1.11	1.13	1.50	2.52	2.55
Italy											
Males	1970s	100	0.96	44	0.66	124	0.75	392	0.97	890	0.80
	1990s	170	1.65	44	1.05	141	1.19	469	1.52	1910	2.72
	Ratios	1.70	1.72	1.00	1.59	1.14	1.58	1.20	1.57	2.15	3.41
Females	1970s	87	0.99	32	1.07	80	1.11	264	1.27	693	0.79
	1990s	188	1.65	31	1.41	99	1.86	347	2.31	1585	2.03*
	Ratios	2.16	2.08	0.97	1.32	1.24	1.67	1.31	1.82	2.29	2.57
Japan											
Males	1970s	44	0.67	31	0.57	86	0.74	222	0.68	392	0.42
	1990s	64	0.79	30	0.79	83	0.84	209	0.88	527	0.60
	Ratios	1.45	1.18	0.99	1.38	0.97	1.13	0.94	1.29	1.35	1.44
Females	1970s	35	0.63	21	0.80	56	0.92	141	0.78	281	0.36
	1990s	57	0.87	19	0.97	56	1.30	151	151	357	0.62*
	Ratios	1.63	1.39	0.90	1.21	1.00	1.42	1.07	1.77	1.27	1.72

(*continued on next page*)

Table 1 (*continued*)

Country/ gender	Time period	OND									
		All ages	%	45–54 years	%	55–64 years	%	65–74 years	%	75 + years	%
The Netherlands											
Males	1970s	107	1.20	50	0.94	116	0.77	455	1.11	1371	1.22
	1990s	126	1.42	44	1.15	115	1.01	432	1.29	1717	1.56
	Ratios	1.18	1.18	0.88	1.22	0.99	1.31	0.95	1.16	1.25	1.28
Females	1970s	90	1.25	24	0.81	97	1.42	274	1.47	827	1.07
	1990s	159	1.83	33	1.26	105	1.67	294	1.76	1511	2.04
	Ratios	1.77	1.47	1.38	1.56	1.08	1.18	1.07	1.20	1.83	1.91
Spain											
Males	1970s	81	0.97	49	0.86	118	0.84	310	0.87	826	0.79
	1990s	132	1.39	49	0.98	139	1.15	425	1.47	1366	1.42
	Ratios	1.63	1.44	1.00	1.14	1.18	1.37	1.37	1.69	1.65	1.79
Females	1970s	71	0.98	31	1.16	70	1.07	207	1.09	611	0.72
	1990s	136	1.70	32	1.58	95	2.00	296	2.26	1132	1.51*
	Ratios	1.92	1.74	1.03	1.36	1.36	1.87	1.43	2.07	1.85	2.10
USA											
Males	1970s	83	0.86	53	0.69	133	0.74	355	0.88	805	0.77
	1990s	171	1.91	55	0.96	141	1.02	485	1.50	2485	2.69
	Ratios	2.06	2.22	1.04	1.39	1.06	1.38	1.37	1.70	3.09	3.49
Females	1970s	68	0.88	37	0.90	92	0.99	214	1.02	498	0.66
	1990s	200	2.36	40	1.24	108	1.30*	341	1.73	2127	2.82*
	Ratios	2.94	2.68	1.08	1.38	1.17	1.32	1.59	1.69	4.27	4.27

Ratio of change and ratio of proportion (%): 1970s vs 1990s. *Significant difference between 1970s and 1990s (male and female) in age group/country. % = Proportion of ONDs to total deaths.

[a] 1970s: Based on 3-year average of WHO (1979–1981) ICD-9 data.[4]

[b] 1990s: Based on 3-year average of WHO (1995–1997) ICD-9 data.[4]

Germany, $F = 14.71$, $P = 0.001$; Italy, $F = 23.44$, $P < 0.001$; Japan, $F = 6.40$, $P = 0.021$; The Netherlands, $F = 8.52$, $P = 0.009$; Spain, $F = 23.21$, $P < 0.001$; USA, $F = 17.73$, $P = 0.001$). This effect for decade was also found within some individual countries, by age group, as shown by the asterisks in Table 1. Most of these appear in the age group for 75 + years, which might be expected. However, the extent of this increase is not (see later). Nonetheless, to address this potential weakness, the effect for decade was recalculated excluding this age group. ANOVA showed that there was still a significant difference between the 1990s and the 1970s ($F = 60.45$, $P < 0.001$).

There was also a significant effect for age group ($F = 6.61$, $P < 0.001$). A post hoc (Sheffé) analysis showed that those aged 75 + years had significantly higher rates of OND, as a proportion of all deaths, than those aged 45–54 years ($P = 0.002$), and that those aged 65–74 years had significantly higher rates of OND, as a proportion of all deaths, than those aged 45–54 years ($P = 0.021$). However, an examination between the decades showed that this effect for age group was not present for the 1970s data, but was for the 1990s data ($F = 12.84$, $P < 0.001$). The post hoc analysis of the 1990s data showed that those aged 75 + years had significantly higher rates of OND, as a proportion of all deaths, than those aged 55–64 years ($P < 0.001$) and 45–54 years ($P < 0.001$). Also, those aged 65–74 years had significantly higher rates of OND, as a proportion of all deaths, than those aged 45–54 years ($P = 0.009$). To address the potential weakness of including those older than 75 years, that age group was excluded and there was still a significant effect for age overall ($F = 10.05$, $P < 0.001$). The post hoc analysis showed that those aged 65–74 years had significantly greater rates of OND than those aged 55–64 years ($P = 0.029$) and those aged 45–54 years ($P < 0.001$). Again, this was apparent in the 1990s data ($F = 12.37$, $P < 0.001$), and not in the 1970s data. Those aged 65–74 years had significantly greater rates of OND than those aged 55–64 years ($P = 0.012$) and 45–54 years ($P < 0.001$).

