The impact on prevalence of dementia in the oldest age groups of differential mortality patterns: a deterministic approach

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**Background** Until recently relatively little data have been available on the prevalence of dementia in the oldest age groups, and yet it is these age groups which are expanding fastest. It is therefore important to understand whether the prevalence of dementia rises inexorably with age ('age-dependent'), or, as some suggest, levels off or even declines in the very oldest age groups ('age-related'). Combined analysis of the many prevalence studies now available has led to modelled curves which do suggest a slowing of rise in prevalence at these great ages, and has been interpreted as meaning that dementia is age-related. This interpretation does not take into account the differential survival of individuals with cognitive impairment compared with normals of the same age.

**Method** Flexible prevalence-incidence-duration models were generated using a deterministic approach applied to published combined analyses of prevalence rates, population death rates and mortality odds ratios.

**Results** The variation in observed prevalence patterns with age is explained to a great extent by the mortality observed in the cognitively impaired. Simple examination of age patterns in prevalence does not answer the fundamental question surrounding the age-dependence of cognitive impairment.

**Conclusion** Inferring biological meaning from these observed curves is not valid without examining the mathematical phenomena of the relationship of incidence, mortality and prevalence. This approach allows an examination of the impact of varying mortality and incidence on the prevalence of dementia and cognitive impairment and will be useful in determining the potential impact of preventive strategies on the population.

**Keywords** Age factors, ageing, dementia, deterministic model, mortality

**Accepted** 1 July 1997

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Studies from around the world show increasing prevalence of dementia with age, but the magnitude of the prevalence appears to vary across continents.\textsuperscript{1,2} Such comparisons are made particularly difficult by cross-cultural variation in the perception of ageing and its relationship to pathological ageing.\textsuperscript{3} Despite this reservation, the reason and actual shape of this rise with age has been much discussed. One view is that dementia is an age-dependent disorder, here every individual will develop a dementing syndrome if he or she lives long enough. An alternative view has been that dementia is merely age-related like osteoporosis where rapid bone loss in women occurs at the menopause. Here dementia can be separated from ageing and the removal of an identified risk factor would eliminate the process. Evidence cited in favour of this hypothesis is that the pattern of rise of prevalence with age levels off or even declines in the very elderly.\textsuperscript{1} This debate is not new, as dementia has alternately been seen as part of ageing and then separated for decades and centuries.\textsuperscript{4} It is a question of more than hypothetical importance as preventive strategies can be targeted towards at risk individuals more easily if the disorder is age-related than if it is age-dependent.

In the debate surrounding the shape of the prevalence curve with age, there is little debate as to the effect of mortality.\textsuperscript{5} and yet mortality can profoundly influence the pattern of prevalence. This is particularly important in dementia, where there is a well documented increase in mortality associated with both manifest and early dementia (approximately four times).\textsuperscript{6-9} There are differences in life expectancy both across continents\textsuperscript{10} and between different cohorts\textsuperscript{11} which may affect comparisons if not taken into account.
Therefore there are three factors which could be influencing the patterns of prevalence seen with age: the mortality differential between demented and non-demented people; mortality differences among countries and cohort mortality differences within populations. By combining prevalence-incidence-mortality models with estimates of dementia amongst the very old we explore the relationship between age and the prevalence of dementia, including the relationship between attenuation in the rate of increase with age (sub-exponential growth), and differential mortality. Secondly we examine whether the difference between prevalence estimates from two studies can be explained by a combination of differential mortality between the demented and non-demented and differential mortality between the two study populations.

### Methods

Prevalence-incidence-mortality models are applied to hypothetical cohorts using a deterministic approach where time is grouped into yearly units. The units could represent either calendar time or age. Without loss of generality, in the examples presented here, the units will represent years of age.

