Change point models in longitudinal aging: motivation, history, and challenges

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Disclosure of Interest

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Consultant

University of Connecticut Health Center
Mount Sinai School of Medicine
Columbia University

Objective: To understand the history of the use of change point models in aging and dementia research, what they have taught us, and challenges for future research.

I own no stocks or equity in any company
Outline

• Motivation
• Some data
• Theoretical model
• Results (from my work, and that of others)
• Another theoretical model
• More results
• Problems – and some solutions
• So what HAVE we learned?
• Future research
Motivation

I had some data to analyze and didn’t know what to do!
Motivation

I had some data to analyze and didn’t know what to do!

More seriously – I wanted to characterize the different natural histories of persons who develop dementia vs. those who don’t.
Bronx Aging Study

488 community dwelling individuals age 75-85 enrolled 1980-1983 – up to 19 years of follow up. 128 have developed dementia.

- 65 probable or possible AD.
- 28 probable or possible vascular dementia.
- 26 mixed dementia.
- 1 Parkinson's disease.
- 8 other or unknown (generally multiple causes).
Bronx Aging Study

366 non-cases. One participant still alive.

3 principal investigators!

Battery of neuropsychological tests given at intervals of approximately 12 months.

Buschke Selective Reminding (memory test). WAIS IQ (subscales), Ravens, Category Fluency, Purdue Pegboard.
Buschke Selective Reminding

Multi-trial recall test administered as follows:

Subjects read a list of 12 unrelated words presented one at a time on index cards at 5-second intervals. Mispronunciations are corrected by the examiner.

Immediately after reading the words, subjects are given up to 2 minutes to recall as many words as possible in any order.

On trials 2 through 6, the subject is reminded only of these words that were not recalled on the immediately preceding trial by verbally repeating the missed words.
Buschke Selective Reminding

Recall is tested immediately after reminding. The sum of 6 trials of recall is used here.

Other recall tests re-p resent all of the to-be-remembered words before each recall.

Intent: Facilitate learning by directing the subjects’ attention to the words not recalled on the previous trial.

In healthy population, scores approximately normally distributed on the original measurement scale with neither ceiling nor floor effects.

Substantive questions

• What are the differences in the natural history of cognition between normal aging and preclinical dementia?
• When do those differences begin to manifest?
• How large are those differences, and how rapidly do they develop?
Non-Cases

![Graph showing data with age and selective reminding on the y-axis and age (years) on the x-axis, labeled as Non-Cases. The graph contains numerous scattered points representing data points.](image-url)
Cases

Time before diagnosis (years)

Selective Reminding

Cases
Theoretical Model

Decline typical of healthy aging

Followed by accelerated decline at some point.
Theoretical progression of a person developing Alzheimer's disease (AD)

Idea – Change Point Modeling!

Model a rate of cognitive decline up to a certain point, and then a different (more rapid) rate!

Hinckley DV. Inference about the Change-Point in a Sequence of Random Variables. *Biometrika* 57, 1-17, 1970.


Inference about the change-point in a sequence of random variables

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SUMMARY

Inference is considered about the point in a sequence of random variables at which the probability distribution changes. In particular, we examine a normal distribution with changing mean. The asymptotic distribution of the maximum likelihood estimate is derived and also the asymptotic distribution of the likelihood-ratio statistic for testing hypotheses about the change-point. These asymptotic distributions are compared with some finite-sample empirical distributions.

1. Introduction

Given a sequence \( (x_1, \ldots, x_T) \) of observations on the variables \( (X_1, \ldots, X_T) \), there are available many techniques for detecting underlying patterns or relationships, most of which assume that a single model is valid for the whole range of the sample. Often the model is of the form

\[
X_t = \theta(t) + \epsilon_t \quad (t = 1, \ldots, T),
\]

where \( \{\epsilon_t\} \) is a sequence of uncorrelated error terms with zero mean and \( \theta(t) \) is a continuous mean function. In practice, however, a single model is sometimes inappropriate. It may be strongly suspected that the model valid near \( t = 1 \) is not valid near \( t = T \). It is then relevant to consider models of the form

\[
\begin{align*}
X_t &= \theta_1(t) + \epsilon_t \quad (t = 1, \ldots, \tau), \\
X_t &= \theta_2(t) + \epsilon_t \quad (t = \tau + 1, \ldots, T),
\end{align*}
\]

(1.1)

where the change-point \( \tau \) is unknown. Experimental and scientific grounds may force us to consider (1.1), or even its generalization to \( (p + 1) \)-model with \( p \) unknown change-points.

Two simple but interesting and important special cases of (1.1) are (a) two constant means \( \theta_1 \) and \( \theta_2 \), and (b) two intersecting regressions \( \theta_1(t) = \alpha + \beta t ) \) \( (t = 0, 1) \), where \( z_t \) is an independent variable and \( z_0 \leq \gamma \leq z_{n+1} \). In both cases it is usual to assume the error terms \( \epsilon_t \) to be \( N(0, \sigma^2) \). Maximum likelihood estimation and inference in the regression case (b) have been discussed in detail by Hudson (1966) and Hinkley (1969). In case (a) the emphasis of published work, in particular that of Peto (1964, 1955, 1967) on cumulative sum schemes, has been on testing the null hypothesis \( H_0: \theta_1 = \theta_2 \) against the two-mean alternative. Chernoff & Zacks (1964) and Bhattacharyya & Johnson (1968) have discussed the same problem within a Bayesian framework. The present paper is concerned primarily with estimating and making inference about the change-point \( \tau \) in this two-segment case.

We consider initially (§2) a generalization of case (a) where \( X_t \) has an arbitrary continuous probability density function \( f(x, \theta) \) with \( \theta \) changing from \( \theta_1 \) to \( \theta_2 \) after index \( \tau \). The asymptotic distribution of the maximum likelihood estimate \( \hat{\tau} \) is derived for \( \theta_1 \) and \( \theta_2 \) known,
A Bayesian approach to inference about a change-point in a sequence of random variables

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SUMMARY

A Bayesian approach is considered to the problem of making inferences about the point in a sequence of random variables at which the underlying distribution changes. Inferences are based on the posterior probabilities of the possible change-points. Detailed analyses are given for cases in which the distributions are binomial and normal, and numerical illustrations are provided. An informal sequential procedure is also noted.

Some key words: Bayesian inference; Change-point; Informative priors.

1. INTRODUCTION

A sequence of random variables \( X_1, \ldots, X_n \) is said to have a change-point at \( r \) \( (1 \leq r \leq n) \) if \( X_i \sim F_1(x|\theta_1) \) \( (i = 1, \ldots, r) \) and \( X_i \sim F_2(x|\theta_2) \) \( (i = r + 1, \ldots, n) \), where \( F_1(x|\theta_1) + F_2(x|\theta_2) \).

We shall consider the situation in which \( F_1 \) and \( F_2 \) have known functional forms, but the change-point, \( r \), is unknown. Given a sequence of observations \( x_1, \ldots, x_n \), the problem we shall be concerned with is that of making inferences about \( r \). The parameters \( \theta_1 \) and \( \theta_2 \), which could be vector-valued, may be known or unknown; in the latter case, it might be of interest to make inferences about these also.

In §2, we present a Bayesian formulation of the problem, which has as its objective the derivation of the posterior probabilities of the change having occurred at the various possible points, \( 1 \leq r \leq n \). From these probabilities, Bayes estimates are easily calculated, and hypothesis tests derived using posterior odds.

In §§3 and 4, the detailed analysis is given for binomial and normal distributions. An informal sequential procedure is outlined in §5, and numerical illustrations are provided in §6.

Previous, non-Bayesian, work on this problem includes that of Page (1954, 1955, 1967) using cumulative sums, and Hinkley (1970) using asymptotic arguments based on maximum likelihood estimates and likelihood ratio tests. The problem has also been discussed within a Bayesian framework by Chernoff & Zacks (1964), Kander & Zacks (1966), and Sen & Srivastava (1972), but the emphasis and the objectives differ from those in the present paper.

2. A BAYESIAN FORMULATION

2.1. Basic assumptions

Assuming that the distributions admit densities \( p_1(x|\theta_1) \) and \( p_2(x|\theta_2) \), the joint distribution of \( x_1, \ldots, x_n \), conditional on \( \theta_1, \theta_2 \) and the change having taken place at \( r \) \( (1 \leq r \leq n) \) is given by

\[
p(x_1, \ldots, x_n| \theta_1, \theta_2) = p_1(x_1, \ldots, x_r|\theta_1)p_2(x_{r+1}, \ldots, x_n|\theta_2) = \prod_{i=1}^{r} p_1(x_i|\theta_1) \prod_{i=r+1}^{n} p_2(x_i|\theta_2). \tag{2.1}
\]

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Hierarchical Bayesian Analysis of Changepoint Problems

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(Received March 1990. Revised April 1991)

SUMMARY

A general approach to hierarchical Bayesian changepoint models is presented, in particular, desired marginal posterior densities are obtained utilizing the Gibbs sampler, an iterative Monte Carlo method. This approach avoids sophisticated analytic and numerical high dimensional integration procedures. We include an application to changing regressions, changing Poisson processes and changing Markov chains. Within these contexts we handle several previously inaccessible problems.