These results reflect the way in which OND rates have increased between the 1990s and the 1970s. However, it is also useful to examine the extent that ONDs as a proportion of all deaths have

changed between those endpoints; this was examined using the ratio of ratios. We previously set a criterion that the rates of change in excess of 20% would be deemed to be substantial; this would be reflected by a ratio of ratios beyond 1.20. Table 1 shows that this was demonstrated for all countries, across all age bands and for both males and females, except in France (male and female 'all ages'; females aged 45-54 years; females aged 55-64 years; males aged 65-74 years; males and females aged 75+ years), Germany (males and females aged 55-64 years), Japan (males 'all ages'; males aged 55-64 years), The Netherlands (males 'all ages'; females aged 55-64 years; males aged 65-74 years) and Spain (males aged 45-54 years). Nevertheless, the 'substantial' increases were generally widespread.

Using ANOVA, the ratio of ratios was found to be significant for age ($F = 15.43$, $P < 0.001$). A post hoc analysis showed that those aged 75+ years had significantly higher rates than all other age groups (45-54 years: $P < 0.001$; 55-64 years: $P < 0.001$; 65-74 years: $P = 0.001$). This was found within the following countries: Australia [$F = 13.08$, $P = 0.016$; individual differences showed that rates for those aged 75+ years were significantly higher than for those aged 45-54 years ($P = 0.015$) and 55-64 years ($P = 0.027$)]; Canada [$F = 12.30$, $P = 0.017$; with rates for those aged 75+ years significantly higher than rates for those aged 45-54 years ($P = 0.031$) and 55-64 years ($P = 0.031$)]; Germany [$F = 6.461$, $P = 0.049$; no individual differences]; Italy [$F = 9.40$, $P = 0.028$; with rates for those aged 75+ years significantly higher than rates for those aged 45-54 years ($P = 0.041$)]; and USA [$F = 38.37$, $P = 0.002$; with rates for those aged 75+ years significantly higher than rates for those aged 45-54 years ($P = 0.004$), 55-64 years ($P = 0.004$) and 45-54 years ($P = 0.007$)]. Again, it could be argued that the observed trends for those aged 75+ years are only to be expected since a greater proportion of deaths are ONDs. Even so, these rates of increase are higher than might be expected. Nevertheless, to address that issue, the age group of 75+ years was excluded and there was still a significant effect for age ($F = 6.10$, $P = 0.004$; 65-74 years > 45-54 years: $P = 0.005$), albeit in fewer countries: Australia [$F = 63.96$, $P = 0.003$; rates for those aged 65-74 years were significantly higher than rates for those aged 45-54 years ($P = 0.005$) and 55-64 years ($P = 0.006$)] and the USA [$F = 113.87$, $P = 0.001$; rates for those aged 65-74 years were significantly higher than rates for 45-54 years ($P = 0.003$) and 55-64 years ($P = 0.002$)].

Mental disorder deaths

General observations

Table 2 demonstrates that the GPR for males, with respect to MDDs, increased in the 1990s compared with the 1970s for every country except Japan. The biggest increases were in The Netherlands (6.65) and Italy (5.40); the lowest increases were in France (1.20) and Germany (1.69). Most countries saw increasing MDD rates for the 1990s vs the 1970s across all age bands, particularly in older age, with the exception of Japan. This pattern was much the same for females, with all countries showing increased rates of MDD in the 1990s compared with the 1970s. The biggest increases were in Italy (15.75) and Spain (12.32); the lowest increases were in Japan (1.35) and France (1.79). Similar patterns to males were observed across the age bands. The higher rates of increase were surprisingly high, and may warrant further investigation (Italians over the age of 75 years showed an increased ratio of MDDs of 21.58 for males and 33.33 for females). The wide variation in these rates may have contributed to the slightly lower significance levels compared with ONDs (despite relatively higher increases).

It was especially noteworthy that MDD rates rose for the 55-64-year age bands in England and Wales, Germany, Italy, The Netherlands and Spain for both genders. Furthermore, every country except France and Japan had notable rises in MDDs for 65-74-year-old men and women.

A univariate ANOVA was conducted for MDDs in respect of effects for age group and year (1990s vs 1990s). Significant main effects were seen for age ($F = 7.663$, df 3160, $P < 0.001$) and year ($F = 33.535$, df 1160, $P < 0.001$), and there was significant interaction between these ($F = 5.978$, df 3160, $P < 0.001$). A stepwise regression analysis demonstrated that only year contributed significantly to the overall variance (22%: $F = 44.728$, df 1159, $P < 0.001$). Year was the significant predictor ($t = 6.688$, $P < 0.001$), although age was nearly significant ($t = 1.743$, $P = 0.083$).