Amongst individuals aged $i$ years, a proportion, $p_i$, of the total alive, $T_i$, are demented. For brevity, the annual probability of dying is referred to as the population mortality rate below. Applying the population mortality rate, $m_i$, to each year, the total alive in each subsequent year can be calculated, $T_{i+1} = T_i (1-m_i)$, until there are no subjects alive in the cohort. From this the number of demented ($x_i = p_i T_i$) and non-demented ($y_i = T_i - x_i$) subjects can be obtained. For this simple model we cannot identify the number of incident cases and hence we cannot calculate the incidence rate. To resolve this we take into account the differential mortality amongst the demented and non-demented.

For any year the non-demented will be in one of three states in the following year, either they will remain non-demented, become demented (incident cases at rate $\lambda$) or die with mortality rate $m_{0i}$. The remaining fraction of non-demented subjects, $m_0$, becomes demented (incidence cases at rate $\lambda$) or die with mortality rate $m_{1i}$. By assuming some relationship between the two mortality rates, in our case a constant mortality odds ratio ($\text{MOR}$), $k$, of $4$, the mortality rates for the demented and non-demented are calculated from two simultaneous equations with two unknowns.

\[
\begin{align*}
m_1(x_i + y_i) &= m_1 x_i + m_0 y_i \quad (1) \\
m_1 (1 - m_0) &= m_{0i} (1 - m_{1i}) \quad (2)
\end{align*}
\]

Then the incidence rate can be calculated as

\[
\lambda_i = \frac{x_{i+1} - x_i (1 - m_{1i})}{y_i (1 - m_{0i})} \quad (3)
\]

Using this null model we apply observed prevalence and mortality rates to find the calculated incidence.

To examine the relationships between age and prevalence, incidence and mortality we use the null model, create new scenarios by modifying either the rates or the paths between the states or both and then calculate the new prevalence using the calculated incidence and the new incidence using the observed prevalence. We consider three scenarios. Scenario 1, where deaths in the cohort are only from dementia (i.e. $m_{0i} = 0$), will give the minimum prevalence and maximum incidence for the cohort (Figure 1). Scenario 2 and scenario 3 show the effect of changes in mortality rates in the non-demented subjects. The death rate amongst non-dements in the null model is reduced by a proportion, $l$, i.e. reduced from $m_{0i}$ to $m_{0i} (1 - l_i)$ (Figure 2). The remaining fraction of non-demented subjects, $m_{0i}$, become demented. For scenario 2 the proportion is equal to the calculated incidence and for scenario 3 the proportion is equal to the observed prevalence. This method is applied to a prevalence curve from a combined analysis by Ritchie et al. with population death rates. 

![Figure 1](image1.png)

**Figure 1** Parameters and paths for the null model and scenario 1 where only subjects who are demented die ($m_{0i} = 0$). For each year $i$, $p_i$ is the prevalence rate, $\lambda_i$ is the incidence rate, $m_{0i}$ and $m_{1i}$ are the mortality rates amongst non-demented and demented subjects respectively and $k$ is the mortality odds ratio.

![Figure 2](image2.png)

**Figure 2** Parameters and paths for scenario 2 and scenario 3 showing the effect of differential mortality. For each year $i$, $p_i$ is the prevalence rate, $\lambda_i$ is the incidence rate, $m_{0i}$ and $m_{1i}$ are the mortality rates amongst non-demented and demented subjects respectively, $k$ is the mortality odds ratio and $l_i$ is the differential mortality effect.
The age and prevalence comparisons are shown in Tables 1 and 2. Of age (the point of inflection), but the prevalence is still rising. In both differential mortality scenarios the rise is relentless. At 75 years of age the observed prevalence is 5.4% compared with 5.6% (2% greater than the observed prevalence) for scenario 2 and 6.0% (10% greater than the observed prevalence) for scenario 3. At 95 years of age, the prevalence rates are 39.7%, 43.9% (10% greater than the observed prevalence), and 48.8% (22% greater than the observed prevalence) respectively.

