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Unexpected and unexplained increase in death due to neurological disorders in 2012 in England and Wales: Is cytomegalovirus implicated?

R P Jones PhD[1], D Goldeck PhD[2]

[1] Healthcare Analysis & Forecasting, Honister Walk, Camberley, UK, GU15 1RQ.
[2] Tuebingen Ageing & Tumor Immunology Group, Department of Internal Medicine, University of Tuebingen Medical School, Waldhoernlestr.22, D-72072 Tuebingen, Germany.
Corresponding author: Rodney Jones, HCAF, Honister Walk, Camberley GU15 1RQ, hcaf_rod @yahoo.co.uk, +44 (0)1276 21061

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Summary

In early 2012 deaths (all-cause mortality) in England and Wales showed an unexpected and unexplained increase which continued for 18 months before abating. The highest percentage increase in deaths was noted to be for neurological degenerations (mainly dementia, Alzheimer's, Parkinson's). This study seeks to understand why increased deaths should focus on these conditions and if an unrecognized infectious outbreak could be implicated. Cause of death statistics for England and Wales were compared for 2012 versus 2011 as was the diagnosis for first outpatient appointment and inpatient admissions for these conditions. Deaths for dementia, Alzheimer's and Parkinson's showed a 15% increase with associated age specificity. The increase could not be explained by changes in the coding relating to cause of death. The increase coincided with increased GP referral (as first outpatient attendance) and inpatient admission for a range of neurological conditions. These increases were also observed on previous occasions of a similar event where deaths peaked in 2003 and 2008. A cascade of debility leading to immobility and institutionalization along with specific immune impairments appears to render those suffering from neurological degenerations sensitive to infectious outbreaks and more specifically to the particular agent behind these events. These and other studies point to outbreaks of a previously uncharacterized agent with the outbreak peaking in 2003, 2008 and 2012 (and in other years prior to these dates). Cytomegalovirus is a potential candidate and the necessary research to test this hypothesis is outlined.

Key Words

Neurological conditions, dementia, Alzheimer's, Parkinson's, death, emerging infectious diseases, cytomegalovirus

Introduction

Neurological degeneration such as dementia, Alzheimer's or Parkinson's are becoming increasingly common in ageing western populations and represent an increasing proportion of the reported cause of death [1,2]. To keep pace with such developments in 2010 the International Classification of Diseases (ICD) changed the way in which dementia and several other conditions were coded as the primary cause of death and in the UK these were implemented from 1st January 2011 [3].

Due to improvements in life expectancy the number of deaths in England and Wales have been declining since the mid-1990's and are expected to reach a minimum around 2015 [4]. However, in early 2012 deaths in England and Wales displayed a totally unexpected increase which remained until the middle of 2013 [5]. Such unexpected and semi-permanent increases in deaths had been observed previously in 2003 and 2008 and at other dates prior to this [6-9]. These 'unexplained' increases in death appear to occur slightly earlier in Scotland [8], show evidence for spatial spread [5-6,8-9] and are related to simultaneous and likewise semi-permanent increases in emergency department attendance, medical hospital admission and GP referral which are wider than just the UK [9-12]. Even more curiously they appear to occur in parallel with subtle changes in the gender ratio at birth [13] which suggests something more fundamental than some quirk of the aging population.

Parallel studies of the increased medical admissions which accompany these events have shown evidence for small area infectious-like spread with a range of initiation dates. Both admissions and deaths jump at the initiation point and stay high for a period of 12 to 18 months before beginning to decline [5,8,14]. The initiation dates tend to cluster during the winter months (submitted).

Preliminary analysis of the increased deaths in 2012 compared to 2011 has revealed that the highest percentage increase (around +15%) was concentrated in two ICD chapters, namely those devoted to mental & behavioral conditions and nervous system disorders [11]. The next highest increases were only +5% in the respiratory and 'signs & symptoms' chapters. This study will investigate the scope of neurological degeneration within this large and unexpected increase in deaths and investigate if these recurring events could be of an infectious nature.