Individual ANOVA analyses showed significant differences in respect of endpoint and age group. MDD rates (as a proportion of all deaths) were significantly higher for the 1990s than the 1970s ($F = 44.73$, $P < 0.001$). This effect for decade was found for all age groups ($P < 0.001$), except in those aged 45-54 years, and within each country except France and Japan (Australia, $F = 6.06$, $P = 0.027$; Canada, $F = 8.13$, $P = 0.013$; England and Wales, $F = 5.06$, $P = 0.041$; Germany, $F = 6.02$, $P = 0.028$; Italy, $F = 20.84$, $P < 0.001$; The Netherlands,

Table 2 MDD (rates per million), proportion (%) to ACDs, by age group and gender.

Country/gender	Time period	MDD							
		All ages	%	55–64 years	%	65–74 years	%	75 + years	%
Australia									
Males	1970s[a]	63	0.77	92	0.56	219	0.53	956	0.86
	1990s[b]	136	1.82	79	0.74	236	0.80	2421	2.58
	Ratios	2.16	2.37	0.86	1.32	1.08	1.50	2.53	3.00
Females	1970s	58	0.89	35	0.44	112	0.55	909	1.11
	1990s	179	2.91	34	0.58	137	0.86*	2421	3.39*
	Ratios	3.09	3.27	0.97	1.31	1.22	1.56	2.66	3.05
Canada									
Males	1970s	68	0.84	158	0.98	249	0.65	770	0.74
	1990s	144	1.91	128	1.18	345	1.19	2480	2.69
	Ratios	2.12	2.26	0.81	1.20	1.39	1.83	3.22	3.64
Females	1970s	44	0.72	51	0.64	94	0.49	596	0.81
	1990s	219	3.24	45	0.71	179	1.11*	3115	4.52
	Ratios	4.98	4.50	0.88	1.12	1.90	2.27	5.23	5.58
England and Wales									
Males	1970s	46	0.38	31	0.17	111	0.24	691	0.54
	1990s	129	1.22	40	0.49	177	0.51	1662	1.57
	Ratios	2.80	3.22	1.29	2.86	1.59	2.13	2.41	2.90
Females	1970s	87	0.76	25	0.26	103	0.42	924	1.00
	1990s	230	2.08	25	0.35	129	0.63	2260	2.72
	Ratios	2.64	2.74	1.00	1.35	1.25	1.50	2.45	2.72
France									
Males	1970s	160	1.48	299	1.85	498	1.29	1269	1.18
	1990s	192	1.98	218	1.71	309	1.10	2011	2.11
	Ratios	1.20	1.34	0.73	0.92	0.62	0.85	1.58	1.79
Females	1970s	140	1.46	79	1.23	218	1.25	1326	1.63
	1990s	251	2.94	65	1.31	158	1.31	2684	3.64
	Ratios	1.79	2.01	0.82	1.06	0.72	1.05	2.02	2.23
Germany									
Males	1970s	105	0.89	197	1.17	226	0.28	295	0.24
	1990s	178	1.75	314	2.36	288	0.85	798	0.71
	Ratios	1.69	1.97	1.59	2.02	1.27	3.02	2.71	2.96
Females	1970s	49	0.43	68	0.84	80	0.34	220	0.24
	1990s	109	0.97	80	1.31	98	0.55	772	0.85*
	Ratios	2.22	2.26	1.18	1.56	1.23	1.62	3.51	3.54
Italy									
Males	1970s	20	0.19	40	0.24	37	0.09	52	0.05
	1990s	108	1.05	49	0.41	152	0.49	1122	1.60
	Ratios	5.40	5.45	1.23	1.71	4.11	5.44	21.58	32.00
Females	1970s	8	0.09	12	0.17	17	0.08	39	0.04
	1990s	126	1.38*	22	0.41*	120	0.80	1300	1.66*
	Ratios	15.75	15.31	1.83	2.43	7.06	10.00	33.33	41.50
Japan									
Males	1970s	27	0.40	43	0.37	92	0.28	352	0.37
	1990s	24	0.30	27	0.27	38	0.16	300	0.34
	Ratios	0.89	0.74	0.63	0.73	0.41	0.57	0.85	0.92
Females	1970s	23	0.41	20	0.33	68	0.37	380	0.48
	1990s	31	0.48	7	0.16	17	0.16	338	0.59
	Ratios	1.35	1.16	0.35	0.49	0.25	0.42	0.89	1.22
The Netherlands									
Males	1970s	23	0.25	30	0.20	60	0.15	320	0.28
	1990s	153	1.72	74	0.65	241	0.72	2972	2.69
	Ratios	6.65	6.90	2.47	3.25	4.02	4.79	9.29	9.62
Females	1970s	31	0.43	20	0.29	40	0.22	431	0.56
	1990s	365	4.20	37	0.59*	253	1.52	4734	6.42
	Ratios	11.77	9.78	1.85	2.03	6.33	6.90	10.98	11.46