Incidence (Table 2) has a theoretical maximum (scenario 1). The change in incidence for scenarios 2 and 3 are minimal up to 80 years of age then increase rapidly. At 75 years of age scenarios 2 and 3 have the same incidence as the null, 1.4%, compared to a maximum of 1.6%. At 95 years of age the calculated incidence is 18.7% compared with a maximum of 23.6% (26% greater). The incident rates for scenarios 2 and 3 are 19.8% (5% greater) and 20.9% (11% greater) respectively.

The difference in prevalence between the African Americans and Nigerian Africans is examined for a range of MOR (American = 1.5, 2, 2.5, 3, 3.5, 4, 5, 6 and 8; Nigerian = 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, and 48) and lags (from no years to 20 years). The 12 smallest mean squared differences in lagged incidence are reported in Table 3. We have not suggested a statistical test for mean squared difference, but it is still apparent that low values correspond to the Nigerian MOR being smaller than the American with a lag of around 11 years.

### Results

The age and prevalence comparisons are shown in Tables 1 and 2. In both the rate of increase for each scenario is sub-exponential.

The observed prevalence (Table 1) based on a modified logistic curve, continually rises with age. The rise is slower after 95 years of age (the point of inflection), but the prevalence is still rising.

#### Table 1 Comparison for selected years of age of the observed prevalence (null model) with the prevalence (and prevalence ratio) for three scenarios: deaths from dementia only (1), incident differential mortality (2) and prevalent differential mortality (3). Prevalence is expressed as a percentage

<table>
<thead>
<tr>
<th>Age</th>
<th>Prevalence</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>1.0</td>
<td>1.0 (0.96)</td>
<td>1.0 (1.01)</td>
<td>1.1 (1.03)</td>
</tr>
<tr>
<td>70</td>
<td>2.5</td>
<td>2.4 (0.94)</td>
<td>2.6 (1.01)</td>
<td>2.7 (1.06)</td>
</tr>
<tr>
<td>75</td>
<td>5.4</td>
<td>5.0 (0.91)</td>
<td>5.6 (1.02)</td>
<td>6.0 (1.10)</td>
</tr>
<tr>
<td>80</td>
<td>10.5</td>
<td>9.2 (0.88)</td>
<td>10.9 (1.03)</td>
<td>12.0 (1.14)</td>
</tr>
<tr>
<td>85</td>
<td>18.1</td>
<td>15.4 (0.85)</td>
<td>19.1 (1.05)</td>
<td>21.3 (1.18)</td>
</tr>
<tr>
<td>90</td>
<td>28.1</td>
<td>23.3 (0.82)</td>
<td>30.3 (1.07)</td>
<td>34.0 (1.20)</td>
</tr>
<tr>
<td>95</td>
<td>39.7</td>
<td>32.1 (0.80)</td>
<td>43.9 (1.10)</td>
<td>48.8 (1.22)</td>
</tr>
<tr>
<td>100</td>
<td>51.4</td>
<td>40.6 (0.78)</td>
<td>59.5 (1.15)</td>
<td>64.7 (1.25)</td>
</tr>
</tbody>
</table>

#### Table 2 Comparison for selected years of age of the calculated incidence (null model) with the incidence (and incidence ratio) for three scenarios: deaths from dementia only (1), incident differential mortality (2) and prevalent differential mortality (3). Incidence is expressed as a percentage

