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A change point model for estimating the onset of cognitive decline in preclinical Alzheimer's disease

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SUMMARY

Dementia is characterized by accelerated cognitive decline before and after diagnosis as compared to normal ageing. Determining the time at which that rate of decline begins to accelerate in persons who will develop dementia is important both in describing the natural history of the disease process and in identifying the optimal time window for which treatments might be useful. We model that time at which the rate of decline begins to accelerate in persons who develop dementia relative to those who do not by using a change point in a mixed linear model. A profile likelihood method is proposed to draw inferences about the change point. The method is applied to data from the Bronx Ageing Study, a cohort study of 488 initially non-demented community-dwelling elderly individuals who have been examined at approximately 12-month intervals over 15 years. Cognitive function was measured using the Buschke Selective Reminding test, a memory test with high reliability and known discriminative validity for detecting dementia. We found that the rate of cognitive decline as measured by this test in this cohort increases on average 5.1 years before the diagnosis of dementia.

INTRODUCTION

Alzheimer's disease (AD) and other dementias are characterized by cognitive deficits in several domains which must include memory. In the preclinical phase of the disease, changes can be gradual and usually difficult to distinguish from the less marked decline associated with normal ageing [1, 2]. As dementia progresses, cognitive impairments become more obvious and decline in function begins to accelerate. Little is known, however, about the time at which these changes begin to

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occur and when they are detectable as distinct from normal ageing. This question is important to developing measures that may be more sensitive to detecting individuals in the preclinical phase of the disease and has important treatment implications. As more effective pharmacological treatments become available for AD, it will become increasingly important to develop and implement preventive strategies to identify individuals with preclinical dementia at an earlier point in the natural history of the disease.

We address the question of when decline in cognitive function begins to accelerate in dementia using data from a longitudinal study of elderly individuals. We examine the nature of cognitive change in elderly persons and the differences in the rate of cognitive change between persons who develop dementia and those who do not. In persons who develop dementia, we assume that progressive changes begin in the brain prior to diagnosis. In addition, we assume that pathophysiologic changes result in accelerated decline in cognitive function relative to persons who do not develop dementia, differences that are observable by reduced performance on neuropsychological tests. Given these assumptions regarding the underlying disease model, we apply a statistical model to longitudinal data to examine decline in memory in a cohort of initially non-demented elderly persons. This model compares the rates of decline among those who develop dementia to those who remain free of dementia throughout the follow-up period. Three questions are of interest:

(i) What is the rate of normal cognitive decline in the ageing process in healthy individuals?
(ii) What is the rate of cognitive decline in persons who develop dementia?
(iii) Is there a period of time before the diagnosis of dementia in which the rate of the cognitive decline changes?

To address these questions, data from the Bronx Ageing Study [3] were used. We propose statistical methods that allow inferences to be made as to the time at which persons who develop AD begin to experience the more rapid decline in cognitive function that characterizes the disease process. Linear mixed models are used to examine cognitive status as a function of follow-up time. A change point is estimated as the time, on average, before diagnosis of dementia, at which the rate of decline among cases and non-cases begins to diverge. Profile likelihood methods are used to develop point and interval estimates for the change point. The conditional variance formula is used to evaluate the loss of precision due to the estimation of the change point.

STUDY METHODS

The Bronx Ageing Study is a longitudinal prospective study of 488 initially non-demented community-dwelling elderly individuals. The study began in 1980 with the enrolment of 75 to 85 year olds. Details of the study are described elsewhere [3]. Of the 488 persons enrolled in the study, 39 participants were still alive as of February 1999 and follow-up continues, 361 participants have had deaths confirmed, and 88 participants were lost to follow-up. Reasons for loss to follow-up include moving out of the study area (13), refusal to continue in the study (59) and loss of contact (16); 125 participants are known to have developed dementia as of June 1998 with the following dementia subtype distribution: 71 with probable or possible AD, 37 with probable or possible vascular dementia, 33 with mixed dementia, one with Parkinson's disease, and 16 with unknown aetiology (generally multiple causes). There are 359 individuals who have not yet developed dementia (non-cases) as of the time of death or the latest follow-up, and diagnoses are missing on four participants.