(*continued on next page*)

Table 2 (*continued*)

Country/gender	Time period	MDD							
		All ages	%	55-64 years	%	65-74 years	%	75 + years	%
Spain									
Males	1970s	31	0.37	58	0.42	89	0.25	271	0.26
	1990s	158	1.67	66	0.54	258	0.89	2683	2.78
	Ratios	5.10	4.50	1.14	1.30	2.90	3.56	9.90	10.69
Females	1970s	22	0.30	20	0.31	55	0.29	267	0.32
	1990s	271	3.39	24	0.51	188	1.43	3289	4.39
	Ratios	12.32	11.30	1.20	1.63	3.42	4.94	12.32	13.73
USA									
Males	1970s	72	0.75	138	0.77	185	0.46	612	0.59
	1990s	137	1.53	145	1.05	262	0.81	1794	1.94
	Ratios	1.90	2.04	1.05	1.36	1.42	1.76	2.93	3.29
Females	1970s	53	0.69	43	0.46	77	0.37	547	0.73
	1990s	190	2.24	48	0.58	149	0.75*	2367	3.14
	Ratios	3.58	3.25	1.12	1.26	1.94	2.04	4.33	4.30

Ratio of change and ratio of proportion (%): 1970s vs 1990s. *Significant difference between 1970s and 1990s (male and female) in age group/country. % = Proportion of MDDs to total deaths.
[a] 1970s: Based on 3-year average of WHO (1979-1981) ICD-9 data.[4]
[b] 1990s: Based on 3-year average of WHO (1995-1997) ICD-9 data.[4]

$F = 4.73$, $P = 0.047$; Spain, $F = 10.49$, $P = 0.006$; and the USA, $F = 8.02$, $P = 0.013$). This effect for decade was also found within some individual countries, by age group, as shown by the asterisks in Table 2. To address the potential weakness of including those aged 75 + years, the relationship between decades was recalculated excluding that age group. ANOVA still showed there to be a significant difference ($F = 27.60$, $P < 0.001$).

There was also a significant effect for 'age group' ($F = 12.75, P < 0.001$). A post hoc analysis showed that those aged 75 + years had significantly higher rates of MDD, as a proportion of all deaths, than those aged 55-64 years ($P < 0.001$) and 65-74 years ($P < 0.001$). However, an examination between the decades showed that there was no effect for age group for the 1970s data, but a significant effect for age group for the 1990s data ($F = 21.58$, $P < 0.001$). The post hoc analysis showed that those aged 75 + years had significantly higher rates of MDD, as a proportion of all deaths, than those aged 55-64 years ($P < 0.001$) and 45-54 years ($P < 0.001$). To address the issue of including those aged 75 + years, that group was excluded and, this time, there was no significant effect for age group.

Using the ratio of ratios, it was possible to examine the proportional rate of change for MDDs between the endpoints. The previously set criterion for ratio of ratios of 1.20, for determining 'substantial increase', was exceeded in all countries and across all age groups except Japan (most age groups, male and female), France (males and females aged 55-64 and 65-74 years) and Canada (females aged 55-64 years). Using ANOVA, the ratio of ratios was found to be significant for age ($F = 5.89, P = 0.005$). The post hoc analysis showed that those aged 75 + years had significantly higher rates than those aged 55-64 years ($P = 0.008$) and 65-74 years ($P = 0.003$). This was found within the following countries: Australia [$F = 1639.15$, $P < 0.001$; individual differences showed rates in those aged 75 + years to be significantly higher than rates in those aged 55-64 years ($P < 0.001$) and 65-74 years ($P < 0.001$), plus rates in those aged 65-74 years were significantly higher than rates in those aged 55-64 years ($P = 0.016$)]; Canada [$F = 6.42$, $P = 0.049$; no individual differences]; France [$F = 17.11$, $P = 0.023$; rates in those aged 75 + years were significantly higher than rates in those aged 55-64 years ($P = 0.036$) and 65-74 years ($P = 0.032$)]; Italy [$F = 692.46$, $P = 0.008$; rates in those aged 75 + years were significantly higher than rates in those aged 55-64 years ($P = 0.019$) and 65-74 years ($P = 0.015$)]; The Netherlands [$F = 31.58$, $P = 0.018$; rates in those aged 75 + years were significantly higher than rates in those aged 55-64 years ($P = 0.018$)]; Spain [$F = 33.15$, $P = 0.009$; rates in those aged 75 + years were significantly higher than rates in those aged 55-64 years ($P = 0.010$) and 65-74 years ($P = 0.023$)]; and the USA [$F = 18.25$, $P = 0.021$; rates in those aged 75 + years were significantly higher than rates in those aged 55-64 years ($P = 0.024$) and 65-74 years ($P = 0.049$)]. Again, it could be argued that the observed trends for those aged 75 + years are also expected, since MDDs

increase with age, particularly in the most elderly. Even so, these rates of increase are higher than might be expected. Nevertheless, to address the issue, the age group of 75 + years was excluded and there was still a significant effect for age ($F = 5.67$, $P = 0.022$; no post hoc analysis necessary, since there are only two age groups remaining). Only Australia showed individual significant differences ($F = 49.97$, $P = 0.019$), although Canada ($P = 0.058$), Spain ($P = 0.059$) and the USA ($P = 0.058$) all approached significance. The effect of removing the age group of 75 + years was greater in MDDs than ONDs, which may reflect the wide variation in the MDD rates.