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>0.3</td>
<td>0.3 (1.05)</td>
<td>0.3 (1.00)</td>
<td>0.3 (1.00)</td>
</tr>
<tr>
<td>70</td>
<td>0.6</td>
<td>0.7 (1.09)</td>
<td>0.6 (1.00)</td>
<td>0.6 (1.00)</td>
</tr>
<tr>
<td>75</td>
<td>1.4</td>
<td>1.6 (1.13)</td>
<td>1.4 (1.00)</td>
<td>1.4 (1.00)</td>
</tr>
<tr>
<td>80</td>
<td>3.0</td>
<td>3.5 (1.17)</td>
<td>3.0 (1.00)</td>
<td>3.0 (1.01)</td>
</tr>
<tr>
<td>85</td>
<td>5.9</td>
<td>7.1 (1.20)</td>
<td>6.0 (1.01)</td>
<td>6.1 (1.04)</td>
</tr>
<tr>
<td>90</td>
<td>10.8</td>
<td>13.4 (1.23)</td>
<td>11.1 (1.02)</td>
<td>11.6 (1.07)</td>
</tr>
<tr>
<td>95</td>
<td>18.7</td>
<td>23.6 (1.26)</td>
<td>19.8 (1.05)</td>
<td>20.9 (1.11)</td>
</tr>
<tr>
<td>100</td>
<td>30.7</td>
<td>39.4 (1.28)</td>
<td>34.3 (1.11)</td>
<td>36.2 (1.17)</td>
</tr>
</tbody>
</table>

To examine the differences in prevalence estimates between two studies the calculated incidences were compared using the mean squared difference in incidence for each age from 65 to 94 years inclusive. A mean squared difference of zero implies that the two incident curves were equivalent. The effect of differential mortality and age on mean squared difference are examined. The age effect is produced by lagging the incidence of one year, incidence at 70 years of age would be considered as incidence at 71 years, i.e. the calculated incidence is shifted by one year. This method is applied using smoothed prevalence data from Hendrie et al. where the same study design was applied to African American and Nigerian African populations and combined with published population death rates. Since the prevalence amongst the African Americans was the greater, the lag was applied to the African American incidence curves.

### Discussion

The main result is that, once mortality is taken into account, incidence must continue to rise into the oldest age groups despite the apparent levelling off of prevalence in the very oldest. Until recently it has been difficult to examine the issue of dementia in the very old, because there have been insufficient data to explore this, and prevalence is the first type of data to emerge. It is important to understand the natural history of chronic disease in this age group, as it is the age group set to expand most rapidly in the next decades. The data collected on these population groups to date have arisen from existing cohort studies (e.g. Skoog et al.), and from specially recruited
cohort of the already very old (e.g. Powell\(^{17}\)). These studies provide more valuable data on this understudied age group, but remain subject to the biases of sample selection, differential attrition and so on, which can lead to falsely healthy cohorts (or conversely falsely unhealthy samples if the sampling frame is a care setting).

The changes in observed prevalence estimates with age cannot answer the question about age dependency or relatedness, because prevalence is influenced by survival and incidence. Our results show that, allowing for mortality differentials with age and dementia status, dementia incidence has to rise inexorably with age in order to generate the observed prevalence estimates. It is possible to explore the impact of changing mortality patterns and differentials, showing that the observed differences between populations can be explained. The prolonged life expectancy in African Americans compared with Nigerian Africans gives an environmental interpretation to the finding. However, the biological perspective suggests that amongst survivors, Nigerians are less biologically aged at the same chronological age.

There are some methodological issues to be considered. This is the first time, to our knowledge, that this approach has been applied to dementia and cognitive decline and impairment. It has been applied usefully in the cancer context, and is based on the relationship between incidence, survival and prevalence. The approach reveals the difficulty in interpreting curves created on the log-scale. Here the rate of increase in observed prevalence slows after the point of inflection but the actual increase is still linear; at 85, 95 and 105 years of age the prevalence rises from 18% to 40% to 62%. Certain mortality patterns for the prevalence data have been assumed and clearly this could be much refined through the examination of very specific populations. The MOR is taken from current literature estimates. One other study considered mortality in subjects of 65 years and over finding a MOR of around two.

The method allows exploration of future scenarios where these mortalities and odds change, as they may if cohort effects in general morbidity are proven or the advent of specific dementia therapies change the natural history of dementia. They also allow comparison of simple prevalence studies to examine the underlying incidence, if mortality and odds can be estimated.

Acknowledgements
We are grateful to Malte Hahama, University of Tampere, Finland and Stephen Duffy, MRC Biostatistics Unit, Cambridge, UK for their comments on the manuscript.

References