A battery of neuropsychological tests was given at intervals of approximately 12 months throughout the study period. The test battery included the Buschke Selective Reminding Test (SRT) [4] which was administered to 405 participants (101 of which had developed dementia as of mid-1998) one to ten times per participant depending on the length of follow-up. While we believe that loss to follow-up in this cohort is probably associated with illness, including dementia, the methods and analyses presented in this paper are concerned primarily with the natural history of preclinical dementia, and we excluded from analysis all participants whose only administrations of SRT were within one year of the clinical diagnosis. Thus informative loss to follow-up should be minimal, if any. Missing observations were associated primarily with logistical issues such as vacations and patient inconvenience and are not believed related to outcome. A total of 365 individuals are included in the analyses; of them, 293 had not developed dementia as of the time of death or last follow-up, 35 had received a diagnosis of probable or possible AD, and 37 had received other dementia diagnoses. These participants ranged in age from 74.7 years to 98.9 years at the times they received the test; the median age across all test administrations was 82.2 years.

The SRT is a memory test with high sensitivity and specificity for discrimination between dementia cases and non-cases cross-sectionally [5] and with good predictive value in a longitudinal setting [1]. It is a multi-trial procedure in which participants are selectively reminded of only those items that were not recalled on the immediately preceding trial, to assess learning without further presentation. It was administered to participants as follows:

(i) On trial 1, 12 unrelated words [6] were shown on index cards and read aloud at five second intervals to the participant, who repeated each word aloud as it was presented. Mispronunciations were corrected by the examiner.
(ii) On each trial, the participant immediately attempted to recall aloud all of the words in any order. The participants were given up to 2 minutes to do this.
(iii) On trials 2 to 6, the participant was reminded only of those words that were not recalled on the immediately preceding trial by verbally repeating the missed words.
(iv) The total number of words recalled over six trials is the score reported and analysed. The theoretical range of scores is thus 0 to 72.

Older recall tests re-present all of the to-be-remembered words before each recall. The intent of Buschke Selective Reminding is to facilitate learning by directing the participant's attention to the words not recalled on the previous trial [4].

From a statistical perspective, Buschke Selective Reminding has many attractive properties as well. Within the range of performance experienced by participants with normal cognition, or experiencing the memory loss characteristic of early dementia, the test has neither ceiling nor floor effects, and has scores which are approximately normally distributed on the original measurement scale. In this sample, reported test scores ranged from 6 to 66 and the distribution of scores was quite symmetric both for baseline administrations and for all scores.

STATISTICAL METHODS

Figure 1 shows a 'spaghetti plot' [7] of the Buschke Selective Reminding scores over time for the 293 participants in the study who have not developed dementia during the follow-up period and were administered Buschke Selective Reminding at any time during the study. There is clearly a downward trend over time on average. One also notes the very noisy pattern that we have found

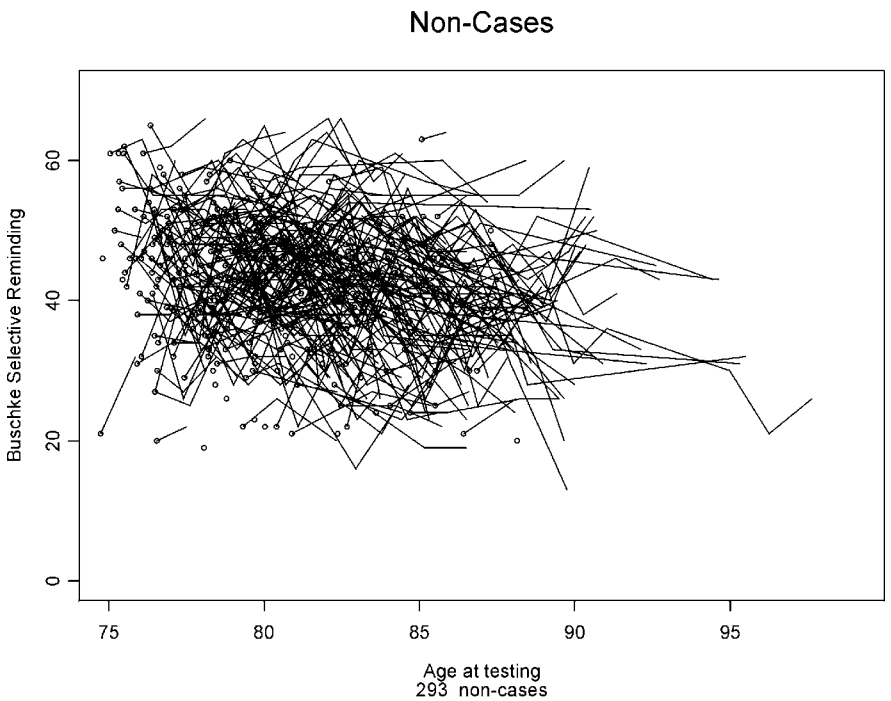

Figure 1. Spaghetti plot of SRT scores as a function of age in 293 participants who did not develop dementia.

to be characteristic of repeated neuropsychological test scores in cohort studies. We anticipated that there would be great residual variance after accounting for within participant effects in a longitudinal model.

