THE INCIDENCE RATES OF EARLY-ONSET ALZHEIMER'S DISEASE ASSOCIATED WITH THE PRESENILIN-2 AND AMYLOID PRECURSOR PROTEIN GENES

By Eng Hock Gui and Angus Macdonald

ABSTRACT

We present estimates of rates of onset of early-onset Alzheimer's disease (EOAD) associated with mutations in the Presenilin-2 (PSEN-2) and Amyloid Precursor Protein (APP) genes. These are based on the Nelson-Aalen method used by Gui & Macdonald (2002a) to build an actuarial model of EOAD and Presenilin-1 (PSEN-1) mutations, but in this case with so little data that we do not attempt to parametrise an actuarial model. It is unclear how the mechanism set up in the United Kingdom — through which insurers can present evidence to the Genetics and Insurance Committee that they should be allowed to use genetic test results for underwriting in certain limited circumstances — should handle mutations for which there is clear qualitative evidence of very high morbidity risk, but which are so rare that reliable evidence, in the conventional statistical sense, may be unattainable.

KEYWORDS

Amyloid Precursor Protein Gene; Early-Onset Alzheimer's Disease; Insurance; Presenilin-2 Gene

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1. Introduction

Early-onset Alzheimer's disease (EOAD) is a form of the disease with onset before about age 65, much younger than the advanced ages at which most Alzheimer's disease (AD) occurs. It is rare, and three genes that are inherited in autosomal dominant fashion are known to cause it; they are the Amyloid Precursor Protein gene (APP), Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2).

In the United Kingdom, the government has set up the Genetics and Insurance Committee (GAIC) to consider applications by the insurance industry to be allowed to use specific genetic tests in underwriting, for applications that exceed the limits of any moratorium on the use of such information. Currently, there is such a moratorium on the use of DNA-based test results, for applications for not more than £500,000 of life insurance cover, or £300,000 of other insurance cover. At the end of 2000, the Association of British Insurers (ABI) submitted applications to GAIC that included tests for PSEN-1 and APP mutations (Daykin *et al.*, 2003). For a variety of reasons, GAIC was delayed from considering these applications, and they had still not given a ruling by early 2003.

For an actuarial model of insurance costs, we need estimates of the rate of onset of EOAD associated with mutations in each gene. These are not available from the

epidemiological literature (see Dartigues & Letenneur (2000)). Gui & Macdonald (2002a) obtained estimates of rates of onset associated with PSEN-1 mutations, based on pedigrees published in the genetics literature. Because there was no *a priori* reason to impose any parametric model on the age-related onset rates, they used a nonparametric (Nelson-Aalen) approach. Although there were some questions about ascertainment bias, these were sufficient to allow models of critical illness and life insurances to be parameterised (Gui & Macdonald, 2002b).

In this note, we summarise the results of carrying out similar analyses on published pedigrees relating to APP and PSEN-2 mutations. However our conclusion is that these data are so sparse that it is not possible to estimate useable rates of onset in the age range of most relevance for insurance. Section 2 gives a brief outline of EOAD and its known causative genes, and emphasises the sparse nature of the epidemiology. Section 3 outlines the method of estimating rates of onset, referring to Gui & Macdonald (2002a) for full details and Gui (2003) for the data. Section 4 describes the results, and our summary is in Section 5.

2. Early-Onset Alzheimer's Disease

AD is a complicated and heterogeneous disorder, a part of which is genetic in etiology and is classified as familial AD (FAD). FAD is further classified into late- and early-onset forms, depending on whether the onset age is after or before age 65. Early-onset FAD (which we abbreviate as EOAD) constitutes about 5–10% of all AD cases, and occurs as a well-defined, highly penetrant disorder with autosomal dominant inheritance (van Duijn *et al.*, 1991). As with all forms of AD, there is not yet any effective treatment.

Three genes, Amyloid Precursor Protein (APP), Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2) have been confirmed as causing EOAD. APP and PSEN-1 gene mutations account for 10–15% and 20–70% of EOAD, respectively (Campion *et al.*, 1999). They are highly penetrant; the absence of AD by age 60 among confirmed carriers is rare. PSEN-1 mutations are usually associated with very aggressive EOAD, with duration of dementia of about 5 years (Russo *et al.*, 2000). PSEN-2 gene mutations are very rare. The ages at onset of EOAD are thought to vary (PSEN-1 25–60, APP 40–65 and PSEN-2 45–84 (Campion *et al.*, 1999)). It is quite possible that other genes with mutations leading to EOAD will be found.