Keywords: Changepoints; Changing Markov chains; Changing Poisson processes; Changing regressions; Gibbs sampler; Hierarchical Bayesian models

1. Introduction

The literature on changepoint problems is, by now, enormous. Here we consider only the so-called non-sequential or fixed sample size version although an informal sequential procedure which follows from Smith (1975) is a routine consequence (see Section 6). Still the literature is substantial and we merely note several reviews which span both parametric and nonparametric approaches. These are Hinkley et al. (1980), Siegmund (1986), Wolfe and Schechtman (1984) and Zacks (1983).

Our focus is on a fully Bayesian parametric approach. Use of the Bayesian framework for inference with regard to the changepoint dates to work by Chernoff and Zacks (1964) and Shiryaev (1963). Smith (1975) presents the Bayesian formulation for a finite sequence of independent observations. In particular he addresses three situations:

(a) both the initial distribution and the changed distribution are known;
(b) only the initial distribution is known;
(c) both are unknown.

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Earlier applications


Change Points in the Series of T4 Counts
Prior to AIDS

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SUMMARY
The absolute number of T4 cells has been established as an important clinical marker of disease progression to acquired immunodeficiency syndrome (AIDS) in persons infected with human immunodeficiency virus (HIV). Series of T4 counts are analyzed from the 131 homosexual men who entered the New York Blood Center Study in 1984, mostly seropositive for HIV, and who developed AIDS as participants by 1986. These series exhibit a gradual decline of the log (T4) count followed by a more rapid decline close to the time of the development of AIDS. Empirical Bayes and hierarchical Bayes change point models are proposed to estimate the distribution of the time before AIDS when this rapid decline begins. Results using the EM Algorithm and Markov chain Monte Carlo indicate that the mean change point occurs approximately 1 year before diagnosis with a standard deviation of 9 months. Detection of a change point may indicate that an AIDS diagnosis is increasingly likely for an individual HIV-positive but AIDS-free.

1. Introduction
The natural history of acquired immunodeficiency virus (AIDS) begins when a person, seronegative for antibodies to human immunodeficiency virus (HIV), becomes infected. Usually less than 6 months after infection, the person seroconverts and becomes positive for antibodies to the virus (Melbye, Goedert, and Blattner, 1987). An individual remains seropositive and may eventually develop AIDS.

It is known that HIV selectively infects and destroys T4 cells, lymphocytes which play a central role in the human immune response (Dalglish, et al., 1984; Gallo, et al., 1984; Klatzmann, et al., 1984). Depletion of T4 cells is one of the immunological abnormalities found in infected people who have reached the end stage of AIDS (Detsky, et al., 1985; Goedert, et al., 1984; Gottlieb, et al., 1981).

The absolute number of T4 cells has been established as a significant predictor of disease progression, although other markers, such as the T8 count and the ratio of T4 to T8, have been considered (Fahy, et al., 1990; Goedert, et al., 1987). The following is a brief account of some longitudinal analyses of the T4 counts which tried to identify patterns in the progression from seroconversion to AIDS.

DeGruttola, Lange, and Dafni (1991) assumed that the decline of the square root of the T4 count was linear over time from seroconversion and estimated this rate using a random effects model on 201 HIV-infected men, who had not developed AIDS, from the San Francisco Men’s Health Study.

Key words: EM algorithm; Empirical Bayes; Hierarchical Bayes; Markov chain Monte Carlo.
A Bayesian Change-Point Problem with an Application to the Prediction and Detection of Ovulation in Women

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SUMMARY

Under the assumptions of independent normally distributed and sequentially observed responses, a Bayesian rule for detecting a change from a constant mean response is derived. It is known that both basal body temperature (BBT) and preovulatory estrogen values undergo such a change in mean value at some random time during the menstrual cycle. The Bayesian rule is applied to estrogen to predict ovulation and to BBT to detect ovulation. Data from an aggregate of women are used to obtain prior information about the change-points and the parameters that define the changes in estrogen and BBT. A method is proposed by which the accumulation of information for a specific woman can be incorporated into the aggregate prior information.

1. Introduction

The sequence of hormonal changes leading up to and following the occurrence of ovulation is the same for most normally menstruating women. Preovulatory plasma estrogen concentrations are characterized by relatively low constant levels followed by a gradual rise to a peak that occurs one to three days prior to ovulation. The rise in estrogen is thought to induce a mid-cycle surge of luteinizing hormone (LH) to a peak, with ovulation following this. Ovulation, in turn, is followed closely by a sharp rise in plasma progesterone. The jump in progesterone causes an increase in basal body temperature (BBT) to a higher level. Thus, the prediction and detection of ovulation can be accomplished by the detection of the change-points in estrogen and BBT, respectively. See Moghissi (1972).

Royston and Abrams (1980) recently proposed a method for detecting the change in BBT that employed the well-known CUSUM test. In the current paper we present sequential Bayesian solutions to the problems of detecting the changes in both estrogen and BBT.

Change-point problems of this type arise in many contexts and have attracted the attention of several authors. Hinley, for example, has examined a variety of such problems from a classical viewpoint; the two-phase regression problem was discussed and analyzed in Hinley (1969). Chernoff and Zacks (1964) appear to be the first to have applied a Bayesian approach to the change-point problem but they studied only the case of a shift in mean. Smith (1975, 1977) and Smith and Cook (1980) used Bayesian methods

Key words: Ovulation prediction; Ovulation detection; Change-point; Bayesian stopping rule; Updated prior information.
First Attempt


Linear Mixed Models for memory as a function of time, age.

Profile Likelihood to determine inflection point. (Try a range of inflection points and pick the best one!)
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 points. The method is applied to data from the Bronx Aging 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 assessed using the Dual-Task 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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expected SRT score vs. age

- Normal aging
- Preclinical dementia
Dementia Cases vs. Non-Demented Change Point

years before diagnosis

profile likelihood
Some problems

Misclassification of preclinical cases as non-cases results in biased estimates of rate of decline (and possibly change point).

First solution: Look only at cases.

Does everyone have the same change point?
Theoretical progression of a person developing Alzheimer's disease (AD)

Attempt to fit that model


- Confirmed cases only.
- Allowed for “random change point” using Bayesian model.
Bayesian and profile likelihood change point methods for modeling cognitive function over time

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Abstract

Change point models are often used to model longitudinal data. To estimate the change point, Bayesian (Bicentennial 52 (1975) 487; Appl. Statist. 41 (1992) 389; Biometrics 51 (1995) 216) or profile likelihood (Statist. Med. 19 (2000) 1555) methods may be used.

We compare and contrast the two methods in analyzing longitudinal cognitive data from the Bronx Aging Study. The Bayesian method has advantages over the profile likelihood method in that it does not require all subjects to have the same change point. Caution must be taken regarding sensitivity to choice of prior distribution, identifiability, and goodness of fit. Analyses show that decline in memory precede diagnosis of dementia by 7.5–8 years, and individual change points are not needed to model heterogeneity across subjects.

Keywords: Change point; Longitudinal data; Mixed models; Cognitive aging; Bayesian analysis; Markov chain Monte Carlo

1. Introduction

Dementia is characterized by accelerated cognitive decline before and after diagnosis as compared to normal aging. Determining the time at which rate of decline begins to
Theoretical progression of a person developing Alzheimer's disease (AD)

different from zero in any model, suggesting that any apparent effect of chronological age on memory performance is accounted for entirely by disease progression, given the strong decline in memory after the change point.

Fig. 4 shows the profile likelihood for the common change point in model MRₚ. The maximum likelihood estimate for the change point is $-7.6$; the approximate 95% confidence interval indicated by the profile likelihood graph is $(-9.0, -4.6)$ years.

Fig. 5 shows the (smoothed) marginal posterior for the change point from the reduced (common change point) model MRₕ. The similarities with Fig. 4 are obvious. For this model, the posterior mode is $-7.33$ with a 95% credible interval (highest posterior...
Surprise!

No heterogeneity in change point.

Lack of power?

Homogeneity in the cohort?
Rigorous statistical treatment of change points


Derived formal (frequentist) hypothesis tests.
Hypothesis testing of a change point during cognitive decline among Alzheimer’s disease patients

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Abstract. In this paper, we present a statistical hypothesis test for detecting a change point over the course of cognitive decline among Alzheimer’s disease patients. The model under the null hypothesis assumes a constant rate of cognitive decline over time and the model under the alternative hypothesis is a general bilinear model with an unknown change point. When the change point is unknown, however, the null distribution of the test statistic is not analytically tractable and has to be simulated by parametric bootstrapping. When the alternative hypothesis that a change point exists is accepted, we propose an estimate of its location based on the Akaike’s Information Criterion. We applied our method to a data set from the Neuropsychological Database Initiative by implementing our hypothesis testing method to analyze MMSE Status Exam scores based on a random slope and random intercept model with a bilinear time effect. Our results show that despite large amount of missing data, accelerated decline did occur for MMSE among AD patients. Our finding supports the clinical belief of the existence of a change point during cognitive decline among AD patients and suggests the use of change point models for the longitudinal modeling of cognitive decline in AD research.

Keywords: Alzheimer’s disease, cognitive decline, change point, mixed effects model, hypothesis testing

1. Introduction

1.1. Background

Although cognitive decline is common in human aging, previous research shows that the process of cognitive decline are different among normal aging people versus people who develop dementia. For those who develop dementia, it is believed that accelerated decline in cognitive function will occur at a certain time point during their course of cognitive decline [6]. A “change point” may be defined as the time when the baseline rate of cognitive decline accelerates and a more rapid rate of cognitive decline occurs. Because it is presumed that the acceleration in cognitive decline occurs before the diagnosis of dementia, it is of research interest to study whether and when it happens during the natural history of Alzheimer’s disease. Determining whether a change point exists is important for selecting more accurate models for the complete pattern of cognitive decline among different patient populations. More accurate models of cognitive decline are valuable for designing clinical trials in AD. If a change point does exist long before AD diagnosis, then the acceleration of its location is useful for early detection of the onset of AD.