Gender differences in ONDs

Females showed significantly higher relative rates of OND than males ($F = 10.95$, $P = 0.001$), which was reflected across all age groups, except those aged 75 + years, and was found for both endpoints. There was no effect for gender in respect of the rates of increase (ratio of ratios).

Table 3 shows the actual numbers of deaths by gender and in each age group for all countries in respect of ONDs, and it is apparent that the rates of OND for gender shifted between the endpoints. ANOVA shows a significant overall effect for gender ($F = 282.09$, $P < 0.001$). However, closer examination shows that 'all-age' males had significantly higher actual rates of OND than females in the 1970s ($F = 200.67$, $P < 0.001$) while the reverse was apparent in the 1990s ($F = 2249.63$, $P < 0.001$). This pattern can be explained by examining these data for the age-related rates from Table 3.

Male rates of OND exceed female rates in all countries, for all ages under 75 years. This is

Table 3 Annual OND (actual numbers) by age group and gender: 1970s vs 1990s.

Country		OND									
		All ages		45–54 years		55–64 years		65–74 years		75 + years	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Australia	1970s	542	448	36	24	77	56	139	103	194	205
	1990s	1206	1311[a]	37	30	77	65	249	184	721	979[o]
Canada	1970s	929	731	65	44	124	104	256	176	302	301
	1990s	2513	3241[b]	93	69	166	140	516	417	1565	2484[q]
England and Wales	1970s	2497	2665	138	93	327	242	739	620	993	1524
	1990s	3766	4269*	139	100	313	239	806	683	2133	3024
France	1970s	4807	5567	194	116	388	263	1248	977	2526	3951
	1990s	4873	5876*	184	98	387	262	1125	993[c]	2771	4259
Germany	1970s	2785	2995	192	134	328	318	831	941	1024	1443
	1990s	5736	7219[d]	226	129	573	406[e]	1324	1255[f]	3230	5199[r]
Italy	1970s	2782	2550	161	118	351	239	988	722	953	1210
	1990s	4725	5533[g]	160	114	460	352	1139	1083[h]	2584	3444
Japan	1970s	2548	2096	231	158	385	313	678	554	562	622
	1990s	3935	3612[j]	293	185	634	446	1079	952	1388	1720
The Netherlands	1970s	754	642	37	18	72	67	195	152	330	333
	1990s	966	1248[k]	48	34	84	78	229	192	523	890[s]
Spain	1970s	1484	1353	111	73	196	133	351	311	453	566
	1990s	2523	2726[l]	107	72	278	207	666	568	1175	1706[t]
USA	1970s	9178	7913	583	436	1352	1066	2408	1893	2890	3234
	1990s	22152	27177[m]	861	655	1436	1218	4050	3516[n]	13788	20506[v]
Overall mean[ø]	1970s	4928	4583	304	228	703	556	1312	1054	1803	2456
	1990s	11727	14601	457	353	764	636	2089	1832	7564	11320

All significant differences are calculated using Yates' continuity correlation (for 2 × 2 tables). [a]12.99: $P < 0.001$; [b]77.74: $P < 0.001$; [c]3.85: $P = 0.049$; [d]24.45: $P < 0.001$; [e]9.16: $P = 0.002$; [f]9.11: $P = 0.004$; [g]52.29: $P < 0.001$; [h]16.27: $P < 0.001$; [j]8.48: $P = 0.004$; [k]37.57: $P < 0.001$; [l]13.09: $P < 0.00$; [m]393.57: $P < 0.001$; [n]6.58: $P = 0.010$; [o]4.82: $P = 0.028$; [q]28.07: $P < 0.001$; [r]8.02: $P = 0.005$; [s]29.83: $P < 0.001$; [t]4.02: $P = 0.045$; [v]104.35: $P < 0.001$. *Approached significance ($P < 0.10$). [ø]All 'overall mean' between-gender differences significant to $P < 0.001$.

apparent in both endpoints, and the difference between males and females remained relatively constant. However, female rates had already exceeded male rates in the 1970s data for those aged over 75 years, but this gap has widened in respect of the 1990s data, and is apparent in almost all countries; in effect, female rates have increased disproportionately to males between the decades. Yates' continuity correlation was used to examine whether rates of increase change proportionally for both males and females; this would be shown by a non-significant Yates' value. This might show that increases in ONDs are artefactual, or possibly as a result of diagnostic changes. A significant Yates' score represents changes that are not uniform for gender, and increases cannot be explained by simple diagnostic changes. In every country, there were significant Yates' values (gender vs endpoint) with respect to the 'all ages' category, with the exception of France which neared significance. Table 3 shows this in more detail, and illustrates the shift in OND rates between genders across endpoints. There were no significant differences in the 45–54-years age group, and only Germany showed significant differences in the 55–64-years age group. There were significant differences in the 65–74-years age group for France, Germany, Italy and the USA, and in all countries except England and Wales, France, Italy and Japan for those aged 75 years and over. The abnormal change in OND rates appears to be more prevalent with advancing age, although earlier than has been reported previously.