3. Estimates of Incidence Rates

Figure 1 shows a model of the incidence of EOAD, in which we may not know which of States 0 or 1 a healthy but at-risk person is in. The aim is to estimate $\mu_{02}(x)$. We refer the reader to Gui & Macdonald (2002a) for full details of the method of estimation and treatment of data.

Pedigree data with ages at onset and survival duration after onset of EOAD associated with mutations in the APP and PSEN-2 genes were gathered from published papers reporting (usually novel) mutations in the two genes. Full details are in Appendices B and C of Gui (2003). Appendices E and F of Gui (2003) provide the databases of the pedigree information collected from these family studies in which APP and PSEN-2 gene

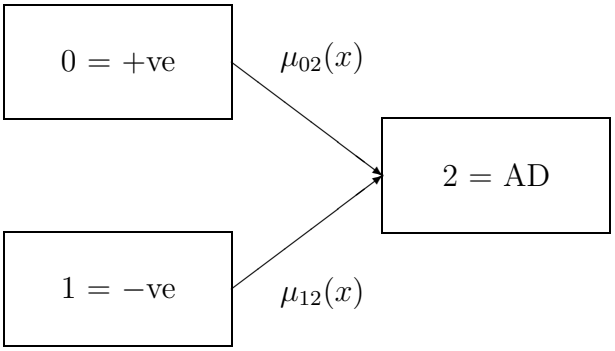

Figure 1: A model of the incidence of Alzheimer's disease where an individual may have an EOAD mutation (State 0, +ve) or may not have an EOAD mutation (State 1, −ve). Source: Gui & Macdonald (2002a).

mutations, respectively, have been found. The rate of onset in respect of any healthy person aged x corresponds to the conditional probability:

$$\text{P[Onset before age } x + dx \mid \text{Information known at age } x \text{].}$$

Note that the 'information known at age x' *cannot* include knowledge of whether or not someone carries the causative mutation, because that information can only be derived from observation of onset, or a genetic test result, at a later age. We chose to condition on a subset of the information, namely including as exposed to risk at age x persons whose parent or sibling had by then already suffered onset of EOAD. Given the rarity of EOAD and the dominant inheritance of the three genes concerned, such a person should have had probability 1/2 at birth of being a mutation carrier, provided the sample of families included in the pedigrees was an unbiased sample of the population of families in which the mutations exist. This was referred to as 'the $p = 1/2$ risk group' in Gui & Macdonald (2002a). (Of course it is highly unlikely that the sample is unbiased in this respect, but more likely that some unusual feature such as a large number of affected persons drew attention to a family included in the sample.)

Persons enter the set of those at risk when their parent suffers onset (in these data parents were always affected before any of their children) and leave it either by themselves suffering onset or by observation being censored while they are still free of EOAD. Because of missing data in some pedigrees we were only able to estimate a minimum and maximum extent of this interval of ages, in respect of some persons.

Figure 2 shows the approximate maximum exposure times in the $p = 1/2$ risk group, arising from PSEN-2 and APP gene mutations. There were not enough data to consider males and females separately.

Nelson-Aalen estimates $\hat{\Lambda}(x)$ were calculated from these data in the usual way. In a group of known mutation carriers, this would estimate the cumulative intensity $\int_0^x \mu_{02}(t)dt$ as in standard survival analysis, but because we do not know *a priori* whether an at-risk person is a mutation carrier, it estimates instead, approximately:

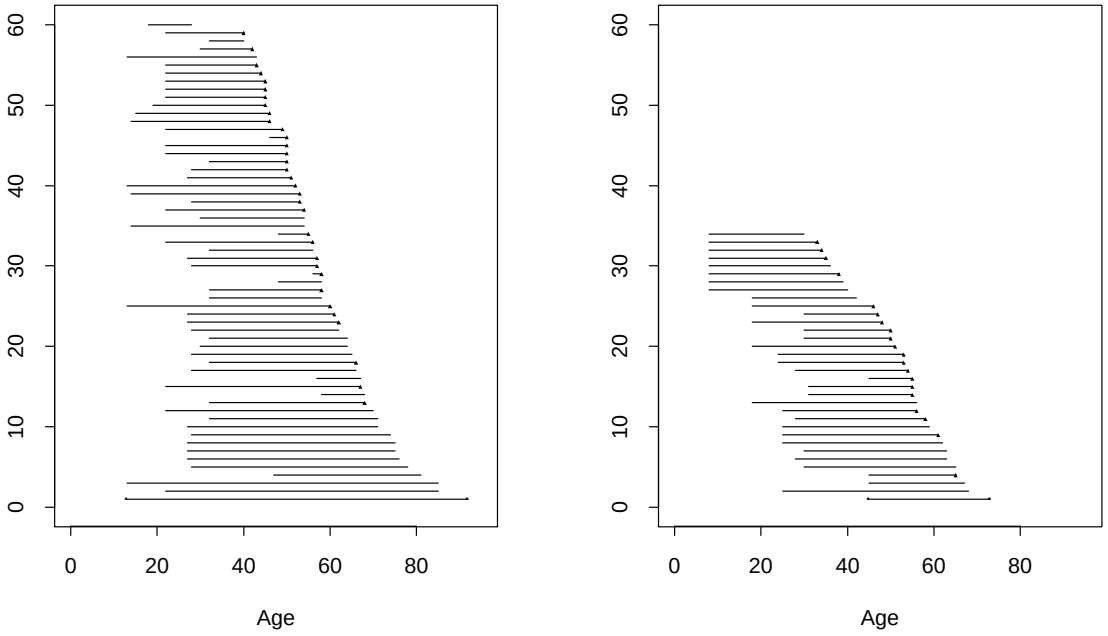

Figure 2: Estimated maximum exposure times for all persons in the $p = 1/2$ risk group. Each line represents the time spent in the risk group by a single individual. The estimated exposure times due to PSEN-2 gene mutation are on the left (60 lives), and the estimated exposure times due to APP gene mutation are on the right (34 lives). Exposures ending with onset of EOAD are indicated by a triangle.

$$\Lambda(x) = \int_0^x \frac{p \exp(-\int_0^t \mu_{02}(s)ds)}{p \exp(-\int_0^t \mu_{02}(s)ds) + (1-p)} \; \mu_{02}(t) \; dt \tag{1}$$

with, by assumption, $p = 1/2$. The Nelson-Aalen estimates were kernel-smoothed using a biweight kernel, with optimal bandwidths of 2.3 and 4.6 years respectively for PSEN-2 and APP mutations (see Figure 3) and the resulting smoothed estimates of the quantity in Equation (1) were solved for estimates $\hat{\mu}_{02}(x)$. Approximate 95% confidence limits were found by bootstrapping, using the so-called 'Weird Bootstrap'.

An important feature of the quantity in Equation (1) is that it is bounded by $-\log(1-p)$, or $\log 2$ if we assume $p = 1/2$. The Nelson-Aalen estimate is not so bounded, however, and it it exceeds it, the derived estimate $\hat{\mu}_{02}(x)$ explodes to infinity. This may be one way in which ascertainment bias reveals itself, because if it is present then we may in fact have $p > 1/2$ in the sampled population.

4. Results

Figures 4 and 5 show the resulting estimates of $\mu_{02}(x)$, for onset of EOAD with PSEN-2 and APP mutations respectively. These have several features:

(a) Although estimates are obtained up to about ages 60 (PSEN-2) and 55 (APP), when $\hat{\Lambda}(x)$ exceeds $\log 2$ (see the end of the previous section), their behaviours seem to change at about ages 57 (PSEN-2) and 52 (APP).