Statistical models for longitudinal data are essential tools for modeling cognitive decline. General discussion of longitudinal modeling of the course of cognitive decline can be found in [3,15]. Applications of
Can look at natural history post-diagnosis

An examination of Bayesian statistical approaches to modeling change in cognitive decline in an Alzheimer’s disease population

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Abstract

The mini mental state examination (MMSE) is a common tool for measuring cognitive decline in Alzheimer’s Disease (AD) subjects. Subjects are usually observed for a specified period of time or until death to determine the trajectory of the decline which for the most part appears to be linear. However, it may be noted that the decline may not be modeled by a single linear model over a specified period of time. There may be a point called a change point where the rate or gradient of the decline may change depending on the length of time of observation. A Bayesian approach is used to model the trajectory and determine an appropriate posterior estimate of the change point as well as the predicted model of decline before and after the change point. Estimates of the appropriate parameters as well as their posterior credible regions or regions of interest are established. Coherent prior to posterior analysis using mainly non-informative priors for the parameters of interest is provided. This approach is applied to an existing AD database.

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Keywords: Alzheimer’s disease; Bayesian; Change point; Mini mental state; Trajectory

1. Introduction

Cognitive decline in Alzheimer’s disease (AD) is often measured by the mini mental state examination (MMSE). It is generally known that over time the performance on this exam declines in AD subjects. The MMSE or Folstein test is a 30-point questionnaire test that is used to assess cognition. It is commonly used in neurological settings to screen for dementia. In an administration time of about 10 min it samples various functions including arithmetic, memory and orientation. It was introduced by Folstein et al. [9] in 1975 and has been widely used with small modifications. A score over 27 out of 30 is considered normal. Below this threshold, 20–26 indicates mild dementia, and below 10 severe dementia. There may be slightly different interpretations of what the threshold values

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Variability can change, too!

A random change point model for assessing variability in repeated measures of cognitive function

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SUMMARY

Some cognitive functions undergo transitions in old age, which motivates the use of a change point model for the individual trajectory. The age when the change occurs varies between individuals and is treated as random. We illustrate the properties of a random change point model and use it for data from a Swedish study of change in cognitive function in old age. Variance estimates are obtained from Markov chain Monte Carlo simulation using Gibbs sampling. The random change point model is compared with models within the family of linear random effects models. The focus is on the ability to capture variability in measures of cognitive function. The models make different assumptions about the variance over the age span, and we demonstrate that the random change point model has the most reasonable structure. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS: change point model; cognitive function; variance estimation; Markov chain Monte Carlo; Gibbs sampling

1. INTRODUCTION

The development of cognitive function in old age is often nonlinear. Several studies have shown that some cognitive functions remain stable into old age, with more marked decline an indicator of impending death within a few years [1,2]. This phenomenon is referred to as terminal rise [3] and can potentially be captured by a random change point model incorporating the individual-specific
What about other domains?

Compare them to memory? Possibly different change points?


Two change points modeled simultaneously.
Estimation of bivariate measurements having different change points, with application to cognitive ageing

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SUMMARY

Longitudinal studies of ageing make repeated observations of multiple measurements on each subject. Change point models are often used to model longitudinal data. We demonstrate the use of Bayesian and profile likelihood methods to simultaneously estimate different change points in the longitudinal course of two different measurements of cognitive function in subjects in the Bronx Aging Study who developed Alzheimer’s disease (AD). Analyses show fast accelerated memory decline, as measured by BACS Selective Reminding, begins between seven and eight years before diagnosis of AD, while decline in performance on speeded tasks as measured by WAIS Performance IQ begins slightly more than two years before diagnosis, significantly after the decline in memory. Copyright © 2001 John Wiley & Sons, Ltd.

INTRODUCTION

In comparison with normal ageing, dementia is characterized by accelerated cognitive decline both before and after the time of diagnosis. Determining the onset, rate and domains of accelerated cognitive decline in persons who develop clinical dementia is important, both for describing the natural history of the disease and for identifying the treatment strategies for preventing diagnosable disease [1, 2]. In addition, the patterns of cognitive decline in different

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Confirm in another cohort

Baltimore Longitudinal Study of Aging.

Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer’s disease

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Abstract
In the Baltimore Longitudinal Study of Aging (BLSA), we examined the temporal unfolding of declining performance on tests of episodic memory (Free Recall on the Free and Cued Selective Reminding Test), executive function (Category Fluency, Letter Fluency, and Trails), and Verbal Intelligence (Nelson, 1982; American Version of the Halec Adult Reading Test (AMNART)) before the diagnosis of dementia in 12 subjects with incident Alzheimer’s disease (AD) followed for up to 13 years before diagnosis. To examine the preclinical onset of cognitive decline, we excluded subjects at the time of initial AD diagnosis. In examining the preclinical onset of cognitive decline, we divided subjects into the time of initial AD diagnosis and examined the cognitive course preceding diagnosis. We found that decline in performance on tests of episodic memory accelerated 7 years before diagnosis. Declining performance on tests of executive function accelerated 2–3 years before diagnosis, and verbal intelligence declined in close proximity to diagnosis. This cognitive profile is compatible with pathologic data suggesting that structures which mediate memory are affected earlier than frontal structures during the preclinical onset of AD. It also supports the view that VIQ as estimated by the AMNART does not decline during the preclinical onset of AD. (JNN, 2008, 14: 266–278)

Keywords: Alzheimer’s disease, Prospective studies, Preclinical dementia, Cognition disorders, Memory disorders, Verbal learning

INTRODUCTION
Numerous studies have demonstrated that patients who develop Alzheimer’s disease (AD) experience elevated rates of cognitive decline for many years before diagnosis. Although memory decline has been a focus (Ellis et al., 2006; Grober et al., 2006; Kawas et al., 2003; Linn et al., 1995; Rebuck et al., 1998), other domains of cognition also show rapid decline in comparison to those who do not develop AD (Buckman et al., 2004). Defining the nature and timing of cognitive changes in AD is important for several reasons. Understanding this natural history will help define prediction models and identify candidates for preventive intervention. Clarity about natural history may improve the measurement of cognitive changes in the context of prevention trials. Understanding the sequential unfolding of cognitive deficits will help inform the optimal combination of neuropsychological and radiographic measures to predict onset and will improve the correlation with AD pathology, which unfolds in a relatively orderly manner in the brain (Brack & Brack, 1991). The usual approach to predicting AD involves assembling a cohort of individuals without diagnosable dementia and following them over time. Factors that predict dementia onset within specific time periods are used to identify high-risk groups. The most widely used approach is to identify individuals with memory impairment who do not meet criteria for dementia (Albert et al., 2001; Larson et al., 2002;
### Clear Differences Across Domains

<table>
<thead>
<tr>
<th>Task</th>
<th>change point</th>
<th>rate of decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free Recall 1</td>
<td>7.1 (5, ∞)</td>
<td>0.00 (NA, NA)</td>
</tr>
<tr>
<td>Free Recall 2</td>
<td>2.6 (1.2, ∞)</td>
<td>1.48 (0.97, 1.98)</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>3.0 (1.7, 5.0)</td>
<td>1.97 (1.50, 2.45)</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>2.5 (1.5, 4.9)</td>
<td>0.91 (2.30, 1.33)</td>
</tr>
<tr>
<td>Trailmaking Speed</td>
<td>2.9 (1.1, 8.3)</td>
<td>1.90 (1.07, 2.73)</td>
</tr>
<tr>
<td>VIQ est. from AMNART</td>
<td>0.4 (-0.1, 1.1)</td>
<td>0.28 (-0.01, 0.58)</td>
</tr>
</tbody>
</table>
More recent work


- Change points much closer to time of dx.
- Speculation as to why (different cohort, different diagnostic criteria, different instruments….)
Longitudinal Study of the Transition From Healthy Aging to Alzheimer Disease

David K. Johnson, PhD; Marthe Storandt, PhD; John C. Morris, MD; James E. Galvin, MD, MHH

Background: Detection of the earliest cognitive changes signaling Alzheimer disease is difficult.

Objectives: To model the cognitive decline in preclinical Alzheimer disease.

Design: Longitudinal archival study comparing individuals who became demented during follow-up and people who remained nondemented on each of 4 cognitive facets: global, verbal memory, visuospatial, and working memory.

Setting: Alzheimer Disease Research Center, Washington University School of Medicine, St. Louis, Missouri.

Participants: One hundred thirty-four individuals who became demented during follow-up and 310 who remained nondemented.

Main Outcome Measures: Infection point in longitudinal cognitive performance.

Results: The best-fitting model for each of the 4 factors in the stable group was linear, with a very slight downward trend on all but the Visuospatial factor. In contrast, a piecewise model with accelerated slope after a sharp inflection point provided the best fit for the group that progressed. The optimal inflection point for all 4 factors was prior to diagnosis of dementia. Global, 2 years; Verbal and Working Memory, 1 year; and Visuospatial, 3 years. These results were also obtained when data were limited to the subjects (n = 44) with autopsy-confirmed Alzheimer disease.