Methods

Cause of death data for 2011 and 2012 in England and Wales was obtained from the Office for National Statistics (ONS) website [15]. Due to the fact that the sudden and unexpected increase in deaths occurred very early in the 2012 calendar year [5] simple comparison of deaths in 2012 against deaths in 2011 was therefore possible. Forecast deaths for males and females in 2012, assuming the ongoing reduction in deaths from the mid 90's were calculated using the polynomial trend method used in earlier studies of the 2003 and 2008 increases [6]. The remainder of deaths due to continuation of the event into 2013 was estimated using a simple proportion of 6 months in 2013 against 10 months in 2012. This is a conservative under-estimate. Due to the fact that there were so few deaths under the age of 64 these deaths were added together as a group for the dementia and Alzheimer's age group analysis. Data relating to the diagnosis associated with outpatient attendance was obtained from the Health and Social Care Information Centre website [16] as were inpatient admissions between 2007/08 and 2012/13 for dementia, Alzheimer's and Parkinson's.

Results

Figure 1 presents the age-banded profile of additional deaths in 2012 versus 2011. To put this Figure in context those aged 95+ were born during World War I, those aged 90-94 were born in the post-WWI baby boom and therefore suffered the highest male mortality during WWII. There is then another cohort arising out of the WWII baby boom. These cohort effects are now some time ago and the use of five year age bands minimizes their impact and hence simple difference between two adjacent years is sufficient to reveal gross differences. As can be seen the effect of age is not general but somewhat age specific. A higher percentage increase in female deaths predominates at ages 70-74 and below while at ages 75-79 and above a higher percentage increase in male death predominates. In the ages 65-69 and 90-94 there are characteristic peaks in deaths. There is a notable trough for those aged 60-64 and another trough in deaths for those aged 95+ especially for females.

While only mental & behavioral and nervous system chapters showed a 15% increase in deaths [11] to appreciate how many extra deaths are involved Table 1 presents the increase in deaths as an absolute number (2012 minus 2011). The calculated expected reduction in deaths that should have occurred in the absence of the event was then added to give the real number of excess deaths against the expected decline in deaths and the remainder of unexpected deaths due to continuation into 2013 was also added to give an estimate of the total unexpected deaths for the entire event. This pattern of increase in deaths will be used to elucidate possible causes in the discussion section. Table 2 provides more detail regarding the specific conditions most affected and shows the effect of the 2011 change in coding relative to the trend in 2009 and 2010. While other CNS conditions are effected it is clear that the majority of the extra deaths are due to dementia (F01, F03) followed by Alzheimer's (G30) and Parkinson's (G20).

Given that the highest increase occurred for dementia (ICD codes F01 and F03) the pattern of increase with age and gender is shown in Figure 2. The actual coding to dementia, Alzheimer's or Parkinson's depends greatly on the ability of the coroner or hospital clinician to accurately diagnose and record these diagnoses in the correct order and the changes in coding introduced in 2011 were designed to overcome these limitations [3]. To test for the possibility of a coding artifact all possible codes that could be used to record any of these conditions (prior to the 2010 changes introduced by ICD) [3] were grouped together. This approach (data not shown) only lead to dilution with inappropriate codes but presents the minimum possible case for any increase. The increase at age 90-94 is reduced from around 23% to 15% but the age profile was slightly altered (reflecting the fact that genuine diagnoses have been diluted with inappropriate codes). However the point is that the increase is still very large and cannot be questioned as a quirk of the changes in the coding of the cause of death.

These events/outbreaks are also known to increase emergency admissions and GP referral for an outpatient attendance. In England the coding of presenting condition is conducted in around 3% of outpatient attendances by specific consultants at individual hospitals. In 2012/13 some 90,600 first attendances with a diagnosis in the ICD chapters F and G enable statistically meaningful analysis. As Figure 3 demonstrates both attendances for Dementia, Alzheimer's and Parkinson's increased as a proportion of total coded first attendances during 2012/13. This was part of a

wider shift in case mix such that apart from dementia, Alzheimer's and Parkinson's some 12 diagnoses in Chapter G and 40 in Chapter F (including various anxiety and mood disorders and mental retardation) increased their proportion above the average in 2012/13, however, of these only three from Chapter G (G93 – other brain disorders, G35 – Epilepsy, G98 – Multiple Sclerosis) and 33 from Chapter F reached a statistically significant increase.

Hospital inpatient admissions also show step-like increases and for the ICD codes covering dementia, Alzheimer's and Parkinson's there were 7% and 9% increases for age 75+ admissions in 2008/09 versus 2007/08 and 2012/13 versus 2011/12 respectively (data not shown). The key message appears to be that a shift in neurological case mix is associated with these events, which in addition to death, also affects both first outpatient attendance and inpatient admissions. These may not necessarily lead to death but may relate to degradation of underlying immune function.