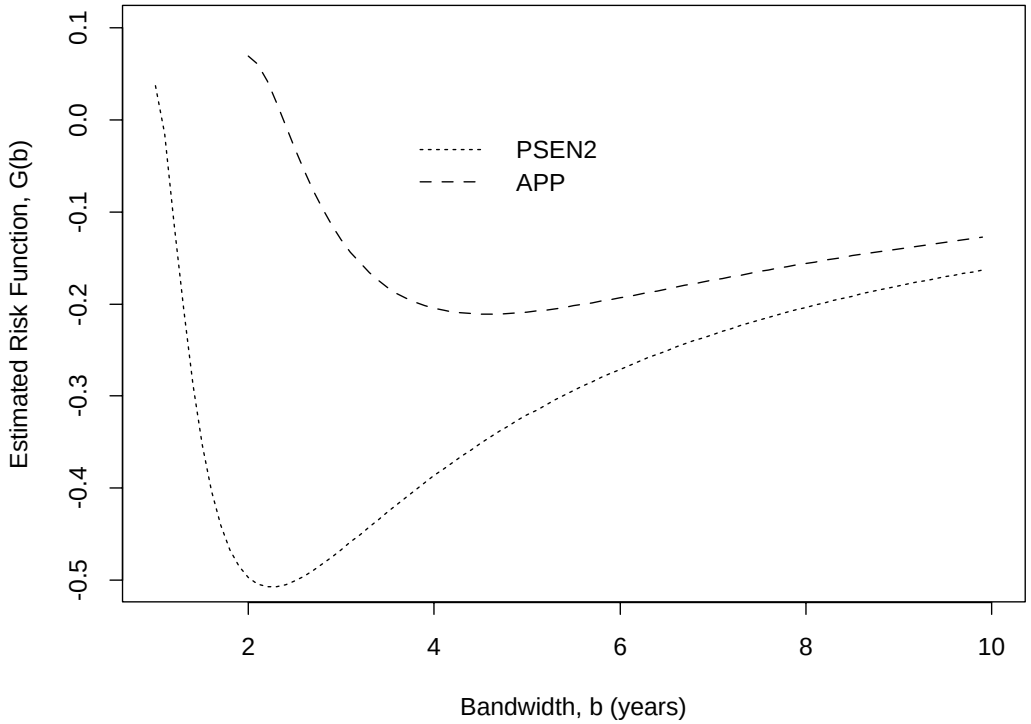

Figure 3: Estimated risk function, G(b), for use in determining the optimal bandwidth for the PSEN-2 and APP mutation data.

(b) The confidence limits are limited to shorter age ranges than the estimates, because in each case, among the 500 simulated experiences there were some in which $\hat{\Lambda}(x)$ exceeded $\log 2$ at a lower age than in the actual sample.

Compared with the estimated incidence rates of EOAD associated with PSEN-1 gene mutations (Gui & Macdonald, 2002a), which were based on samples of about 300 persons, these estimates are not as regular, due to the much smaller sample sizes. Slightly surprisingly, the ages at which $\hat{\Lambda}(x)$ exceeds $\log 2$ are higher, at about 57 for PSEN-2 and 52 for APP, compared with about 50 for PSEN-1). These could indicate less severe ascertainment bias in the PSEN-2 and APP data than in the PSEN-1 data. We would expect, instead, the much larger number of families in which PSEN-1 mutations have been reported to include more which were not selected on the basis of unusually high incidence of EOAD.

Estimated probabilities of survival free of EOAD ($\exp(-\int_0^x \hat{\mu}_{02}(t)dt)$) are shown in Figures 6 and 7, with bootstrapped 95% confidence limits. These survival probabilities are very low (< 0.4) just after age 55 as a consequence of the high penetrance of PSEN-2 and APP mutations. However, ascertainment bias makes it difficult to interpret these results, and quite strong sensitivity analysis would be recommended were these survival functions to be used in practice (see Gui & Macdonald (2002b) for an example).

Though the incidence rates of EOAD are very irregular after smoothing, the survival curves are more regular, as is to be expected since integration itself imposes a degree of