Conclusions: There is a sharp inflection point followed by accelerating decline in multiple domains of cognition, not just memory, in the preclinical period in Alzheimer disease when there is insufficient cognitive decline to warrant clinical diagnosis using conventional criteria. Early change was seen in tests of Visuospatial ability, most of which were speeded. Research into early detection of cognitive disorders using only episodic memory tasks may not be sensitive to all of the early manifestations of disease.

Arch Neurol. 2009;66(10):1294-1299
Longitudinal course of the stable, progressed, and autopsy-confirmed Alzheimer disease (AD) groups before and after diagnosis of AD (DX) on Global factor (A), the Verbal Memory factor (B), the Visuospatial factor (C), and the Working Memory factor (D)

MCI as the outcome


Logical Memory inflection point *later* than for animal fluency or block design.

Test? MCI definition? (Used 2 consecutive CDR 0.5’s.)
Trajectory of mild cognitive impairment onset

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Abstract

The objective was to identify the trajectories of onset of memory and other cognitive loss in persons destined to develop mild cognitive impairment (MCI) or dementia. Healthy, community dwelling, cognitively intact elders (n = 156, mean age at entry = 82 years) were examined annually for an average of greater than 7 years. Those who developed at least two consecutive Clinical Dementia Rating ≤ 0.5 were classified as having MCI. Longitudinal mixed effects models with a change point were used to model the aging process in those with and without an MCI diagnosis during follow-up and to model the rate of change relative to the age of onset of MCI. MCI had a preclinical stage of accelerated cognitive loss that was observed 3 to 4 years before the diagnosis of MCI or tests of verbal memory, animal fluency, and visuospatial construction. Evidence from memory performance before the change point suggests that a slow decline in memory precedes the period of accelerated decline in the development of MCI. Aging reactions leading to MCI and dementia are characterized by unique linear and nonlinear cognitive changes in several domains that precede the diagnosis of MCI and dementia by at least several years. (JNNS, 2008, 14, 192–198.)

Keywords: Dementia, Alzheimer disease, Aging, Aged 80 and over, Episodic memory, Longitudinal studies

INTRODUCTION

Alzheimer disease (AD) has an insidious onset that goes unrecognized in the earliest stages. Mild cognitive impairment (MCI) often represents an early transition stage between normal functioning and dementia and occurs to cognitive impairment greater than expected for age but without meeting criteria for a dementia diagnosis (Winblad et al., 2004). MCI would be expected to have an insidious onset as well. The purpose of this project was to understand how the trajectories of performance on cognitive tests in those who develop MCI differ from those who maintain cognitive function.

Longitudinal studies of predementia and MCI have reported changes in cognitive domains before the onset of AD and the usefulness of these changes in predicting dementia (Tunstall et al., 2006). Study procedures have varied, including the length of follow-up before dementia diagnosis and statistical analyses. In general, these studies have not been able to systematically address when the changes occur in the development of MCI and have not addressed when a subject destined to develop MCI starts to diverge from the normal aging trajectory.

One of the earliest areas of cognitive decline in MCI is commonly thought to precede dementia is impairment in learning and retaining new information (Albert et al., 2007; Bondi et al., 1999; Petersen et al., 1999). This state is termed amnestic MCI (Winblad et al., 2004) when other nonmemory cognitive functions are essentially preserved, although mild decline may be observed in these other areas (Devanand et al., 1997; Grandin et al., 2004; Tummler et al., 2006). In their study, Devanand and colleagues found that low scores on delayed recall, category naming for animals, and the Wechsler Adult Intelligence Scale–Revised (WAIS-R; Wechsler, 1981) Digit Symbol, Picture Arrangement, and Block Design subtests were predictive of diagnosis of dementia 2 to 5 years later.

This study provides a comprehensive look at several cognitive domains change in normal elderly before developing MCI and how the change differs from normal aging.
Brain size and MCI


Difference in initial rates of change in ventricular volume, which accelerated prior to MCI diagnosis.
Trajectories of brain loss in aging and the development of cognitive impairment

ABSTRACT

Background: The use of volumetric MRI as a biomarker for assessing transitions to dementia presumes that more rapid brain loss marks the clinical transition from benign aging to mild cognitive impairment (MCI). The trajectory of this volume loss relative to the timing of the clinical transition to dementia has not been established.

Methods: The authors annually evaluated 79 healthy elderly subjects for up to 15 consecutive years with standardized clinical examinations and volumetric brain MRI assessments of ventricular volume. During the study period, 37 subjects developed MCI. A mixed effects model with a change point modeled the pattern of brain volume loss in healthy aging compared with subjects diagnosed with MCI.

Results: The brain loss trajectory of subjects developing MCI during follow-up differed from healthy aging in a two-phase process. First, the annual rate of expansion of ventricular volume decreased with age; however, the annual rates of expansion were greater in those who developed cognitive impairment during follow-up compared with those who did not. Further, subjects who developed MCI had an acceleration of ventricular volume expansion approximately 2.3 years prior to clinical diagnosis of MCI.

Conclusions: Ventricular expansion is faster in those developing mild cognitive impairment years prior to clinical symptoms, and eventually a more rapid expansion occurs approximately 24 months prior to the emergence of clinical symptoms. These differential rates of preclinical atrophy suggest that there are specific windows for optimal timing of intervention of dementia prevention therapies in the future. Neurology® 2006;66:828–833

GLOSSARY

AD = Alzheimer disease; BMI = body mass index; CDR = Clinical Dementia Rating Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.

Healthy brain aging is conventionally conceived of as a slow, selective loss of neuronal elements and associated brain parenchyma in contrast to Alzheimer disease (AD) where there is a more severe loss of neurons as well as an accumulation of characteristic lesions defining the disease.1 However, the contrast between normative aging and AD is not sharp, with most contemporary models encompassing a continuum of pathologic change. Characteristic AD neuropathology found at autopsy has been associated ante mortem with both rates of cognitive decline3 and rates of brain volume loss assessed with MRI4 in healthy aging and in those developing mild cognitive impairment (MCI) or dementia. Thus, brain volume loss may be used as an index of the degree to which one might predict the development of more benign aging change or MCI leading to dementia.2,5

Up until now, the use of MRI as a surrogate marker tracking preclinical transitions to dementia has been limited to a few studies of longitudinal samples with limited numbers of subjects. The authors thank Dr. Paul Robinson for assistance with collecting data and for providing critical comments improving the present report.

1. The authors report no conflicts of interest.

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Figure 14

2.3 yrs (95% CI: 0.3, 5.6 yrs) prior to diagnosis, trajectory further accelerates 2.3% annually, \( p = 0.0023 \)

Annual rates of change differ between cognitively intact and those destined to develop MCI, \( p = 0.081 \)

Age at diagnosis: 89.6 yrs

Carlson, N. E. et al. Neurology 2008;70:828-833
Decline in cognition prior to mortality


Used a global measure of cognition and showed that cognitive loss accelerates about 4 years prior to death. (Two cohorts.)
Terminal decline in cognitive function

R.S. Wilson, Ph.D; A.A. Beckett, Ph.D; J.L. Bienias, Sc.D; D.A. Evans, MD; and D.A. Bennett, MD

Abstract—Background: Impending death is thought to be associated with age-related cognitive decline, but this association has not been well studied. Methods: Participants were 703 older Roman Catholic nuns, priests, and brothers without dementia at baseline. They completed an average of 5.6 annual evaluations (range 2 to 9), with 85% follow-up participation in survivors. Each evaluation included administration of 19 cognitive function tests (sets from previously established measures of global cognition (mean = 0.13, SD = 0.50) and specific cognitive functions were derived. In a series of change point random effects models, the average age of death when rate of cognitive decline changed was identified, and rates of cognitive decline before and after the optimal change point were estimated, controlling for the effects of age, sex, and education. Results: There were 122 deaths during the observation period. Those who died had lower global cognitive function at baseline than survivors (by 0.103 unit, p < 0.001), and beginning about 41 months before death, their annual rate of global cognitive decline sharply accelerated from an annual loss of 0.026 to 0.172 units, a more than 7-fold increase. Results were comparable in analyses that controlled for baseline health and disability. Terminal cognitive decline was evident in nearly all of those who died, but at highly variable rates. Remarkably little cognitive decline was evident in survivors. Decline in episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability also greatly increased about 3 to 6 years prior to death. Conclusion: On average, cognitive decline sharply accelerated in the last years of life.

NEUROLOGY 1999 52 1700-1707

Less of cognitive function is among the most common and feared problems of older persons. Age-related cognitive decline is highly variable, however, with little or no decline in many persons and slight to precipitous decline in others. Understanding the basis of this heterogeneity is a matter of substantial public health importance, therefore. Prospective studies have identified a number of environmental and genetic factors that predict change in cognition (e.g., age, education, cognitive activities, depressive symptoms, vitamin E, APOE allele status). Another factor thought to be related to cognitive decline is impending death. According to a longstanding hypothesis, cognitive underlies a period of terminal decline in the last years of life, and this terminal cognitive decline substantially contributes to age-related loss of cognitive ability. The hypothesis has been difficult to investigate, however, because it requires multiple observations of cognitive function over a several year period on persons with a wide spectrum of cognitive ability who did and did not die during the observation period. As a result, knowledge about the existence and extent of terminal cognitive decline has remained limited.