Discussion

Given that the increase in deaths endured for around 18 months such an event cannot be ascribed to weather as this would require that such extreme conditions endure for the entire period [5] nor to winter mortality which is generally restricted to a maximum of four months [4]. Changes in funding can likewise be excluded as neither 2012 or the two previous spikes in 2003 and 2008 were associated with dramatic changes in NHS funding. Table 1 shows that deaths in the two ICD chapters where the three conditions are coded had the highest increase during 2012 and that this increase is an underestimate since the underlying expected reduction of 4,120 male and 3,160 female deaths need to be spread back across the increases in 2012 as does the fact that the event was still ongoing until around mid-2013. The strongest evidence appears to point to some form of infectious-like event, namely, there appears to be a point of initiation (always in Scotland) from which there is subsequent spread across the entire UK [8-9,12,14]. This northerly initiation point may be related to vitamin D levels and its role in immune regulation [9]. This spread shows the necessary granularity expected of an infectious outbreak, however, the spread is relatively slow and takes around 18 to 24 months to reach all parts of the UK. At local level such as a Local Authority (approximately 100,000 population) the spread at very small areas (clusters of 5,000 head) takes around 12 months to affect the entire spatial area [8,14].

If we are dealing with an infectious event how do we explain the large increase in deaths due to selected neurological conditions and especially in those with neurodegenerative Alzheimer's, Parkinson's and Dementia? To answer this question we first need to understand the nature of how the primary cause of death is assigned. The underlying or primary cause of death is defined as [2]:

1. The disease or injury that initiated the train of events directly linked to death; or
2. The circumstances of the accident or violence that produced the fatal injury.

Hence Parkinson's, Alzheimer's or dementia are coded as the cause of death because they are the disease which initiates the train of events leading to ultimate death. In all three cases the actual event precipitating death is usually an infection, neoplasm or cardiovascular event [18-19]. The most clinically relevant observations regarding these diseases is that toward the end of life persons with these degenerative conditions tend to become bed ridden (i.e. poor lymphatic system flow and function and little exposure to sunlight), have eating problems (i.e. poor nutritional status), have distressing levels of poor comfort, including symptoms of illness, which

they are usually not able to communicate [18]. Hence the very high reported levels of pneumonia and febrile conditions [18-19]. This cascade is illustrated in Figure 4. In addition they will almost certainly have an impaired blood/brain barrier as the primary cause of the disease onset [20-21]. This population can be viewed as highly immune compromised and therefore susceptible to any type of infectious outbreak especially since the majority will be in an environment such as a nursing home or other health care institution which presents a high risk of institution-acquired infection [22]. In this respect enhanced deaths in care homes have been noted to accompany the 2007 and 2012 events [14,23].

It is pleasing to note that the change in age profile evident when grouping all possible codes using the pre-2011 coding suggests that the coding changes introduced in 2011 have been applied consistently and the old coding simply introduces inappropriate data. Hence the large increase in deaths specific to these diagnoses is real. The event which occurred in early 2012 is possibly infectious in that this particular group of frail people so readily succumbed to death. The previous two occurrences of this presumed infectious outbreak which peaked in England in 2003 and 2008 have also been observed to lead to higher deaths in this particular group [2]. These were not as marked as that observed in 2012; however this was before the coding changes were introduced.

Other evidence pointing to an infectious cause is the pattern of effect relating to age seen in Figures 1 and 2 which is reminiscent of antigenic original sin [24], i.e. exposure of the immune system to one strain of an infectious agent primes the immune response which may benefit or hinder the response to a second strain. This process creates a characteristic saw tooth pattern in the age profile which has also been observed in the increase hospital admissions which accompany these events [14, submitted] and is even more evident when single year of age data is used for the deaths [25]. Since these outbreaks do not appear to correspond to outbreaks of known agents such as influenza it has been proposed that the infectious agent could be an unrecognized role for the ubiquitous herpes virus cytomegalovirus [9-10].