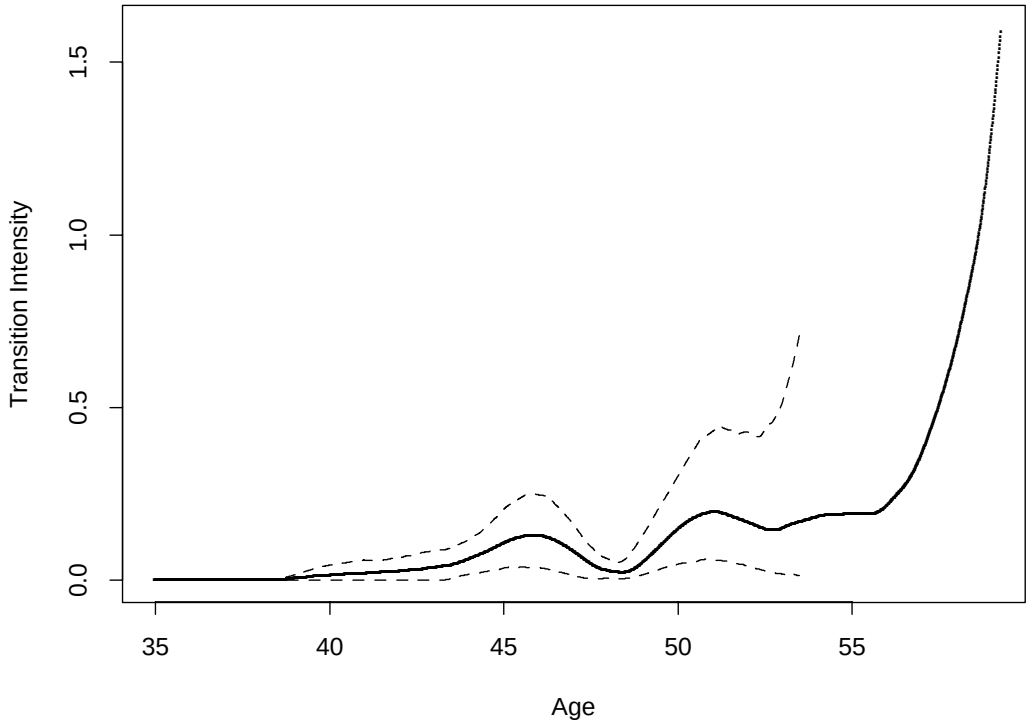

Figure 4: Estimated incidence rates of EOAD with PSEN-2 mutations, with approximate 95% confidence limits.

smoothing. Therefore it might be possible to fit a reasonably regular curve to the survival probabilities and proceed with modelling the insurance cost due to the two genes, if not for the uncertain reliability of the estimates due to scarce data.

4.1 *Comparing Rates of Onset Associated With APP and PSEN-2 Mutations*

For PSEN-2, onset of EOAD begins at around age 38, and the rate of onset reaches about 0.2 by age 50. While for APP, onset of EOAD starts at around age 30, and the rate of onset reaches about 0.1 by age 50. These features are consistent with the high penetrance but slightly later onset of EOAD associated with mutations in the PSEN-2 and APP genes when compared to EOAD associated with PSEN-1 gene mutations. For PSEN-1, onset of EOAD starts at around age 25, and the rate of onset reaches about 0.1–0.2 by age 45 (Gui & Macdonald, 2002a).

However, our estimates suggest that PSEN-2 is more severe than APP. This may not be consistent with the suggestion by Campion *et al.* (1999) that PSEN2 was the less severe of the two. The age ranges for onset of EOAD due to PSEN-2 from Campion *et al.* (1999) extend well into the 80s (when it is impossible to ascribe AD to an EOAD mutation) while nonpenetrance of APP mutations by age 60 is infrequent. Iwatsubo (1998) has also shown that the number of senile plaques and the percentage area of the senile plaques covered by Aβ_{42} or Aβ_{43} in EOAD patients with APP gene mutations are significantly higher than in EOAD patients with PSEN-2 gene mutations.