We investigated the relation of mortality to change in cognitive function in old age using data from the Religious Orders Study, an ongoing longitudinal clinical-pathologic study of aging and AD in older Roman Catholic clergy members. Participants were free of clinical evidence of dementia at baseline. For up to 8 years, they underwent annual evaluations that included detailed cognitive function testing, with follow-up participation exceeding 85% in survivors. Random effects models allowing for a change point in rate of decline were used to determine whether cognitive decline accelerated prior to death and to estimate the extent and duration of the effect. Measures of specific cognitive functions were examined in subsequent analyses.

Methods. Subjects. Subjects are older Catholic nuns, priests, and brothers who were recruited from about 40 groups across the USA. They agreed to annual clinical evaluations and to brain donation at the time of death. The study was approved by the Institutional Review Board of Rush-Presbyterian-St. Luke's Medical Center.

At baseline and annually thereafter, each person had a uniform structure clinical evaluation that has been previously described. A total of 72 people met criteria for dementia at baseline, and they are excluded from analyses. Of the remaining 890 people, 34 died before the first follow-up evaluation and 28 had not yet reached the data of their first follow-up. This left 782 persons eligible for follow-up. 709 (77.1%) had at least two valid global cognitive function scores (see below), and analyses are based on this group. They completed an average of 5.6 annual evaluations.
Figure 2. Predicted 8-year paths of global cognitive decline in two typical participants: one who survived (solid line) and one who died after 8 years (dotted line)

Wilson, R. S. et al. Neurology 2003;60:1782-1787
Terminal Cognitive Decline: Accelerated Loss of Cognition in the Last Years of Life

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Objective: To test the hypothesis that rate of cognitive decline accelerates in the last years of life. Methods: Participants are 853 older persons without dementia at study onset. For up to 8 years, they underwent annual clinical evaluations that included a battery of 19 cognitive tests from which previously established composite measures of global cognition and specific cognitive domains were derived. In analyses, we used linear mixed-effects models to allow rate of cognitive decline to change at a given point before death to estimate the onset of a terminal decline period and rate of cognitive decline before and after that point. In subsequent analyses, we tested potential meddles of terminal decline. Results: There were 115 deaths. Those who died did not differ from survivors in their level of global cognitive function at study onset, but beginning a mean of 42 months before death, their rate of global cognitive decline sharply increased. The duration and cuedness of terminal decline in global cognition differed from person to person. Terminal cognitive decline was not modified by age, sex, education, or the presence of mild cognitive impairment, but it was present in those with vascular disease (e.g., strokes and heart attack) or in those without at least one copy of the apolipoprotein E ε4 allele, suggesting that Alzheimer’s disease pathology may contribute to the phenomenon. Conclusion: In old age, cognitive decline markedly accelerates during the last 3 to 4 years of life, consistent with the terminal decline hypothesis. Why might mortality, longitudinal studies, cognitive function, terminal decline, apolipoprotein E.

INTRODUCTION

A longstanding question in cognitive aging research is whether cognitive function precipitously declines at some point before death. The hypothesis was proposed more than 40 years ago by Ehrlich, who suggested that factors related to death may cause cognitive decline beginning several years before death (1). Kister and others could not be more specific because his hypothesis was based on longitudinal observations of only 13 people who only 3 died. Although many longitudinal studies have subsequently tried to identify terminal cognitive decline, the results have been mixed, with a recent review questioning the existence of the concept (2). The main problem is that these studies were not designed to investigate terminal decline and, in varying degrees, the ingredients needed to test it: multiple closely spaced assessments of cognition (to capture nonlinear change) over a several-year period in a group of older persons of varying cognitive ability with some deaths during the observation period. One previous study meeting these criteria found evidence of a sharp acceleration in global cognitive decline beginning in the last 3 to 4 years of life (3). Participants were highly selected (Cognitive diagnostic; generally, however, the generalizability of the results turns out to be demonstrated.

In the present study, we investigated the terminal decline hypothesis with data from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study of risk factors for common chronic conditions of old age. Community-dwelling older persons without dementia at baseline had annual cognitive function testing for up to 8 years. We constructed a series of linear mixed-effects models to test if cognitive decline tended to accelerate at some point before death and to examine factors that might modify terminal cognitive decline.

METHODS

Participants

Subjects are from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study of risk factors for common chronic conditions of old age (4). The study began in 1997, expanded in 2001, and is continuing. The subjects were recruited from continuous care retirement communities, assisted living facilities, and social service agencies in the Chicago area. As each site, a presentation about the project ensured the public health burden posed by dementia patients and for the clinical-pathologic research to better understand its neurobiologic bases and help reduce the burden for future generations. After the presentation, persons expressed their level of interest in participation. Interested persons were later contacted by project staff who explained the study in detail, answered questions, and obtained informed consent. The study was approved by the Institutional Review Board of Rush University Medical Center.

At enrollment, each participant completed a uniform clinical evaluation that was repeated annually thereafter. The evaluation included a medical history, complete neurologic examination, and detailed testing of cognitive function. On the basis of this evaluation and an in-person examination of the participant, his or her medical diagnosis in dementia using the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (5), which requires a decline of cognitive function and impairment in at least two cognitive domains (6).

At the time of these analyses, 1088 people had completed the baseline clinical evaluation. We excluded those who did not meet the dementia criteria at baseline. Of the remaining 1080 individuals, 38 died before the first annual follow-up evaluation and 15 had been enrolled for <1 year. This left 909 people eligible for follow-up, and 855 (94.0%) completed at least one full follow-up evaluation (6-9 completed evaluations per individual). Analyses are based on this group. They had a mean age at baseline of 80.4 years (SD = 6.3), a mean of 14.2 years of schooling (SD = 3.1), and a mean baseline score of 27.8 (SD = 5.1) on the Mini-Mental State Examination. 14.8% were women, 51.6% were white and non-Hispanic, and 27.6% had mild cognitive impairment defined as having impaired cognition on testing but not meeting the criteria for dementia, as applied in this (7) and other (8) cohorts.

Assessment of Cognitive Function

A set of 21 cognitive tests was administered at each annual evaluation in an approximately 1-hour session. The Mini-Mental State Examination was...
Episodic memory decline prior to death?


Change point in memory over *eight* years prior to death in Bronx Aging Study.
Distinguishing Preterminal and Terminal Cognitive Decline

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Abstract. This paper reviews different methodological approaches taken to examine terminal decline in cognitive function, and presents new findings from the Bronx Aging Study (BAS). Numerous approaches have been taken to assess mortality effects on cognition, comparing survivors and non-survivors and identifying differences in cognition associated with time-to-death. However, few studies have actually modeled within-person change in cognition as a function of time-to-death. Using linear mixed models with a change point, intrapersonal change in specific memory was modeled as a function of both age and time-to-death. A dramatic increase in the rate of decline was detected at 8.4 years prior to death, providing clear evidence of a terminal-decline phase that is much longer than previously estimated. These results emphasize the importance of modeling the time course and effects of terminal cognitive decline for understanding cognitive change in aging adults.

Keywords: cognitive decline, mortality, terminal decline, dementia

Researchers who study both aging and cognition have shown a persistent interest in the phenomenon of terminal decline, or “sudden drop in performance occurring within 5 years prior to death” (Riegel & Riegel, 1972, p. 396). Studies on the relationship between cognition and mortality, however, have taken a much broader approach than the focus on abrupt decline that was emphasized by Riegel and Riegel. For example, some (e.g., Haxton, Small, von Strauss, Panagiotakos, & Bickman, 2003) have focused on terminal decline as one of understanding why “poor cognitive performance among elderly individuals is associated with impending death” (p. 285). Still others have been interested in how cognitive status can predict long-term mortality (Deary & Der, 2009). The purpose of this paper is to examine why terminal decline is important for cognitive aging research, and how this phenomenon has been, and should be examined. We illustrate how to model the time course of terminal decline and to distinguish between age-graded and mortality-related cognitive change.

Why is Terminal Decline Interesting?

Batters and Neugarten (1976) identified this primary objective of developmental research as the direct identification of intrapersonal change and its causes. Critical to this objective is the distinction between age-graded normative and nonnormative influences that can drive intrapersonal change. Normative age-graded influences refer to those processes that apply to all or most individuals and that are well measured by chronological age. In contrast, nonnormative influences do not operate in all or even most individuals and are not tightly coupled with chronological age. Terminal-decline effects do not fall neatly into either of these categories. The fact that everyone dies makes these effects normative. However, these effects are not necessarily age-graded because time from birth (i.e., chronological age) does not provide an adequate index of time-to-death. Kessler (1962) first noted that factors related to mortality may cause intellectual decline that might otherwise be inconsequential as age-related effects. Some (e.g., Horn, Veitch, & Juel, 1992; Juel, Horn, Veitch, Bohman, & Rayens van Brun, 1993) have even suggested that mortality effects may account for the Kier’s share of cognitive decline in aging adults. Others have made more modest claims that at least some portion of observed age differences in cognition may be attributable to mortality effects (Brown & Schaie, 1990; Howarth, Schaie, Willis, & Siegler, 1999). Thus, one reason why understanding terminal decline is important is that it could reflect the effects of progressive pathologic processes that are distinct from the effects of other normative age-graded processes.