Figure 2 shows the same plot but for the 72 participants who develop dementia at least one year after an administration of Buschke Selective Reminding. Persons who were diagnosed with dementia less than one year after the first administration of Buschke Selective Reminding are excluded from this graph and from all other analyses. Again, there is clearly a downward trend over time. With Figures 1 and 2 on the same scale we note that persons who will develop dementia have on average lower Buschke Selective Reminding scores throughout the follow-up period. This is consistent with the past research describing this test's ability to distinguish between dementia cases and non-cases both at cross-section and longitudinally.

Figure 3 shows the Buschke Selective Reminding scores for the participants who develop dementia as a function of the time before the clinical diagnosis. The participants seem to show an accelerating decline on average although it is not clear whether that is true for the entire length of follow-up shown here or just the few years prior to diagnosis.

Figure 4 is the same graph as Figure 3, but only for the 35 participants who were diagnosed with probable or possible AD. The general time course of the disease process is similar, although the non-AD cases seem to add additional heterogeneity.

We determined to fit models that would:

(i) allow for dementia cases and non-cases within the cohort to differ both in average SRT score and in rate of decline;

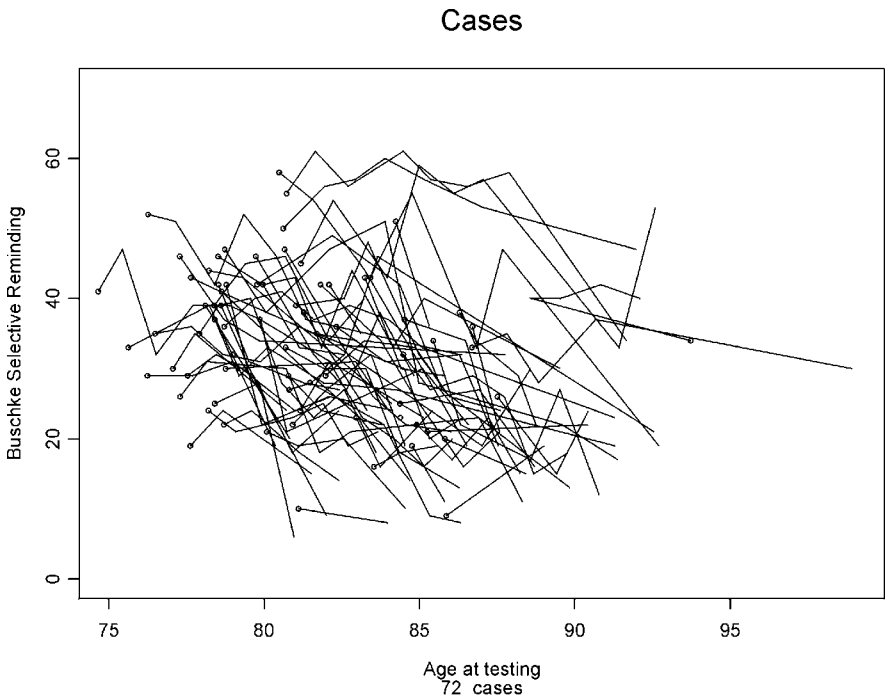

Figure 2. Spaghetti plot of SRT scores as a function of age in 72 participants who developed dementia.

(ii) determine whether or not the rate of decline in cases accelerates relative to the time of dementia diagnosis, and if so, how long before diagnosis.

All our models may be expressed in the usual mixed linear model notation:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{b} + \mathbf{e} \tag{1}$$

$$\text{var}(\mathbf{b}) = \mathbf{D}, \ \text{var}(\mathbf{e}) = \sigma_e^2\mathbf{I}$$

$$\text{cov}(\mathbf{b}, \mathbf{e}) = \mathbf{0}$$

Here, $\boldsymbol{\beta}$ is a vector of fixed effects parameters, $\mathbf{b}$ is a vector of random effects, $\mathbf{e}$ is the residual error term, $\mathbf{D}$ is an unstructured block-diagonal matrix containing the variances and covariances of the random effects, $\mathbf{I}$ is the identity matrix of appropriate dimension, and σ_e^2 is the residual error term. Gaussian priors are assumed for the random effects.