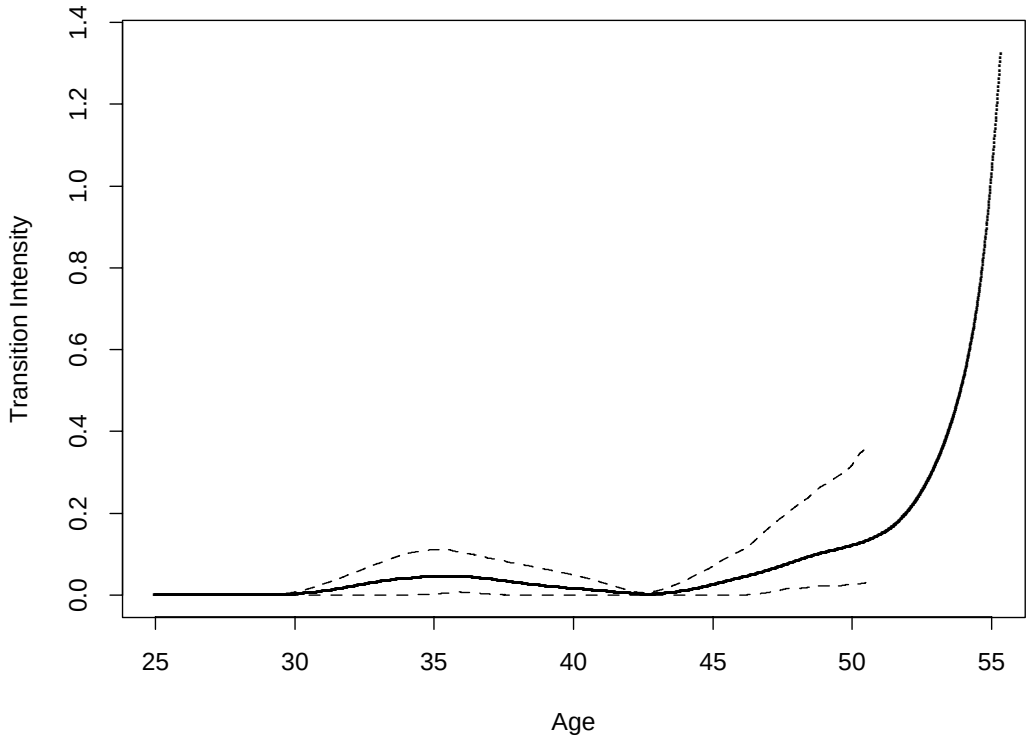

Figure 5: Estimated incidence rates of EOAD with APP mutations, with approximate 95% confidence limits.

5. Summary

In this paper, we have estimated the rates of onset of EOAD due to PSEN-2 and APP gene mutations, based on published pedigrees. Missing data, mainly those of unaffected siblings of sufferers, have been a major problem. These estimates for the incidence rates of EOAD were not applied to insurance model as the data available from the published pedigrees were too scarce.

The question of the uncertainty surrounding the epidemiology of PSEN-2 and APP raises an important question about how such apparent risks should be handled by insurers. The information is inadequate to construct a model as was done for PSEN-1, but what there is points to considerably increased insurance risk. This is different from the cases with multiple endocrine neoplasia type 2 (Gui & Macdonald, 2003) where there is also a lack of epidemiological information but the etiology, natural history and clinical management of both disorders suggest an absence of increased insurance risk.

We note the exceeding rarity of PSEN-2 mutations in the U.K. and the exclusion of PSEN-2 when the ABI made submissions to GAIC (in December 2000) for EOAD, in respect of tests for PSEN-1 and APP mutations.

Should the fact that no kind of statistical model can be established mean that the insurer is obliged to treat PSEN-2 risk as 'ordinary rates' ? This could be consistent with existing legislation on sex and disability discrimination, that requires some degree of actuarial or statistical justification for discriminatory pricing, but it would lead to