Another difference is that understanding the relationship between cognition and mortality is important comes from work that examines how intellectual status predicts mortality (Deary & Der, 2005; Deary, Whiteman, Steeple, Whitall, & Fox, 2004; Snowdon et al., 1996; Whal...
Figure 2. Predicted mean memory score and 95% confidence intervals for an individual who was tested annually from age 77 to 91 and who died 6 months after their last assessment. Sliwinski et al *European Psychologist*, 2006.
Figure 1. Profile likelihood values for change point as a function of years before death. The Y-axis shows the normalized profile likelihood values corresponding to models with varying values for change points. The model with the highest likelihood value (corresponding to 8.4 years) is selected as the best fitting model. The dashed horizontal line shows the critical value for the 95% confidence interval for the change points. All change points with likelihood values falling above the line fall within the 95% interval.
Decline in cognition in different domains prior to mortality


- Multiple domains (Wilson used global measure)
- Different change points depending on domain
Onset of terminal decline in cognitive abilities in individuals without dementia

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ABSTRACT

Objective: To identify time of onset and rate of mortality-related change (terminal decline) in cognitive abilities in later life.

Methods: The sample consisted of 288 individuals without dementia born 1901–1909 drawn from the population of Göteborg, Sweden. Participants were followed from age 70 until death, with up to 12 measurement occasions on three cognitive abilities. Change-point analysis was performed using an automated piecewise linear mixed modeling approach to identify the inflection point indicating accelerated within-person change related to mortality. A profile likelihood method was used to identify the change-point that best fit the data for each of three cognitive abilities.

Results: Onset of terminal decline was identified 8.8 years prior to death for verbal ability, 7.8 years for spatial ability, and 14.8 years for perceptual speed.

Conclusions: There is substantial acceleration in cognitive decline many years prior to death among individuals without dementia. Time of onset and rate of terminal decline vary considerably across cognitive abilities. Neurology 2008;71:382–387.

Terminal decline in cognition refers to acceleration in within-person change prior to death and is distinct from, but possibly moderated by, aging-related changes. Several studies have demonstrated terminal decline by comparing survivors and nonsurvivors but relatively few longitudinal studies have identified terminal decline at the level of the individual with complete information about age at death in a population-based representative sample. Little is therefore known about time of onset of terminal decline, rate of change, and whether terminal decline rates across cognitive abilities.

We are aware of two studies that have identified terminal decline as accelerated in within-person change before death and relative to prior within-person age-related change. One study reported a terminal decline period ranging from 2.75 years to 6 years before death on various cognitive abilities based on data from a sample of Roman Catholic nuns, priests, and brothers. Another study reported a longer terminal decline period ranging over 6.4 years in a measure of episodic memory based on data from a sample of community-based North Americans. Explanations for the discrepancy between these findings in terms of the length, and magnitude, of the terminal decline phase is somewhat unclear but is likely related to different sample compositions, testing instruments, and design (i.e., differences in length of the follow-ups).

Deznelia, including its prodromal phase, has been shown in longitudinal studies to be a major contributor for age-related heterogeneity in cognitive change. Most studies of terminal decline in dementia have failed to identify the terminal stage and thus may have been unable to detect DEZNELIA.

Supplemental data at www.neurology.org

Editorial, page 674

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Figure 45">
Decline in life satisfaction prior to mortality


- Life satisfaction decline accelerates 4 years prior to death.
Decline in Life Satisfaction in Old Age: Longitudinal Evidence for Links to Distance-to-Death

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Using 12-year longitudinal data from deceased participants of the Berlin Aging Study (324, age 70-102 years, at baseline; 46-87 years, FID 811), the authors examined whether and how old and very old individuals exhibit terminal decline in reported life satisfaction at the end of life (4). To age-related decline, mortality-related decline (i.e., distance-to-death) accounted for more variance in cross-sectional differences in life satisfaction and explained steeper rates of decline. By a factor of 2. By applying change-point growth models, the authors identified a point about 1 year before death, at which decline showed a two-fold increase in steepness relative to the potential phase. For the oldest 10% (82 years), a thinned rate was observed. Established mortality predictors including sex, comorbidities, dementia and cognition, accounted for only small portions of interindividual differences in mortality-related changes in life satisfaction. The authors conclude that life changes in neuropsychological well-being are related to mechanisms leading to death and suggest routes for further inquiry.

Keywords: selective mortality, terminal decline, successful aging, psycho-social factors, wellbeing

In the lifespan and gerontological literature, it has been proposed that trajectories of psychological change at the end of life reflect a combination of age-related, mortality-related, and pathology-related processes (Baltes, 1997; Birren, 1990; Birren & Poon, 1985). Few longitudinal studies in which researchers have examined such proposals have been focused primarily on questions about the existence of terminal decline in cognitive abilities (i.e., pronounced late-life deterioration as a function of distance-to-death; e.g., Bickman & MacDonald, 2006; Roese & Singler, 2002; Streibach, Hoffs, Hali, Bruns, & Lippel, 2005; Small & Bickman, 1999). In the present study, longitudinal data is used to compare models of age-related and mortality-related change in subjective well-being. This is of interest because in cross-sectional research age has typically not been associated with individuals' reported levels of well-being (e.g., Diener, Lucas, & Scollon, 2006), whereas mortality has been associated with reduced well-being (e.g., Dannefer, Snowdon, & Friesen, 2001; Levy, Skale, & Kunkel, 2002; Mather & Smith, 1999). Specifically, using 12-year longitudinal data from deceased participants of the Berlin Aging Study (BASE; Böhm & Mayer, 1999; N = 464; M = 87 years and T = 8.1 years at initial assessment, Time 1 = T1), we (a) contrast age-related and mortality-related trajectories of life satisfaction, a key component of well-being; (b) examine whether, indicators of terminal decline, decline in life satisfaction is more pronounced in a time interval closer to death versus further from death; and (c) explore covariates that may mediate interindividual differences in the observed terminal changes in life satisfaction.

The researchers examined such proposals have been focused primarily on questions about the existence of terminal decline in cognitive abilities (i.e., pronounced late-life deterioration as a function of distance-to-death; e.g., Bickman & MacDonald, 2006; Roese & Singler, 2002; Streibach, Hoffs, Hali, Bruns, & Lippel, 2005; Small & Bickman, 1999). In the present study, longitudinal data is used to compare models of age-related and mortality-related change in subjective well-being. This is of interest because in cross-sectional research age has typically not been associated with individuals' reported levels of well-being (e.g., Diener, Lucas, & Scollon, 2006), whereas mortality has been associated with reduced well-being (e.g., Dannefer, Snowdon, & Friesen, 2001; Levy, Skale, & Kunkel, 2002; Mather & Smith, 1999). Specifically, using 12-year longitudinal data from deceased participants of the Berlin Aging Study (BASE; Böhm & Mayer, 1999; N = 464; M = 87 years and T = 8.1 years at initial assessment, Time 1 = T1), we (a) contrast age-related and mortality-related trajectories of life satisfaction, a key component of well-being; (b) examine whether, indicators of terminal decline, decline in life satisfaction is more pronounced in a time interval closer to death versus further from death; and (c) explore covariates that may mediate interindividual differences in the observed terminal changes in life satisfaction.

Starting with seminal work in the 1960s and 1970s (Kohnstamm, 1952; Pahlson & Cheadle, 1979; Bengt & Ringsl, 1972; Singler, 1976), a substantial body of evidence has accumulated showing that low levels of, or pronounced decline on, cognitive abilities including perceptual motor speed, memory, executive functioning, and crystallized abilities are related to terminal tasks (Roese & Schlen, 1999; Gilhula, McCaul, & Lindenberger, 2006; Jo-
Change points in incidence!

- Nonlinear trends not just in time but in risk factors.
- Allows better description of “U” or “V” shaped exposure-response relationships.
Two examples from WHAS I


DHEAS Levels and Mortality in Disabled Older Women: The Women’s Health and Aging Study I

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Background. Dehydroepiandrosterone sulfate (DHEAS) is an endogenously produced sex steroid that has been hypothesized to have anti-aging effects. Low DHEAS levels are associated with mortality in older men, but the relationship between DHEAS levels and mortality in women is not clearly defined.

Methods. The relationship between serum DHEAS level and 5-year mortality was analyzed in a cohort of 3,398 disabled women aged 65–100 years enrolled in the Women’s Health and Aging Study I (WHAS I). Using Cox proportional hazards models, we calculated multivariate-adjusted mortality risks by DHEAS quartiles and by DHEAS continuously, allowing for a nonlinear relationship. We also examined cross-specific mortality.

Results. We found a U-shaped relationship between DHEAS level and mortality. After adjusting for multiple covariates, women in the top and bottom DHEAS quartiles had a more than 2-fold higher 5-year mortality than did those in the middle quartile (hazard ratio, 2.11; 95% confidence interval [CI], 1.18–3.83 for the top quartile and 2.05; 95% CI, 1.27–3.34 for the bottom quartile, each compared to the middle quartile). Women with higher DHEAS levels tended to have greater cancer mortality, whereas those with lower DHEAS levels tended to have greater cardiovascular mortality.

Conclusion. Disabled older women with either low or high levels of DHEAS are at greater risk for death than those with intermediate levels. More research is needed to determine if targeted dehydroepiandrosterone supplementation would provide clinical benefit to disabled older women.