The majority of annual deaths occur during the winter months with only 45% of deaths in the six summer months of May to September [4]. Regarding the winter of 2012/13 it was observed that there were elevated levels of several typical winter viruses [26]. Based on analysis of the 1996 outbreak in England it was concluded that there may be some degree of additive or synergistic interaction between the two infectious agents especially when the proposed outbreak occurs prior to an influenza outbreak [9-10,14]. In this respect recent research has shown that those aged 65+ with the highest CMV antibody titre have over a 4-times lower response to influenza vaccination [27-28] indicating impaired ability to withstand influenza and other research indicates that CMV induced immune changes in the elderly may be responsible for delayed clearance of the influenza virus from the lung [29-30]. The presence of CMV has also been shown to alter the response of chronic hepatitis-C-virus infected patients to interferon-based therapy [31]. The immune response to a dual CMV and EBV infection in the elderly is also affected where CMV-induced expansion of CD8 T cells occurs with a specific reduction in effector function which is specific to EBV, but not influenza [32]. Synergistic effects between CMV and a range of respiratory and other infections seem to be commonplace.

Children infected with CMV are known to have statistically higher infections with the common respiratory viruses, i.e. respiratory syncytial virus (RSV), rhinovirus, Enterovirus, [33] identified to have been prevalent in the winter of 2012/13 [26]. The increased respiratory deaths in the

winter is consistent with this observation and is in agreement with a potential role for CMV where CMV pneumonitis may not be recognized and misdiagnosed as unspecified pneumonia [9-10,14,34] or the previously discussed role in enabling influenza and other infections to thrive. Regarding excess deaths for the over 65's it has been noted that a similar increase occurred in several countries across Europe [26]. In Berkshire, England the 2012 event resulted in a large increase in hospital admissions and deaths for pneumonia and other respiratory conditions (in preparation). It should be noted that for admission to hospital the primary diagnosis is more likely to be recorded as pneumonia with a secondary diagnosis of dementia, etc which would be given greater prominence in the coding of cause of death (which is a separate process to inpatient coding).

It has been proposed that somewhere up to 20% of the population is susceptible to these broad effects of CMV which probably arise through a number of genetic mutations [10,34]. These susceptible members of the population are characterized by elevated levels of anti-CMV antibodies and/or elevated levels of C-Reactive Protein (CRP) [34]. Additional complexity arises as different strains of CMV interact with the different immune impairments present in individuals and when present, multiple strains act cooperatively [35].

Hence what evidence is there to suggest that CMV is involved via wider immune manipulation? The risk for AD development is increased twofold in elderly exposed to systemic infections and pro-inflammatory mediators are reported prior to the development of dementia and enhance disease progression [36]. The development and exacerbation of Parkinson's is likewise associated with systemic inflammation [37]. Independently of whether CMV infection is a cause or consequence of neurodegenerative diseases, it can be considered as a driving force in the inflammation cascade. In affected brains microglia clear apoptotic cells and due to their enhanced receptor expression they are more susceptible to activation by peripheral innate immune signals in case of viral infections or environmental stressors causing systemic inflammation. This might enhance the recruitment of further peripheral cells into the brain and result in a vicious cycle [36].

High levels of anti-CMV antibodies are a known risk factor for cognitive decline [38-39] and both CMV and neurodegeneration contribute to the ageing of the immune system which could increase the risk for secondary diseases. Age related decrease of naïve T-cells and increase of late-differentiated T-cells is associated with CMV-seropositivity [40]. In addition in mild AD, patients have even lower frequencies of naïve CD4+ T-cells compared to young and age-matched controls were observed [41]. This suggests additive effects of CMV and neurodegeneration. One possible mechanism is the enhanced secretion of pro-inflammatory cytokines by CMV reactive CD4+ T-cells which disturb endothelial cells promoting migration [42]. Brain infiltration with immune cells could enhance inflammation and disease progression. In a mouse model of Parkinson's disease brain-infiltration of CD4+ lymphocytes contributed to neurodegeneration [43]. Several herpesviruses are found in brains of patients with neurodegenerative diseases, and HHV-6 and EBV are considered risk factors for cognitive impairment [44], but in contrast to CMV, HSV and EBV do not affect T-cell differentiation [39]. Antibody responses to CMV, but not to EBV, and anti-CMV CD4+ T-cell responses were more pronounced in elderly (≥ 85) with poor health and correlated negatively with cognitive and functional activity [45]. The anti-CMV CD4+ T-cells produced higher levels of IFNγ and so contributed to inflammation in these elderly with poor health [51]. demonstrated that CMV seropositive AD patients had lower frequencies of CMV-specific CD8+ T-cells compared to

controls. The authors hypothesised that this could reflect a partially impaired cellular immunity, so that CMV reactivation in brain macrophages or vascular endothelial cells could contribute to inflammation and disease progression [46].