We fit linear mixed models that included linear and quadratic trends with age for both cases and non-cases, allowing all terms to differ between the cases and non-cases. In addition, spline terms were added to allow the linear and quadratic trends to change at some point prior to dementia diagnosis. Initially we allowed the predictor matrices $\mathbf{X}$ and $\mathbf{Z}$ to contain the same data, thus treating all predictor coefficients as random effects with an unstructured variance-covariance matrix. Maximum likelihood under Gaussian assumptions was used to fit the model for a variety of change points τ. The outcome vector contains the Buschke Selective Reminding scores for each participant i at each observation t.

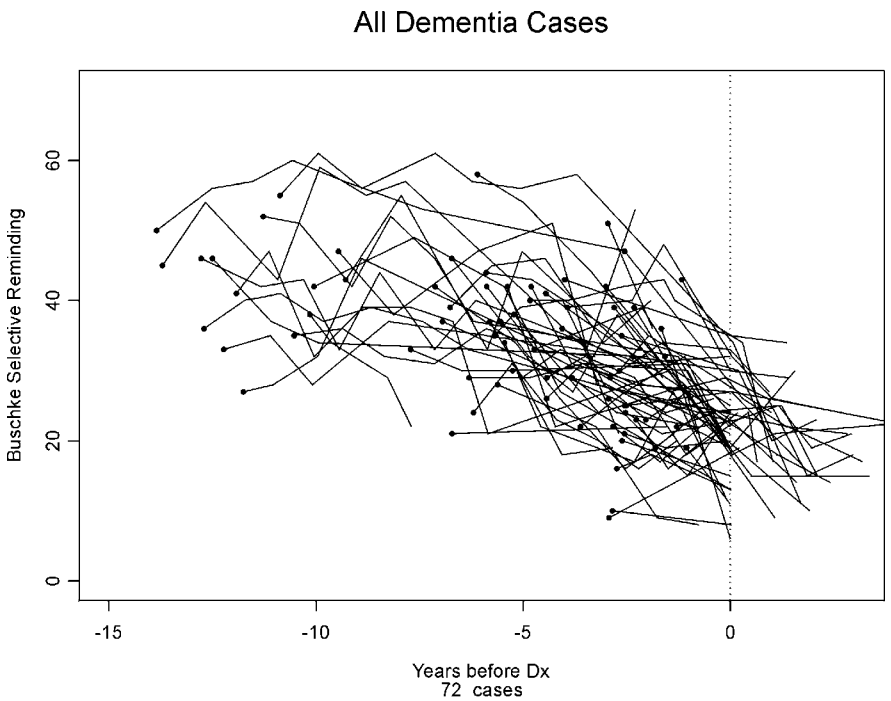

Figure 3. Spaghetti plot of SRT scores as a function of time before diagnosis in 72 participants who developed dementia.

The predictors for observation t on participant i were an intercept, $(\text{age}_{it} - 75)$, $(\text{age}_{it} - 75)^2$, case_i, $(\text{age}_{it} - 75) \times \text{case}_i$, $(\text{age}_{it} - 75)^2 \times \text{case}_i$, $(\text{age}_{it} - \text{agedx}_i + \tau)^+$, and $[(\text{age}_{it} - \text{agedx}_i + \tau)^+]^2$ where age_{it} is the age in years of participant i at observation t, case_i takes the value one if participant i developed dementia during the follow-up period, and zero otherwise, agedx_i is the age at which dementia is diagnosed in participant i, and $(\text{age}_{it} - \text{agedx}_i + \tau)^+ = \max(0, \text{age}_{it} - \text{agedx}_i + \tau)$. This last 'max' term allows the decline in Buschke Selective Reminding score to differ between cases and non-cases beginning τ years before the clinical diagnosis is made. For example, if a participant is diagnosed with dementia at age $\text{agedx}_i = 83$ years, the 'max' term will be zero for observations at which the participant is age $\text{age}_{it} < 83 - \tau$ years, the 'max' term will be equal to τ minus the number of years before the diagnosis of dementia for observations at which the participant is age $\text{age}_{it} > 83 - \tau$. The fixed effect for the 'max' terms reflect the average difference in the rate of cognitive decline between participants experiencing normal ageing and participants who are experiencing the rapid cognitive decline characteristic of the time immediately preceding a dementia diagnosis. The subtraction of 75 in the age terms was done for interpretability of the intercept.