DHEA and DHEAS (dehydroepiandrosterone) are the major sex steroids produced by the adrenal gland. As more than 99% of all DHEA is sulfated to DHEAS before secretion from the adrenal gland, DHEAS represents the major circulatory form of DHEA, with a long plasma half-life and little diurnal variation (1). DHEAS is the most abundant sex steroid, with concentrations more than 100-fold higher than any other sex steroid (2). DHEAS is thought to act principally as a prohormone via extra- and intracellular conversion to biologically active androgens and estrogens (2,3). Because of the widespread distribution of estrogen and androgen receptors, tissue-level conversion of DHEAS has the potential for pervasive systemic effects (4). Furthermore, due to differences in the underlying sex steroid androgenic profile, sex-specific effects may arise from DHEAS conversion (2,5).

Circulating DHEAS levels decline significantly with age, resulting in mean levels at age 65 that are less than one fifth of mean levels at age 20 (6,7). The implications of age-associated DHEAS decline and differences in DHEAS levels between older individuals are poorly understood. Low DHEAS has been associated with increased all-cause and cardiovascular mortality in older men (8–11). The relationship between DHEAS and mortality is not clearly defined in healthy women, and not defined at all in disabled women (8,10–14), however.

Understanding the role of endogenous DHEAS is critical to understanding the biology of aging, potentially preventable outcomes such as frailty or premature mortality, and whether there are appropriate targets for DHEAS supplementation. Although mean DHEAS levels are low in old age, DHEAS levels vary widely in both sexes (5,15). Despite insufficient data to support DHEAS therapy in older age (16), the Dietary Supplement Health and Education Act of 1994 allows its over-the-counter purchase (17), and many older individuals take DHEA supplements, regardless of their DHEAS levels.

We sought to examine the relationship between underlying DHEAS levels and mortality in a large population-based sample of disabled older women. Due to evidence suggesting adverse effects in women from either high or low DHEAS levels (18–20), we hypothesized a nonlinear relationship between DHEAS and mortality, and a cause-specific mortality difference between those women with low and those with high DHEAS levels.

Methods
Participants
The Women’s Health and Aging Study I (WHAS I) is a study of the causes and course of disability among women.
What Constitutes Normal Hemoglobin Concentration in Community-Dwelling Disabled Older Women?

Paulo H. M. Chaves, MD, PhD,* Qian-Li Xue, PhD,* Jack M. Guralnik, MD, PhD,† Luigi Ferrucci, MD, PhD,‡ Stefano Volpato, MD, MPH,* and Linda P. Fried, MD, MPH**

OBJECTIVES: To examine the associations between hemoglobin (Hb) concentration and (1) 5-year all-cause mortality and (2) serum erythropoietin (EPO), as the basis for the identification of data-driven thresholds, and to assess the clinical relevance of mildly low Hb.

DESIGN: Prospective study.


METHODS: Proportional hazards regression was used to model the relationship between baseline Hb (available for 686 subjects) and time to death. A generalized linear model was used to assess the cross-sectional association between Hb and EPO in 641 subjects.

RESULTS: A curvilinear slope of steady mortality decrease up to the Hb threshold of 13.5 g/dL was observed. Hb of 11 g/dL was independently associated with greater mortality than the World Health Organization (WHO) low-normal cutoff of Hb of 12 g/dL (hazard ratio = 1.2, 95% confidence interval = 1.1–1.4), whereas Hb of 14 g/dL was linked to 24% lower mortality (HR = 0.76, 95% CI = 0.63–0.92), after comprehensive adjustment for major health status and disease-burden indicators. A curvilinear, statistically significant slope of steady EPO decrease with increasing Hb up to the threshold of 14.3 g/dL was consistently observed.

CONCLUSION: The seemingly lower mortality risk with higher Hb levels provides empirical evidence against the notion that Hb currently perceived as mildly low is clinically benign. Furthermore, the mortality risk gradient observed even within the WHO normal Hb range suggests that Hb levels higher than what is currently recommended might offer clinical advantage. The relationship between Hb and EPO provided supporting physiological evidence for this hypothesis. J Am Geriatr Soc 52:1311–1316, 2004.

Key words: anemia, hemoglobin, erythropoietin, frail elderly, mortality.
Heterogeneous disease processes

• Change point might depend on many factors, some of which are measurable.
• Early work did not find significant overall heterogeneity – possibly from lack of power.
• Model change point as function of measured risk factor
Theoretical model for cognitive reserve

- Greater neuronal capacity, or greater compensational ability, can mitigate the effects of developing dementia pathology.
- Accelerated cognitive decline should begin later in persons with greater reserve.
- Decline should be more rapid once it accelerates in persons with greater reserve.
Figure 3. Theoretical model to explain the observation of more rapid progression in patients with higher educational or occupational attainment

Two tests in Bronx Aging Study


Education delays accelerated decline on a memory test in persons who develop dementia

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M.J. Katz, MPH
J. Vergesee, MD, MS
R.B. Lipton, MD

ABSTRACT
Objective: To test the cognitive reserve hypothesis by examining the effect of education on memory decline during the preclinical course of dementia.

Background: Low education is a well-known risk factor for Alzheimer disease (AD). Persons destined to develop AD experience an accelerated rate of decline in cognitive ability, particularly in memory. The cognitive reserve hypothesis predicts that persons with greater education begin to experience acceleration in cognitive decline closer to the time of diagnosis than persons with lower education, but that their rate of decline is more rapid after the time of acceleration due to increased disease burden.

Methods: We studied the influence of education on rates of memory decline as measured by the Buschke Selective Reminding Test in 117 participants with incident dementia in the Bronx Aging Study. Subjects had detailed cognitive assessments at entry and at annual follow-up visits. We estimated the time at which the rate of decline begins to accelerate (the change point), and the pre- and post-acceleration rates of decline, from the longitudinal data using a change point model.

Results: Each additional year of formal education delayed the time of accelerated decline on the Buschke Selective Reminding Test by 0.21 years. Post-acceleration, the rate of memory decline was increased by 0.16 points per year for each year of additional formal education.

Conclusions: As predicted by the cognitive reserve hypothesis, higher education delays the onset of accelerated cognitive decline, once it begins it is more rapid in persons with more education.

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GLOSSARY
AD = Alzheimer disease, BRT = Buschke Selective Reminding Test, VaD = vascular dementia, WAIS = Wechsler Adult Intelligence Scale

Numerous studies have shown that low education is a risk factor for the onset of dementia and particularly for Alzheimer disease (AD), while high education has a corresponding protective effect. The cognitive reserve hypothesis was proposed to explain the low correlation between observed pathologic markers of dementia and clinical presentation. It suggests that some individual characteristics result in maintenance of cognitive function in the face of brain pathology. Specifically, it assumes that on average, individuals with high education have greater brain reserve or compensational ability. This hypothesis would explain the delayed onset of clinically diagnosable dementia in individuals with high education.

The cognitive reserve hypothesis generates a number of testable predictions. One prediction is that for a given level of cognitive status, highly educated individuals would have more brain pathology than individuals with less education. Clinical-pathologic correlations are consistent with this prediction.

From the Bronx Aging Study (C.D.H., C.D., J.Y., R.B.L.), Department of Epidemiology and Population Health (C.D., C.D., R.B.L.) and Neurology (C.D., C.D., J.Y., R.B.L.), Albert Einstein College of Medicine, Bronx, NY, and W.F. Casby School of Business (A.L.L.), Arizona State University, Tempe, Arizona.

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Cognitive activities delay onset of memory decline in persons who develop dementia

ABSTRACT

Background: Persons destined to develop dementia experience an accelerated rate of decline in cognitive ability, particularly in memory. Early life education and participation in cognitively stimulating leisure activities later in life are 2 factors thought to reflect cognitive reserve, which may delay the onset of the memory decline in the proximal stages of dementia.

Methods: We followed 458 initially cognitively intact community residing individuals with epidemiologic, clinical, and cognitive assessments every 1.5 to 1.9 months in the Bronx Aging Study. We assessed the influence of self-reported participation in cognitively stimulating leisure activities on the onset of accelerated memory decline as measured by the Buschke Selective Reminding Test in 201 individuals who developed incident dementia using a change point model.

Results: Each additional self-reported day of cognitive activity at baseline delayed the onset of accelerated memory decline by 0.13 years. Higher baseline levels of cognitive activity were associated with more rapid memory decline after that onset. Inclusion of education did not significantly add to the fit of the model beyond the effect of cognitive activities.

Conclusions: Our findings show that late life cognitive activities influence cognitive reserve independently of education. The effect of early life education on cognitive reserve may be mediated by cognitive activity over the life. Alternatively, early life education may be a determinant of cognitive reserve, and individuals with more education may choose to participate in cognitive activities without influencing reserve. Future studies should examine the efficacy of increasing participation in cognitive activities to prevent or delay dementia.

GLOSSARY

AD = Alzheimer disease; BI = baseline; CAS = Cognitive Activity Scale; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; MCAD = Mini-Cog; NBSM = National Bureau of Statistics; NIA = National Institute on Aging; NRT = National Reading Test; WAIS-R = Wechsler Adult Intelligence Scale Revised.

The cognitive reserve hypothesis suggests that some individual characteristics result in maintenance of cognitive function in the face of accumulating dementia pathology in the brain. Cognitive reserve may reflect structural or functional brain characteristics that protect against neuropathologic damage caused by the progression of dementia, or compensatory processes that allow the damaged brain to use intact networks or alternative cognitive strategies that offset neuropathologic damage. Cognitive reserve has been proposed to explain delayed onset of clinically diagnosable dementia, increased levels of brain pathology for given cognitive status, and later onset of cognitive decline and more rapid post-onset decline in persons with higher education, a possible marker for cognitive reserve. Participation in cognitively stimulating leisure activities has also been associated with reduced rates of dementia and mild cognitive impairment, possibly through some delay in the acceler-

Supplemental data at www.neurology.org

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What activity is responsible?