Having discussed the potential roles for CMV in those with neurodegenerative diseases the issues relating to additional immune impairment due to increasing frailty and institutionalization need to be considered. Given the fact that CMV relies on the presence of specific immune impairments to pose a risk to health [9-10] a potential link with vitamin D insufficiency is of interest given widespread deficiency in institutionalised populations [47]. Vitamin D deficiency is linked to mortality in nursing homes and after hospital admission for pneumonia and other conditions, increased incidence of community acquired blood infections and pneumonia [47-50].

The role of vitamin D in thymic function has been proposed as a factor in allowing CMV to play a more prominent role in elderly/institutionalised populations [9-10,34]. The clearest evidence for such a link comes from the observation that in kidney transplant recipients those with the recessive form of the vitamin D receptor (VDR) gene are most susceptible to post-transplant CMV reactivation and disease [51] while other VDR genetic polymorphisms are involved in cellular rejection in liver transplantation [52]. On these occasions the genetic impairment is acting as the equivalent to vitamin D deficiency. Recent research has also shown that the infectious-like outbreak associated with the extra deaths shows small area spread which is most frequent in winter and reaches a minimum in August which is the point of maximum blood vitamin D levels (submitted).

The proposal that CMV is only affecting a proportion of the population sensitive to the above effects can be checked using the information in Table 1 where there are 36,000 excess deaths. This figure is roughly similar to calculated excess deaths arising from the 2002 and 2007 outbreaks which had their respective peaks in 2003 and 2008 [6]. If we assume that the excess deaths are concentrated in those aged over 65 (Figures 1-2) then the excess deaths are matched against 4.13 million and 5.16 million living males and females in England and Wales aged 65+ respectively and leads to a figure of 0.4% of the elderly population being sensitive to death. As has been pointed out previously these outbreaks appear to affect health and hospital admissions far more than death [9-10]. Such a small death rate is consistent with the effect of something like CMV working indirectly via immune modulation rather than an overt infection. Given that around 10-times this number appear to require hospital admission leads to around 5% of the elderly population sensitive to hospital admission and/or death and if we include the wider affects leading to GP referral, as witnessed in Figure 3 and other studies [12,53-54] then a proportion of up to 20% seems feasible. If this is the case and if the outbreak were due to the introduction of a new strain of CMV then overall changes in CMV seropositivity could be difficult to detect and population sampling would need to be concentrated around the exact time of the outbreak and especially focused on those aged over 60.

The relevance of Figure 4 is that the specific agent of all this apparent chaos is at the least capable of exacerbating particular neurodegenerative conditions and other immune-sensitive conditions as observed by specific increases in outpatient attendance in dermatology, neurology, rheumatology, urology and nephrology [55]. All of these are highly reminiscent of the known clinical effects of CMV [34,56].

In conclusion, a recent review of the role of CMV in infection, inflammation and autoimmunity has concluded that while CMV may not be a major player in terms of direct infection/initiation

(of brain, nerves, etc.) it is almost certainly widely involved in disease exacerbation [34] probably via its ability to affect both innate and adaptive immunity and the cross-talk which regulates the coordination between these two immune functions [57].

Testing the Hypothesis

Resolution of the issue as to whether we are looking at initiation or exacerbation can be achieved by interrogation of databases holding the detail of first diagnosis by the GP. Two such databases have sufficient coverage to be of value, namely, the record linkage data covering every Scottish resident held by the Scottish NHS which goes back to the 1990's and in England the PRIMIS data base at the University of Nottingham.

Time studies of the level of anti-CMV IgM and IgG antibodies especially in medical inpatients would indicate if CMV is involved in some manner. Whether CMV is the direct cause or is acting as an opportunistic pathogen is an important consideration and in this respect it should be noted that in the early days of HIV/AIDS research CMV was considered a potential causative agent. It is now known that CMV was merely taking opportunistic advantage of the specific immune impairment afforded by direct infection of CD4 T-cells by HIV. Given the evidence regarding age specificity arising out of original antigenic sin we should therefore be looking for a change in the pattern of CMV strains present in the population rather than blunt measures of CMV seroprevalence which ignore strain diversity.