For change points τ between 1 and 10 years prior to diagnosis, neither the quadratic terms nor the diagnosis/age interaction were statistically significant. In addition, the corresponding variance components proved not to significantly improve the fit of the model as measured by a penalized likelihood criteria corresponding to the log-likelihood less twice the number of parameters. This criterion is equivalent to a likelihood ratio test under the usual asymptotic regularity conditions.

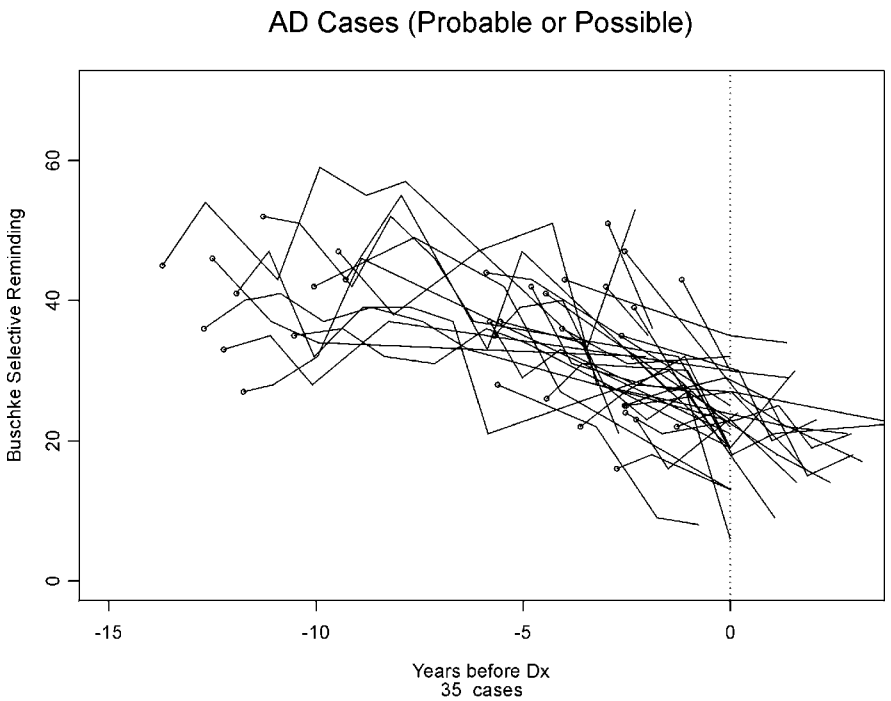

Figure 4. Spaghetti plot of SRT scores as a function of time before diagnosis in 35 participants who developed probable or possible Alzheimer's disease.

Hence we used reduced models using only the intercept, $(\text{age}_{it}-75)$, case_i, and $(\text{age}_{it}-\text{agedx}_i+\tau)^+$ as predictors. If effect, we place a kink in the line representing the expected Buschke Selective Reminding score for each case at a point τ years before that case is diagnosed.

While we found that these models fit well for a variety of change points, we were faced with the need to estimate the change point rigorously with little prior information. We adopted a profile likelihood approach. The profile likelihood for τ is defined as

$$\mathscr{L}_{\mathrm{p}}(\tau)=\max_{\boldsymbol{\beta},\mathbf{D},\sigma_{\mathrm{e}}^2}\mathscr{L}(\boldsymbol{\beta},\mathbf{D},\sigma_{\mathrm{e}}^2,\tau)$$

Given any fixed value for τ, $\mathscr{L}(\boldsymbol{\beta},\mathbf{D},\sigma_{\mathrm{e}}^2,\tau)$ is a multivariate normal likelihood. The profile likelihood as a function of τ is calculated by maximizing that likelihood with respect to all the other parameters in the model for the desired range of values for τ over which the profile likelihood is to be evaluated. Standard software (for example, SAS PROC MIXED) may be used to evaluate this likelihood. The maximum likelihood estimate for the change point is simply

$$\hat{\tau}=\arg_{\tau}\max\mathscr{L}_{\mathrm{p}}(\tau)$$

which is the value of τ for which $\mathscr{L}_{\mathrm{p}}$ is greatest. $\mathscr{L}_{\mathrm{p}}(\tau)$ may also be used to create approximate large sample confidence intervals for τ [8]:

$$\{\tau\colon -2\times[\log\mathscr{L}_{\mathrm{p}}(\tau)-\log\mathscr{L}_{\mathrm{p}}(\hat{\tau})]\leqslant\chi^2_{1.095}=3.84\}$$

Table I. Age and SRT score at baseline.