Reading, writing, group discussions, board games, crossword puzzles, musical instruments used for the activity scale.

Strongest effect from crossword puzzles.
years before dementia diagnosis
Strong crossword puzzle effect!

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Crossword puzzle activity</th>
<th>No crossword puzzle activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change point (years prior to diagnosis)</td>
<td>Estimate: -2.60, 95% LCL: -4.05, 95% UCL: -1.67, p: 0</td>
<td>Estimate: -5.40, 95% LCL: -8.69, 95% UCL: -3.96, p: &lt;.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRT score at time of change point (model intercept)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rate of decline (SRT points/year) prior to change point</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rate of decline (SRT points/year) after change point</td>
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Problems – and Some Solutions

Misclassification of cases and controls.
Death as a competing cause of cognitive decline.
Lack of power from using only confirmed cases.
Combine incidence model with model for cognitive decline


Even more dramatic effect of education.
CONSULTANT'S FORUM

Random Changepoint Model for Joint Modelling of Cognitive Decline and Dementia

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SUMMARY. We propose a joint model for cognitive decline and risk of dementia to describe the pre-diagnosis phase of dementia. We aim to estimate the time when the cognitive evolution of subjects in the pre-dementia phase becomes distinguishable from normal evolution and to study whether the shape of cognitive decline depends on educational level. The model combines a piecewise polynomial mixed model with a random changepoint for the evolution of the cognitive test and a log-normal model depending on the random changepoint for the time to dementia. Parameters are estimated by maximizing likelihood using a Newton-Raphson-like algorithm. The expected cognitive evolution given age to dementia is then derived and the marginal distribution of dementia is estimated to check the log-normal assumption.

KEY WORDS: Joint model; Longitudinal data; Mixed model; Random effects.

1. Introduction

Dementia is a progressive disease defined by cognitive impairment in memory and at least one other cognitive function with consequences for the activities of daily living. Several studies have shown that cognitive impairment is present long before all criteria for dementia diagnosis are fulfilled (Masur et al., 2014, Dartigues et al., 1997). However, little is known about the shape of this decline and about the time at which cognitive evolution of subjects who develop dementia becomes distinguishable from that of normal elderly subjects.

Using a piecewise linear mixed model, Hall et al. (2009) have compared the evolution of a cognitive test for incident cases of dementia in the years preceding the diagnosis and for subjects free of dementia at their last visit. However, these analyses may be biased by right censoring of dementia (subjects without dementia at their last visit may be in preclinical phase of dementia) and by loss of follow-up which may be associated with poor cognitive functioning and high risk of dementia (Jacqumin-Gadda et al., 1997). More recently, Hall et al. (2009) have proposed a random changepoint model to describe the cognitive decline of dementia subjects but, as time-to-dementia was not jointly modeled, parameters were estimated using only data from subjects diagnosed as demented during the follow-up. This reduces the power of the study, does not allow the comparison of normal and pathological aging, and does not avoid selection biases (subjects must be seen as demented before the end of the follow-up to be included in the sample).

To deal with the above problems, the aim of this article is to propose a joint model for time-to-event and repeated measures of a marker (Wolffohr and Taitz, 1997; Rocchesso, Diggel, and Delbecq, 2003) to describe the cognitive decline in the pre-diagnostic stage of dementia and, especially, to estimate the time between the acceleration of the cognitive decline and the diagnosis of dementia. Another important point is to study whether the shape of the cognitive decline before dementia depends on the educational level of the subject. We have previously proposed another joint model for cognitive decline and dementia using a linear stochastic process that represents the cognitive ability and defining dementia as the crossing of a barrier by the latent process (Jacqumin-Gadda and Commenges, 2003). However, in this model, the mean evolution was assumed to be linear and common for future demented subjects and future nondemented subjects; this is not suitable for the study of the accelerated cognitive decline in the pre-diagnostic stage of dementia. In the present work, to take account of nonlinearity of the cognitive decline, we combined a piecewise polynomial mixed model with a random changepoint for the evolution of the cognitive test and a log-normal model depending on the random changepoint for the time-to-dementia diagnosis.
Figure 1. Expected BVRT score given the age at acceleration of cognitive decline (and 95% confidence interval). Plain line: high educational level and changepoint at 85 years; short dashed line: 95% confidence interval; long dashed line: low educational level and changepoint at 70 years; dotted line: 95% confidence interval. Jacqmin-Gadda et al *Biometrics* 2006.
Figure 2. Expected BVRT score in the years before the diagnosis given age at dementia. Plain line: high educational level, dementia at 75 years; long dashed line: high educational level, dementia at 90 years; short dashed line: low educational level, dementia at 75 years; dotted line: low educational level, dementia at 90 years. Jacqmin-Gadda et al Biometrics 2006.
Death as a competing risk?

Joint Modeling for Cognitive Trajectory and Risk of Dementia in the Presence of Death

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SUMMARY. Dementia is characterized by accelerated cognitive decline before and after diagnosis as compared to normal aging. It has been known that cognitive impairment occurs long before the diagnosis of dementia. For individuals who develop dementia, it is important to determine the time when the rate of cognitive decline begins to accelerate and the subsequent gap time to dementia diagnosis. For normal aging individuals, it is also useful to understand the trajectory of cognitive function until their death. A Bayesian change-point model is proposed to fit the trajectory of cognitive function for individuals who develop dementia. In real life, people in older ages are subject to two competing risks, e.g., dementia and dementia-free death. Because the majority of people do not develop dementia, a mixture model is used for survival data with competing risks, which consists of dementia onset time after the change point of cognitive function decline for dementia- and death-free individuals. The cognitive trajectories and the survival process are modeled jointly and the parameters are estimated using the Markov chain Monte Carlo method. Using data from the Honolulu Asia Aging Study, we show the trajectories of cognitive function and the effect of education, apolipoprotein E genotype, and hypertension on cognitive decline and the risk of dementia.

KEY WORDS: Change point; Competing risks; Dementia; Markov chain Monte Carlo.

1. Introduction
Dementia is a progressive degenerative disease that generally presents with decline in cognitive function over a period of many years. In the preclinical phase, changes can be gradual and usually difficult to distinguish from the less marked decline associated with normal aging. As dementia progresses, cognitive impairments become more obvious and decline in function begins to accelerate. It is important to understand the shape of this decline and the time at which cognitive evolution of subjects who develop dementia becomes distinguishable from that of normal aged subjects (Wilson et al., 2003; Silverman et al., 2006). With more effective treatments becoming available for dementia, it becomes increasingly important to develop and implement strategies to identify individuals with preclinical dementia at an earlier phase.

Change-point models have been used to describe the trajectory and trend of longitudinal outcomes (Smith, 1975; Stephens, 1994; Hall et al., 2006) using a piecewise linear mixed model to compare the trajectories of cognitive function for incident cases of dementia and for subjects free of dementia at their last follow-up. Later, Hall et al. (2006) used a Bayesian change-point model to describe the cognitive decline of demented subjects. As Jacquelin-Gadda, Connelly, and Dartigues (2006) point out, because subjects who are not demented before the end of the follow-up are classified as nondemented, the analysis may be biased or lack statistical power due to misclassification. Subsequently, Jacquelin-Gadda et al. (2006) combine a piecewise polynomial mixed model with a random change point for the evolution of the cognitive test and a log-normal survival model for the time from change point to dementia onset. A Gauss-Hermite quadrature is used to approximate the likelihood functions and the maximum likelihood estimates (MLEs) are obtained using the Mixmax optimization algorithm. The model is attractive, but the computation is difficult.

In addition, there are several complicated issues of modeling the trends of cognitive function in aging studies. First, because of the long history of disease progression, subjects without dementia at the last visit may be in the preclinical phase of dementia. Treating them as nondemented will bias the comparison between normal and pathological aging. Second, prevalent cases of dementia are excluded because their onset ages are not known, thus creating left truncation. Third, people may die from other causes without having dementia. Although dementia is a common disease for older people, most people do not develop dementia in their lifetime and are dementia free at death, producing a competing risk.
Trajectories of the CASI score by dementia status and education level in both demented and nondemented. For nondemented, the scores are 90 and 93 at age 70 for individuals with lower and higher education and the trajectories are parallel by education level. For demented, the change points are at ages 73 and 85 for lower and higher education levels, respectively. The change point for subjects with higher education occurs later but the cognitive score declines with a faster rate compared to those with lower education. At age 95, all demented subjects have similar cognitive function regardless of their education level. Yu and Ghosh *Biometrics* 2009.
So what HAVE we learned?

• Rigorously shown that “preclinical” dementia is for real.
• Quantified natural history of preclinical dementia for multiple cognitive domains measured by multiple instruments, with multiple operational outcomes (AD, MCI).
So what HAVE we learned?

- Rigorously shown that terminal decline is for real, and quantified it globally and in multiple domains (including life satisfaction).
- Produced evidence in favor of theoretical model for cognitive reserve.
- Begun to examine natural history of cognitive decline as a function of risk factors.
Future research

• Dependence on instrument quality.
• Impact of different diagnostic criteria.
• Diagnostic circularity.
• Missing data – the elephant in the room.
• How far can we take this?
Thanks!

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