The role of vitamin D deficiency and/or variants in VDR genes as an additional enabling factor will be resolved by simultaneous direct measurement of vitamin D levels and screening for variants in VDR genes and linking these with both increased hospital admission and death during these infectious-like outbreaks.

Conflicts of Interest

DR has no conflicts of interest to declare. RJ provides consultancy to health care organisations.

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Table 1: Higher deaths in 2012 versus 2011 and total for the event

ICD Chapter(s)	Male	Female	Total
Mental Conditions & Nervous System	2,723	4,719	7,442
Respiratory	1,430	1,558	2,988
Neoplasms	1,372	842	2,214
Circulatory	-71	1,727	1,656
Signs & symptoms	176	354	530
Genito-urinary	145	117	262
Endocrine, nutritional, metabolic	143	70	213
Musculo-skeletal	6	144	150
Congenital & perinatal	34	25	59
Skin	11	5	16
Digestive	-143	134	-9
Blood, infections, external causes	-161	-324	-485
Total above	5,665	9,371	15,036
+ Expected reduction	4,120	3,260	7,380
Actual Excess Deaths	9,785	12,631	22,416
+ Remainder of deaths in 2013	5,870	7,580	13,450
Total for the event	**15,655**	**20,211**	**35,866**

Footnote: The increase in deaths in 2012 due to diseases of the circulatory system are understated due to a long-term downward trend in I20-I25 (Ischaemic heart disease) of approximately 3% p.a. and I60-I69 (Cerebrovascular diseases) of approximately 1% p.a. [17]

Table 2: Primary diagnoses showing a high and statistically significant increase in deaths in 2012

ICD Code	Description	Female				Male				Difference as SD	
		2009	2010	2011	2012	2009	2010	2011	2012	Female	Male
F00-F99	**Mental and behavioral conditions**	**12,112**	**13,617**	**20,960**	**24,155**	**5,909**	**6,299**	**10,088**	**11,710**	**11.7**	**12.3**
F01,F03	Dementias	11,645	13,124	20,645	23,787	4,779	5,225	9,612	11,211	11.6	11.8
F01	Vascular dementia	289	375	4,536	5,390	198	301	2,752	3,375	11.4	9.9
F03	Unspecified dementia	11,356	12,749	16,109	18,397	4,581	4,924	6,860	7,836	7.1	7.6
G00-G99	**Diseases of the nervous system**	**9,405**	**9,932**	**10,150**	**11,674**	**8,003**	**8,551**	**8,398**	**9,499**	**9.9**	**6.0**
G04.9	Encephalomyelitis, unspecified	*43*	*52*	*34*	*52*	44	41	39	52	1.5	2.6
G20-G26	Extrapyramidal and movement disorders	2,000	2,030	1,562	1,802	2,824	3,033	2,185	2,580	5.3	4.0
G20	Parkinson's disease	1,980	2,011	1,543	1,778	2,809	3,010	2,167	2,560	5.2	4.1
G30-G32	Other degenerative diseases of the CNS	4,434	4,814	5,638	6,678	2,076	2,268	3,067	3,528	8.8	4.9
G10-G13	Systemic atrophies	947	1,008	1,035	1,124	1,123	1,251	1,188	1,355	3.8	4.8
G12	Spinal muscular atrophy (mainly motor neuron)	834	875	*913*	*976*	991	1,118	1,060	1,218	4.0	4.8
G30	Alzheimer's disease	4,264	4,635	5,122	6,086	1,930	2,122	2,383	2,773	8.3	4.1
G31	Other degenerative diseases	170	179	516	592	146	146	684	755	2.9	2.7
G35-G37	Demyelinating (mainly Multiple sclerosis)	683	663	691	788	345	362	397	455	4.5	2.1
G82	Paraplegia and tetraplegia	32	29	33	41	64	49	59	77	1.9	4.3

Footnote: Numbers in italics and grey shade are not statistically significant but are part of a male/female pair. SD = difference between 2012 and 2011 expressed as standard deviation (SD) difference (Poisson).

Figure 1: Percentage change in deaths (all-cause mortality) by age group - 2012 versus 2011.