	AD cases	Non-AD cases	All cases	Non-cases	Overall
N	35	37	72	293	367
Age at baseline (years)	80.3 (2.9)	81.4 (3.4)	80.9 (3.2)	80.2 (3.2)	80.5 (3.3)
Baseline SRT score	36.1 (9.2)	32.7 (11.3)	34.3 (10.4)	42.5 (10.4)	39.1 (11.1)

This is just the inversion of the likelihood ratio test. The maximum likelihood estimates for the other parameters *at that change point* $\hat{\tau}$ are the overall maximum likelihood estimates.

Nominal standard errors that are reported by standard methods that condition on the particular value of the change point do not take into account the loss of precision from not knowing the change point. The standard errors must therefore be adjusted or we will have estimates that are generally 'too precise'. The conditional variance formula

$$\text{var}(\hat{\beta}) = E[\text{var}(\hat{\beta}|\tau)] + \text{var}[E(\hat{\beta}|\tau)] \tag{2}$$

allows the variances of the fixed effects and variance component estimates to be properly adjusted for this lack of precision. The averages are taken over all change point values considered, weighted by the profile likelihood, which would be approximately proportional to the posterior distribution of τ in a Bayesian analysis.

RESULTS

Table I shows the age and SRT scores at baseline by case status. There were no significant differences in age at baseline between cases and non-cases, or between AD and non-AD cases. Cases had significantly lower SRT scores at baseline, but the difference in score between AD and non-AD cases was not significant.

After a number of exploratory models were fit, the model with linear terms described above was fit to dementia cases and non-cases for values of τ between 1.0 and 9.9 years in steps of 0.1 years. The maximized likelihood values are plotted against τ in Figure 5. This graph approximates the profile likelihood, which is continuous. The horizontal dotted line indicates the critical value for an approximate large sample 95 per cent confidence interval. Values of τ for which the likelihood is above the critical value are within the confidence interval.

The value of τ for which the profile likelihood is maximized is $\hat{\tau}$, the maximum likelihood estimate for τ, and the parameter estimates found from the maximum likelihood estimates using the estimated likelihood $f(y; \boldsymbol{\beta}, \mathbf{D}, \sigma_e^2, \hat{\tau})$ assuming that the change point is known to be $\tau = \hat{\tau}$ are the maximum likelihood estimates for the full likelihood $f(y; \boldsymbol{\beta}, \mathbf{D}, \sigma_e^2, \tau)$. We see that the maximum likelihood estimate for τ is $\hat{\tau} = 5.1$ years, with an approximate 95 per cent confidence interval of 4.2 to 6.1 years. Similar analyses were performed excluding non-AD dementias; the maximum likelihood estimate for τ was $\hat{\tau} = 4.3$ years, with approximate 95 per cent confidence interval (2.6, 5.5) years. The greater width of the interval estimate is consistent with the smaller number of cases (35 versus 72) contributing to the estimate of the change point.

As stated above, the precision of the estimates for $\boldsymbol{\beta}$ and $\mathbf{D}$, are expected to be overstated because of the uncertainty in the estimation of the change point. We applied the conditional