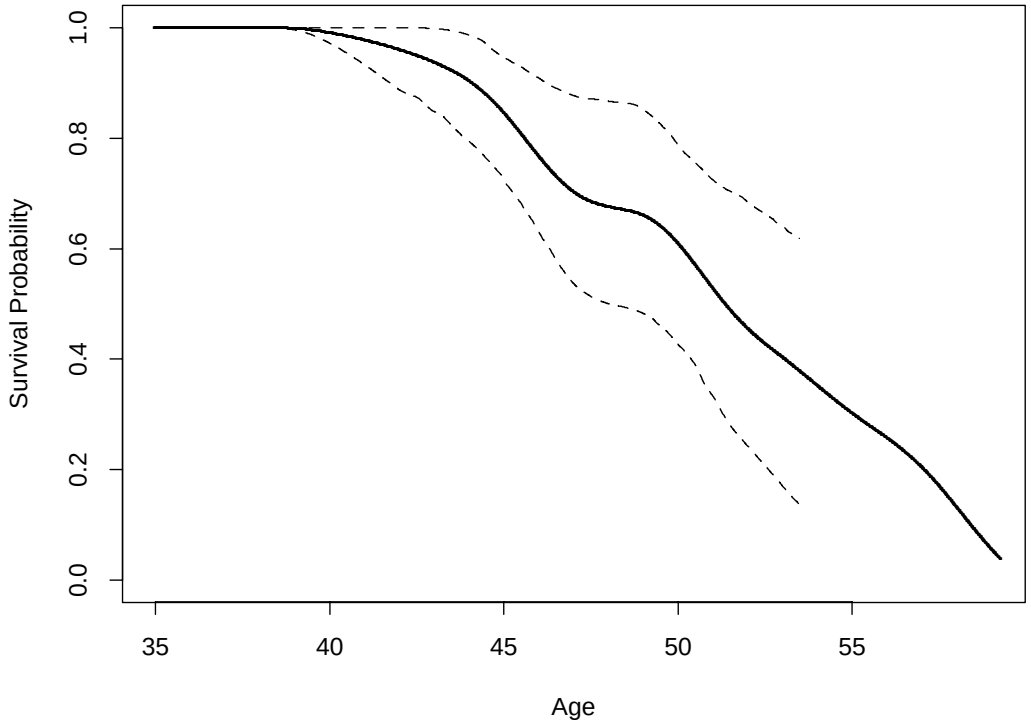

Figure 6: Probabilities of surviving free of EOAD among persons with PSEN-2 mutations, with approximate 95% confidence limits.

increasingly impractical underwriting as advances in knowledge split up genetic disorders into heterogeneous subgroups (as the discovery of the APP, PSEN-1 and PSEN-2 genes did for EOAD). Finding a balance will be difficult but input from actuarial modelling will be important. We note that the question only arises for applications beyond the limits imposed by any moratorium in force, which could be few in number.

This note has highlighted the need for further research into the epidemiology of EOAD due to PSEN-2 and APP to provide reliable estimates of onset rates and survival rates after onset, so that actuarial modelling can be done. The application process to GAIC needs to be strengthened with more credible actuarial research, as suggested by Wilkie (2000).

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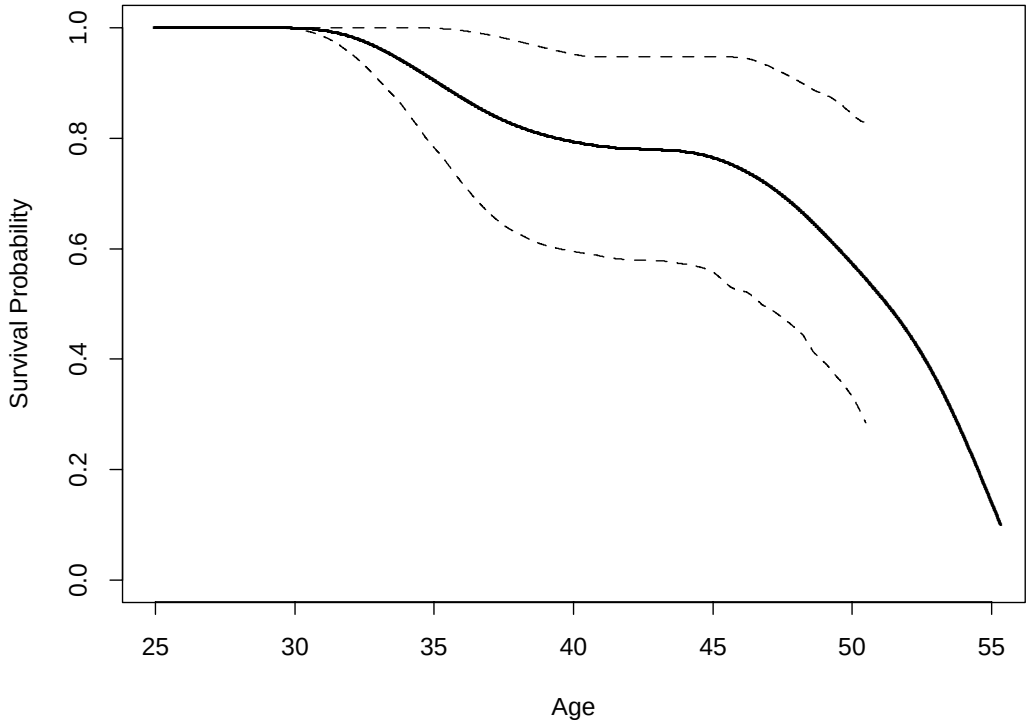

Figure 7: Probabilities of surviving free of EOAD among persons with APP mutations, with approximate 95% confidence limits.

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