Table 4 Three-year average MDD (actual numbers) by age group and gender: 1970s vs 1990s.

Country		MDD							
		All ages		55–64 years		65–74 years		75 + years	
		Male	Female	Male	Female	Male	Female	Male	Female
Australia	1970s	463	426	45	13	59	23	172	291
	1990s	1174	1541[a]	60	15	58	26	650	1264
Canada	1970s	807	527	113	42	158	56	255	314
	1990s	2119	3298[b]	117	44	160	58	1394	2939[t]
England and Wales	1970s	1116	2204	42	36	81	72	631	1771
	1990s	3290	6100	127	58[c]	101	66	2191	5535[v]
France	1970s	4220	3993	732	204	710	206	1424	2919
	1990s	5426	7790[e]	584	180	599	190	2683	6749[w]
Germany	1970s	3087	1590	737	235	476	240	379	583
	1990s	7102	4579[f]	1258	342	1639	430[g]	1242	2937[x]
Italy	1970s	564	224	114	25	104	36	50	56
	1990s	3013	3688[h]	104	36	160	77	1517	3561[y]
Japan	1970s	1552	1381	287	66	191	113	505	841
	1990s	1486	1942[k]	172	58*	202	56[l]	787	1623[z]
The Netherlands	1970s	160	223	21	6	19	14	77	173
	1990s	1177	3012[n]	45	18	54	28	903	2775[aa]
Spain	1970s	564	420	117	19	96	38	149	237
	1990s	3033	5422[o]	81	17	132	51	2308	4889[ab]
USA	1970s	7930	5838	1199	421	1401	492	2196	3556
	1990s	17767	26302	1814	522[r]	1481	539	9968	22829[ac]
Overall mean[ø]	1970s	4662	3569	776	265	845	284	1331	2385
	1990s	9523	13816	1214	335	1170	350	5259	12035

All significant differences are calculated using Yates' continuity correlation (for 2 × 2 tables). [a]20.76: $P < 0.001$; [b]198.33: $P < 0.001$; [c]4.61: $P = 0.032$; [d]7.58: $P = 0.006$; [e]217.77: $P < 0.001$; [f]38.29: $P < 0.001$; [g]46.54: $P < 0.001$; [h]199.04: $P < 0.001$; [j]7.03: $P = 0.008$; [k]57.59: $P < 0.001$; [l]15.15: $P < 0.001$; [m]12.15: $P < 0.001$; [n]31.07: $P < 0.001$; [o]170.95: $P < 0.001$; [q]1268.18: $P < 0.001$; [r]6.79: $P = 0.009$; [s]20.22: $P < 0.001$; [t]35.45: $P < 0.001$; [v]3.88: $P = 0.049$; [w]26.59: $P < 0.001$; [x]33.47: $P < 0.001$; [y]13.92: $P < 0.001$; [z]8.84: $P = 0.003$; [aa]4.55: $P = 0.033$; [ab]6.84: $P = 0.009$; [ac]139.97: $P < 0.001$. *Approached significance ($P < 0.10$). [ø]All 'overall mean' between-gender differences significant to $P < 0.001$.

Gender differences in MDDs

Unlike ONDs, there was no effect for gender with respect to MDD rates (although there was a near significant trend for females over 75 years to show higher rates than males in the 1990s: $P = 0.065$), nor was there any difference with respect to gender for the rate of increase in MDDs (ratio of ratios).

Table 4 shows the actual numbers of deaths by gender in each age group for all countries with respect to MDDs. The shift between genders appears to be less marked than for ONDs, but is still apparent in most countries. ANOVA showed that there was a significant effect for gender ($F = 6264.79$, $P < 0.001$). Similar to actual ONDs, there was also a significant effect in respect of the 'all ages' group, but in opposite directions with respect to endpoint; males had significantly higher actual rates of MDD than females in the 1970s ($F = 1784.71$, $P < 0.001$), while the reverse was seen in 1990s ($F = 5801.71$, $P < 0.001$). Rates of increase in MDDs across the endpoints were again disproportionate between males and females; males exceeded females in all countries for the 1970s data for those aged 55–64 and 65–74 years, and this gap widened with the 1990s data. On the other hand, females over 75 years exceeded their male counterparts across all countries in the 1970s, and this gap widened with the 1990s data. Yates' continuity correlation showed significant differences with respect to the 'all ages' category in all countries except England and Wales. Table 4 shows this in more detail, and illustrates the shift in MDD rates between genders across endpoints. There were significant differences for England and Wales and USA in the 55–64-years age group (with Japan nearing significance), significant differences for Germany and Japan in the 65–74-years age group, and significant differences in all countries except Australia for those aged 75 + years. The abnormal change in MDD rates appears to be more prevalent with advanced age, although earlier than has been reported previously.