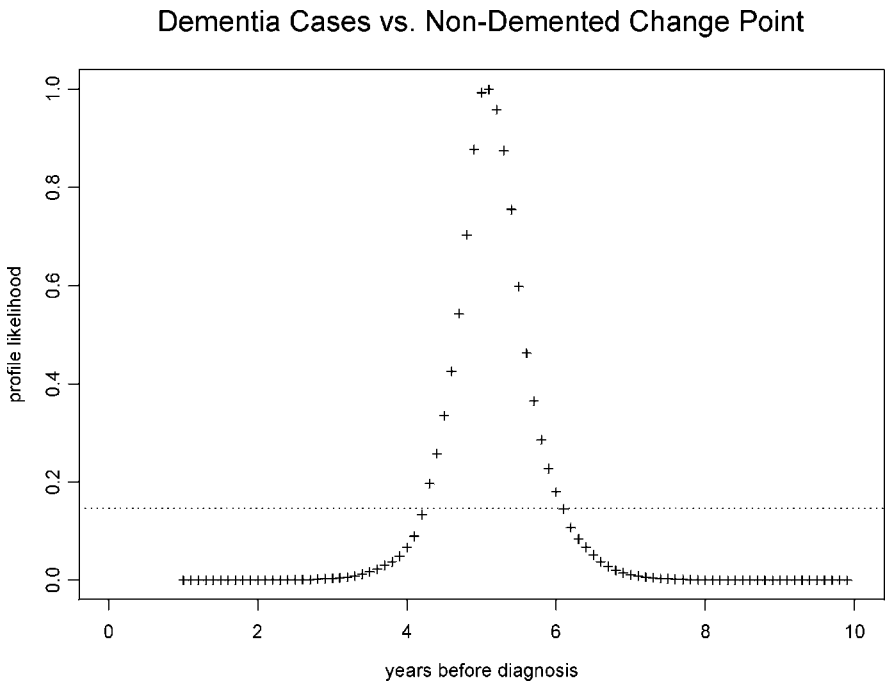

Figure 5. Profile likelihood values for change point as a function of time before diagnosis.

variance formula (2) to assess this difference but found that there was little difference, either for the fixed effects parameters or for the variance components, between the conditional standard errors based on naively assuming that the change point is known and the standard errors adjusting for that lack of precision. The reason for this is that there is little difference in the fixed effects or variance component estimates for the range of values of τ that are best supported by the data (as measured by the profile likelihood), hence little contribution from the var$(E(\hat{\beta}|\tau))$ term (or the corresponding term for the variance components). The conditional standard errors are reported below.

The fixed effect intercept, which may be interpreted as the expected Buschke Selective Reminding score at age 75 for the 293 participants who will not develop dementia, was estimated as 46.04 (standard error 0.6964). The fixed effect for case status estimate indicates that the 72 participants who developed dementia scored on average 6.336 (SE 1.192) points lower at the same age. Both cases and non-cases decline at a rate of 0.6132 (SE 0.0814) points per year until the change point is reached for the non-cases. After the change point, the 72 cases declined 1.488 (SE 0.2686) points per year faster than the non-cases until a diagnosis of dementia was given. Variance components were statistically significant for all terms except for case status, indicating (as expected) substantial heterogeneity in the data. (The variance component for case status was estimated to be on the boundary of the parameter space (zero), for all $\tau \geqslant 4.8$ years.)

Ordinary least squares analyses showed an average decline in SRT score of 0.6103 (SE 0.0794) points per year in non-cases and in cases before the estimated change point (5.1 years before dementia diagnosis). Cases declined in SRT score at an average rate of 2.338 (SE 0.2630) points

per year after the change point. These are close to the estimates of decline from the change point mixed models analyses, which properly take into account the repeated measures nature of the data.

DISCUSSION

We have demonstrated the use of an approximate profile likelihood change point method to determine the length of time before a clinical diagnosis of dementia is made that the rate of cognitive decline accelerates in persons who develop dementia compared to normal healthy individuals. The maximum likelihood estimate for that change point is 5.1 years, with an approximate 95 per cent confidence interval of 4.2 to 6.1 years. In this sample from the Bronx Ageing Study using the Buschke Selective Reminding test as the measure of cognitive function, little adjustment needs to be made to the precision of the parameter estimates for the model describing the cognitive decline due to the uncertainty in the estimation of the change point.

This type of natural history model would be applied ideally to homogeneous participant groups with well defined disease subtypes. AD is the dementia subtype of greatest interest both because it is the most common type of dementia in most countries [9] and also because efficacious treatments are becoming available. For several reasons, however, we address these questions in this paper to all forms of dementia rather than restricting ourselves to clinically diagnosed Alzheimer's disease. First, Alzheimer's disease is itself heterogeneous; there have been a number of different genetic subtypes identified [10]. Second, many older persons suffering from dementia have multiple aetiologic causes for their disease [11], even in this sample [12]. Third, this and other factors result in clinical subtyping of dementia being participant to misclassification. In addition, greater statistical power is achieved by pooling all dementia cases. Our model and methods will be particularly applicable to future studies having larger cohorts in which participants may be stratified by pathology and genotype.

Analysing only the non-cases, we discovered a small but statistically significant non-linear trend in the relationship of Buschke Selective Reminding test with age, modelled either as a linear spline with a knot in the early 80s, or as a quadratic function. These non-linear trends may result from the misclassification of persons with preclinical Alzheimer's disease as non-cases, and were non-significant in the analyses presented here. In the future we will analyse a normative sample of non-cases, using independent algorithms to exclude those with future preclinical dementia, to see if these non-linear trends may disappear.