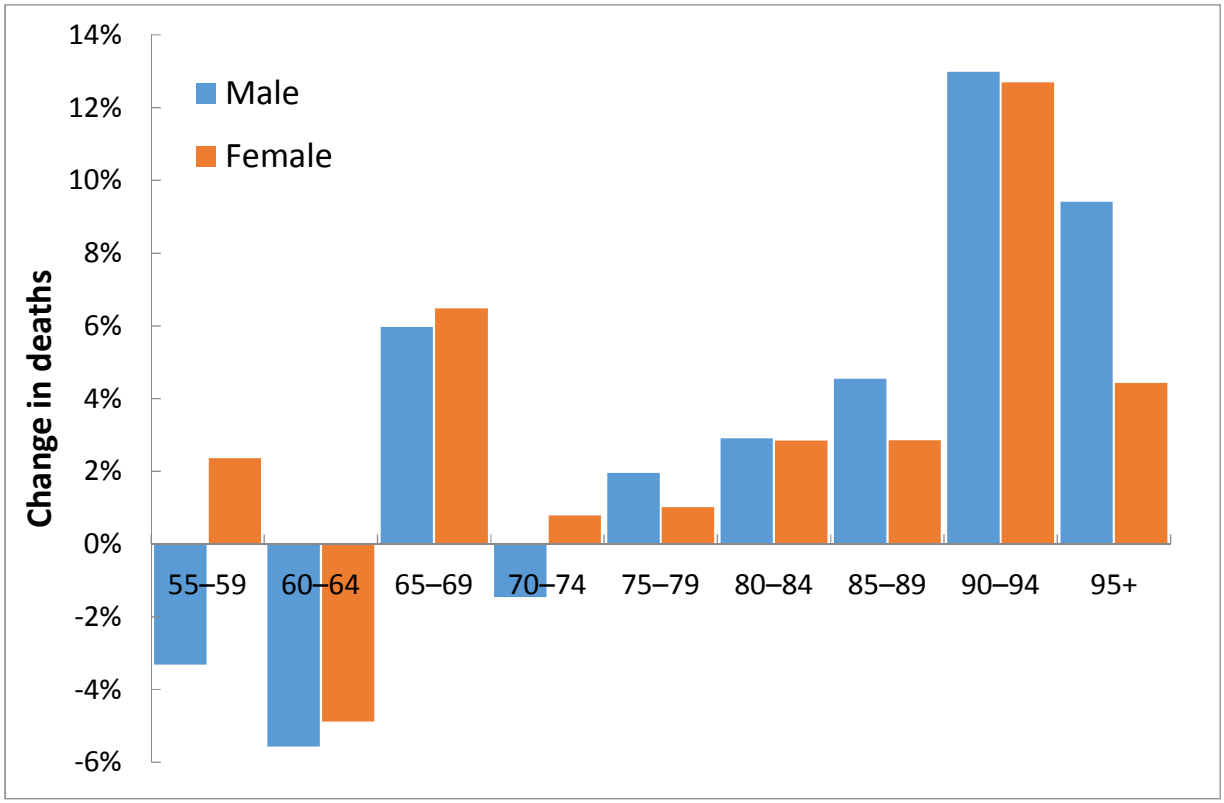


Figure 2: Change in deaths due to dementia (F01, F03) – 2012 versus 2011

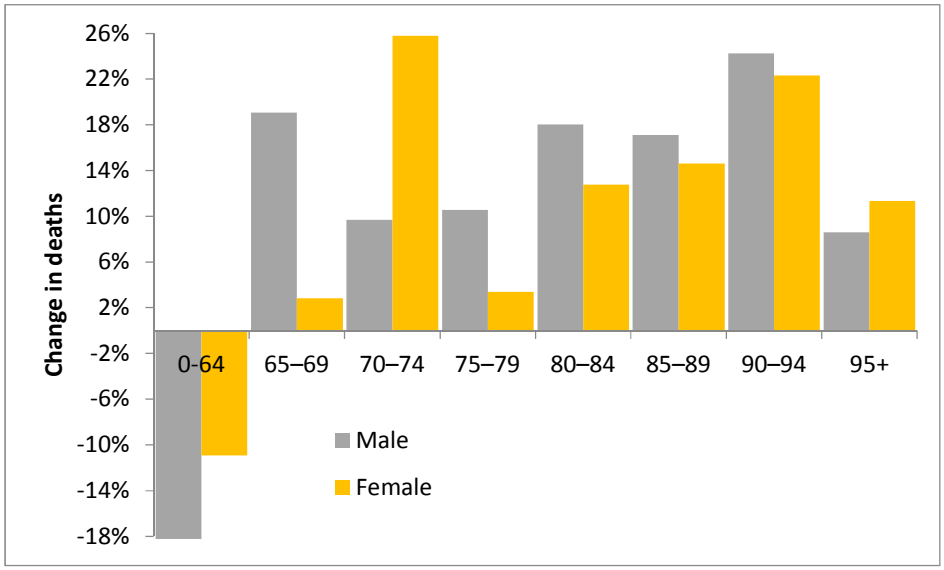
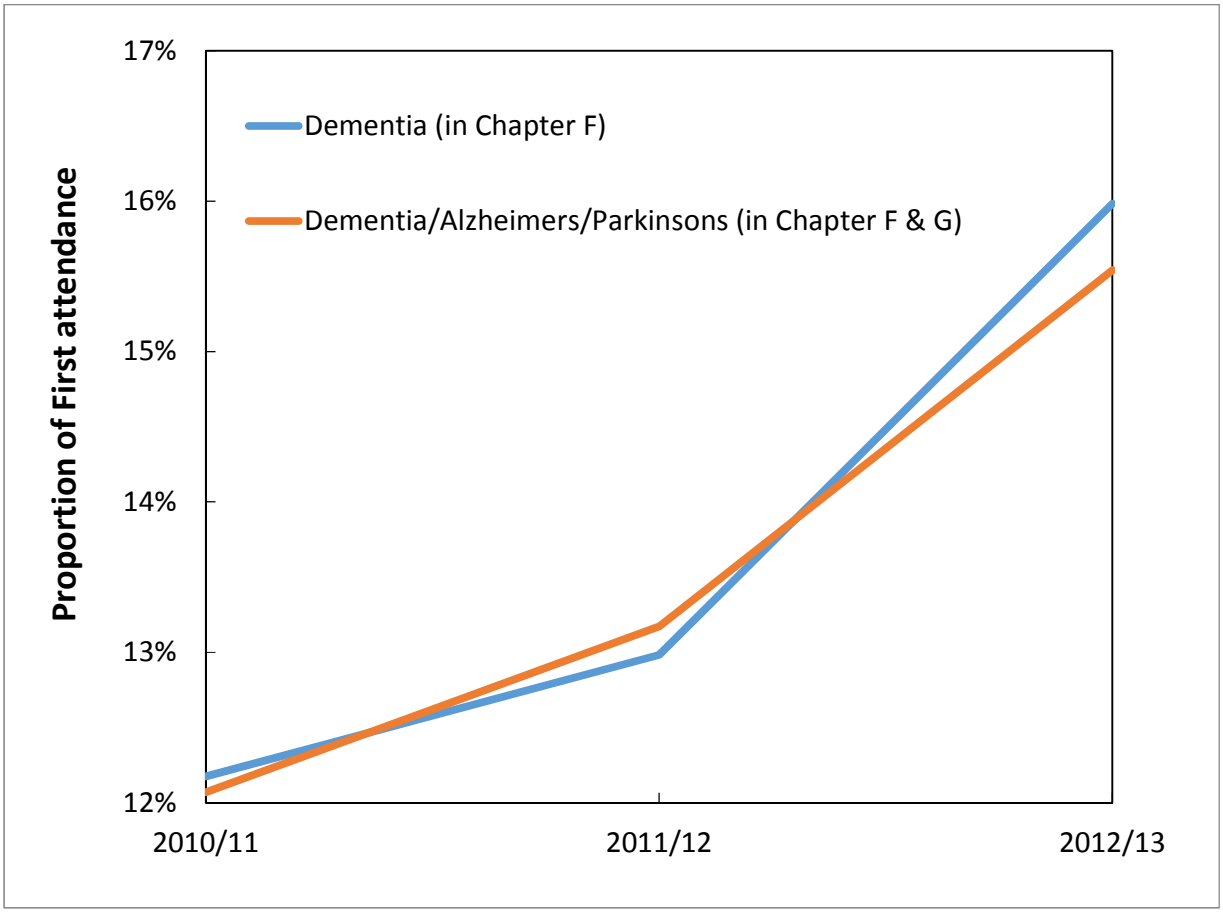


Figure 3: Change in dementia, Alzheimer's and Parkinson's as a proportion of outpatient first attendances



 Medical Hypotheses 2014; 83(1): 25-31.

Figure 4: The debility cascade in neurological degenerative disease