Conclusions

Study limitations

Analysis of national data enables identification of large-scale trends but provides little information about individuals. Furthermore, changes in the incidence of a condition may represent real changes or merely apparent changes, secondary to variations in case identification or recording.

Diagnostic techniques have advanced, and neurological pathology can be identified and determined more widely.[30,31] Greater physician awareness of neurological disease may well lead to increased rates of diagnosis.[1,13] An illustration of this phenomenon accounted for the rise in the incidence of Creutzfeldt–Jakob disease in Austria, from 0.8 to 1.5 pm, as Austria had no recorded cases of bovine spongiform encephalopathy.[35] Therefore, raised awareness and improved diagnostics may have contributed something to the OND results, although it seems unlikely to account for the extent of the changes found.

Indeed, OND mortality rates may be an underestimate of the extent of these conditions. Many patients in the later stages of Huntington's chorea die from suicide,[36] and those in the terminal stage of chronic neurological disease may die from other causes, such as pneumonia or congestive cardiac failure.[37] However, if the results were mainly because of improved diagnosis, the changes would be expected to be broadly uniform across the developed nations between the age bands, but this was not the case. However, we cannot say the same with regard to diagnosis and gender. There may have been constituent diagnoses within the OND category, which might have affected one specific disease within this broad category, and this disease may have had a different age/gender pattern than the other causes within this group.

If the results were an artefact of advances in technology, this would not explain the results concerning the WHO-reported neurological categories of epilepsy, meningitis and multiple sclerosis. Falls in meningitis mortality would be expected with education and improved use of antibiotics. Epilepsy is the most prevalent neurological disorder, affecting 3% of the population,[1] but deaths related to epilepsy are still relatively rare. The lifetime prevalence of multiple sclerosis appears fairly stable (600–1000 pm), but the Anglo-Welsh death rate is only 15 pm.

Other diseases of the nervous system and sense organs

The rises in ONDs not only occur in the elderly group,[38] where they might be expected, but also in the 65–74-years age group. As this corresponds with a falling rate of ACDs, it is at odds with the artefact explanation. Nonetheless, it is appreciated that those factors that drove down the ACD rates are

unlikely to have affected neurological deaths; two examples would be the improved treatment for diabetes mellitus[17] and major reductions in road deaths.[49]

The OND category includes some of the rarest conditions, such as motor neurone disease, which increased slightly over the period.[39] The only relatively common condition is Parkinson's disease, in which increases have also been reported,[1] so Parkinson's disease may have influenced the increase in OND rates. There would have been benefit in being able to compare the various single diseases within the portmanteau category of OND, but this was not possible as there are no standardized statistics to allow an international comparison to be made on these diseases.

Which diseases within the general category may have contributed most or least is beyond the scope of our data and is another research project. Nonetheless, the fact that these data are collected uniformly allows general changes to be noted in the countries reviewed. Despite the advantage of using WHO data, disentangling the combined OND category will require further research, especially for the 65–74-years age group, which was an objective of this hypothesis-stimulating study.

Death rates from epilepsy, meningitis, and multiple sclerosis have generally fallen or remained stable at a time when ONDs rose. As in the 1970s, the 1990s data suggest that more women over 75 years die from ONDs than men of this age, but this gap now appears to be widening. This is probably because women continue to live longer than men. However, in both genders, ONDs have risen at a time when ACDs have fallen. When controlling for age, ONDs rose substantially at the time of lowest-ever mortality rates in the middle- and old-age bands, i.e. between 55–74 years, which is below the average age of death in most of the countries under review.[44] Whilst rises in ONDs and MDDs in those aged 75 + years can be explained by improved medicine and social conditions, keeping people alive when they would have been vulnerable to die from other conditions, this is likely not to be the case for those aged 55–74 years.

The effect for age, seen in the 1990s data, was not present in the 1970s data. These findings reflect trends over the past two decades, and in view of improved treatments, rises in ONDs for the 65–74 year olds may imply an earlier age of onset for the underlying neurological diseases.

Mental disorder deaths

There is much interest in the incidence of dementia.[8,15,34,38,40–44] Over-reporting may result from the inclusion of cases of mild cognitive impairment,[41] and under-reporting can occur because of 'missed cases',[41] but the incidence rises linearly with age, especially in the most elderly.[30,32] There are, however, marked differences in the mortality of age-standardized groups between genders, countries and different regions within a country, providing a degree of confirmation to a suggested environmental contribution to the development of these conditions.[9,10,16,25,34,41–47]

This same phenomenon was noted in the case of MDDs, with marked and often significant rises, particularly amongst 55–64 year olds and 65–74 year olds, reinforcing the possibility that these conditions are beginning earlier, and in real and proportionally higher numbers than before. The marked change in MDDs is seen when compared directly with ACD mortality changes over the period. Whilst Japan was the exception, even allowing for possible influences of raised reporting awareness around the dementias, the ratio of ratios represents considerable change. This may have profound public health implications in view of the already identified growing cost of disability related to the dementias.[48]