Before the change point, there was also a difference in the rate of decline with respect to age between the cases and non-cases that was not statistically significant. This fact along with the difference in intercepts represented by the 'case status' parameter above may reflect an earlier inflection point at which the rate of decline in cases begins to accelerate more than a decade before clinical diagnosis.

We were concerned that the estimation of the change point might be unduly influenced by possible outliers. We performed a 'leave one out' sensitivity analysis; we repeated the analysis over and over again, deleting each participant in turn, one at a time. All estimated change points were within the range 5.0 to 5.3 years. We are therefore confident that a single unusual participant is not driving the analysis.

It is natural to ask if there might be more than one change point. We examined the possibility of a second change point closer to the time of diagnosis using the same methods and found no evidence for one. One reason might be that the data are inherently interval censored because of the

intervals between evaluations, as is the case in most longitudinal studies, and it will be essentially impossible to detect any change point less than the typical between-evaluation interval. We also considered models in which age at baseline evaluation and follow-up time were separated [13] and found little difference in our results. Because most cases were followed for five to nine years before diagnosis, there is little power to detect any change point that might occur much before the one that we have found here; this is a difficulty in all longitudinal studies of chronic diseases in that inferences as to the disease processes are naturally limited by the length of follow-up.

Only 34 dementia cases (16 of whom had probable or possible AD as a diagnostic subtype) had follow-up longer than the change point estimate (5.1 years). In a crude analysis the other 38 cases would contribute nothing to the estimation of the change point. However, in our model, cases with follow-up prior to diagnosis less than the estimated change point do contribute indirectly to the estimation of the change point because the cognitive decline in such cases contributes to the estimation of the fixed and random effects parameters for all possible change points, and also to the likelihood.

Smith [14], Carlin *et al.* [15], and Lange *et al.* [16] used Bayesian approaches to change point modelling. While we have no philosophical objection to the Bayesian approach, we have little prior information to use to aid in Bayes estimation of any parameters other than possibly the change point itself. Lange allowed each participant to have his/her own change point, a model that would necessitate a Bayesian approach given the current state of statistical methodology and computation. The change point in this type of model would be correctly considered to be a random effect. The average change point in such a model would be some potentially unequally weighted average of the change points of the individual participants. We considered and rejected such a model for several reasons. First, our exploratory analyses, including the graph in Figure 3, indicated that it was unlikely that allowing heterogeneity in change points would help address the major question of interest, which was to determine the time at which cases typically diverge from non-cases and the rate of divergence. (Lange *et al*. found that their random change point did not improve the model fit in their example.) Second, we did not wish to make assumptions on prior distributions that would be necessary for a full Bayesian analysis. As more prospective studies of ageing are conducted a Bayesian approach would be more appealing to us, especially for possible meta-analyses. Third, it would be difficult to model the change point distributions given the limited follow-up available on many of the participants. As stated above, 34 cases had less than 5.1 years of follow-up available; the predicted change point for those participants would in many cases be censored. Modelling that censoring is an open methodological issue; we will consider it in future work. This methodology presented here addresses important scientific questions, allowing proper inferences to be drawn using available software.

Our display of the profile likelihood uses the actual profile likelihood values on the y-axis, as per Royall [17]. The profile likelihood from our data approximates a normal likelihood function, as is clear from the graph. Earlier texts [18, 19] typically use log-likelihood values; when that is done the graph approximates a quadratic function. We believe that the plot of profile likelihood values on the original scale shows exceptionally clearly that there is utterly no support for a change point being outside an interval of approximately three years to seven years – the value of the profile likelihood outside of that interval is essentially zero. Plots on the log scale would not show this.

Persons who develop dementia have significantly lower scores on the Buschke Selective Reminding test regardless of the age of administration, at least in this cohort. It is possible that the pre-dementia group has poorer memory throughout the life span, and it is also possible that there

is an earlier divergence years before age 75; obviously no evidence for either hypothesis can be gained from this study.

We are currently applying this methodology to other tests of cognitive function administered in the Bronx Ageing Study (category fluency, WAIS subscales, Fuld Object Memory test). Results will give evidence for the relative robustness of different cognitive domains in the disease process. Results also need to be confirmed in other longitudinal studies. These methods may be applicable to other illnesses with measurable decline prior to diagnosis, such as the bone density changes prior to diagnosis of osteoporosis.

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