Towards a tentative explanation

Mortality rates reflect the general health of society. Government targets to reduce mortality in such disparate areas as suicide, cancer and coronary heart disease acknowledge that there are some environmental aetiological factors.[44] As female MDDs and possibly ONDs worsened more than males, this points to 'socio-environmental' influences, as women's lives have changed more than men's in the past 20 years. This is reflected in the variation of cancer incidence and mortality, where since the mid-1980s, female rates are worse than males, even after controlling for women's greater longevity, which reversed the pattern of decades.[3,22,23] There is a growing recognition that environmental factors can influence the course of some neurological disorders, although the mechanism is not fully understood,[10,16,17,25,44,44–47] and there are examples of changing neurological morbidity reflecting the interaction of genetic and environmental factors.[9,10,16,25,44–47]

At a time of unprecedented medical advances, these findings imply a rise in the incidence and an earlier age of onset of certain underlying neurological conditions contained within MDD and OND categories. This reflects changes found in motor neurone disease where Martyn[39] pointed out "the central question concerns the extent to which the rise in mortality can be explained by improved recognition, diagnosis and recording on the death certificate",[39] but "if the trend in mortality truly reflects a rapid increase… it provides powerful evidence that environmental factors are decisive in determining the risk of the disease". Placed in this context, the rises in ONDs in 65–74-year olds and MDDs require detailed country-specific research to explain the changing pattern of neurological mortality and the underlying morbidity, which suggests a potential major public health problem in the not-too-distant future.

Appendix A. Constituent diseases ICD-9 classification, Table A1

Table A1

Category	Includes
Mental disorders 21 → 290–319	Senile and presenile conditions, alcoholic psychosis, drug psychosis, other organic condition including Huntington's chorea, hepatolenticular degeneration, psychoses, drug dependence, unspecified mental retardation
Multiple sclerosis 223	Disseminated or multiple sclerosis, NOS, brain stem, cord, generalized
Epilepsy 225	Generalized convulsive and non-convulsive epilepsy, excluded progressive myoclonic epilepsy
Meningitis 220	Inflammatory disease of the CNS, bacterial meningitis, meningitis due to other organism
OND 23-360–379	Disorders of the globe, ophthalmia nodosa, disseminated choriortinitis, disseminated retinochoroiditis, disorder of iris and ciliary body
24-380–390	Disorders of external ear, Eustatian tube disorders
221–332	Parkinson's disease
222–330, 331, 333–336	Cerebral degeneration in childhood, other extrapyramidal disease, including Hallervorden-Spatz disease, olivopontecere, Shy-Drager syndrome, strionigral degeneration, spinocerebral disease, anterior horn disease, other diseases of spinal cord
224 → 343–344	Infantile cerebral palsy, Little's disease, hereditary cerebral palsy, other paralytic syndromes
229 → 323–326, 337, 341, 346–359	Acute disseminated encephalomyelitis (excluding bacterial meningitis), encephalitis, hereditary degenerative diseases of CNS, disorders of the ANS, neuromyletis optica, Schilder's disease, Balo's concentric sclerosis, migraine, trigeminal nerve disorders, facial nerve disorders, nerve root and plexus disorders, mononeuritis of limbs, hereditary peripheral neuropathy, inflammatory neuropathy, myoneural disease, muscular dystrophies and other myopathies

Appendix B. All-cause deaths: 1970s vs 1990s (rates per million), Table B1

Table B1

Country		All ages		45–54 years		55–64 years		65–74 years		75 + years	
		M	F	M	F	M	F	M	F	M	F
Australia	1970s	8183	6522	6512	3354	16386	8040	41356	20426	110936	81537
	1990s	7440	6154	3598	2188	10708	5884	29597	15953	93691	71415
Canada	1970s	8154	6085	6483	3461	16194	7967	38075	19370	104638	73182
	1990s	7571	6755	3890	2400	10840	6300	28983	16089	92111	68959
England and Wales	1970s	12196	11502	6364	3929	18184	9658	46984	24609	126873	92324
	1990s	10539	11052	4012	2657	8229	7106	34602	20475	105983	83153
France	1970s	10788	9571	7950	3190	16152	6429	38589	17390	107735	81301
	1990s	9686	8545	5606	2358	12765	4970	28072	12026	95345	73815
Germany	1970s	11842	11449	7058	3564	16861	8064	79789	23616	122944	92442
	1990s	10176	11197	5468	2776	13322	6095	33770	17790	112295	90905
Italy	1970s	10423	8755	6617	2986	16492	7202	40290	20762	110809	87665
	1990s	10303	9146	4196	2191	11884	5329	30922	15017	70109	78097
Japan	1970s	6686	5575	5232	2633	11600	6115	32596	18102	94406	79108
	1990s	8119	6523	3818	1959	9936	4294	23870	10917	87430	57516
The Netherlands	1970s	8941	7174	5330	2978	15105	6826	40861	18598	112563	77101
	1990s	8875	8682	3835	2609	11396	6278	33521	16677	110323	73754
Spain	1970s	8339	7223	5718	2681	13965	6528	35441	18935	105149	84674
	1990s	9478	7993	4981	2021	12118	4751	28965	13119	96501	74871
USA	1970s	9619	7704	7666	4115	18005	9249	40430	21027	104407	74595
	1990s	8971	8487	5744	3223	13806	8276	32364	19747	92487	75407

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