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## **When does cognitive decline begin? A systematic review of change point studies on accelerated decline in cognitive and neurological outcomes preceding mild cognitive impairment, dementia, and death**

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### **Abstract**

Older adults who ultimately develop dementia experience accelerated cognitive decline long before diagnosis. A similar acceleration in cognitive decline occurs in the years before death as well. To evaluate preclinical and terminal cognitive decline, past researchers have incorporated change points in their analyses of longitudinal data, identifying point estimates of how many years prior to diagnosis or death that decline begins to accelerate. The current systematic review aimed to summarize the published literature on preclinical and terminal change points in relation to mild cognitive impairment (MCI), dementia, and death, identifying the order in which cognitive and neurological outcomes decline and factors that modify the onset and rate of decline. A systematic search protocol yielded 35 studies, describing 16 longitudinal cohorts modeling change points for cognitive and neurological outcomes preceding MCI, dementia, or death. Change points for cognitive abilities ranged from 3-7 years prior to MCI diagnosis, 1-11 years prior to dementia diagnosis, and 3-15 years before death. No sequence of decline was observed preceding MCI or death, but the following sequence was tentatively accepted for Alzheimer's disease: verbal memory, visuospatial ability, executive functions and fluency, and lastly verbal IQ. Some of the modifiers of the onset and rate of decline examined by previous researchers included gender, education, genetics, neuropathology, and personality. Change point analyses evidence accelerated decline preceding MCI, dementia, and death, but moderators of the onset and rate of decline remain ambiguous due to between-study modeling differences, and coordinated analyses may improve comparability across future studies.

## Keywords

change point; mild cognitive impairment; dementia; cognitive decline; systematic review

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An estimated 5.5 million Americans are currently living with Alzheimer's disease (AD); and with the aging baby boomer generation and longer life expectancies, it is anticipated that this number will exceed 13 million by the year 2050 (Alzheimer's Association, 2017).

Additionally, many individuals who experience subjective cognitive decline or Mild Cognitive Impairment (MCI) present with AD biomarkers (e.g., neurodegeneration, Meiberth et al., 2015, Spulber et al., 2012; amyloid burden, Amariglio et al., 2012) and some will go on to develop AD or another type of dementia (Mitchell & Shiri-Feshki, 2009).

Individuals who ultimately receive a diagnosis of MCI or dementia typically have observable neurological and cognitive differences many years prior to diagnosis (Bäckman, Jones, Berger, Laukka, & Small, 2005; Ewers, Sperling, Klunk, Weiner, & Hampel, 2011). An appreciation for these preclinical differences has enhanced research focus on the early detection of cognitive change over the course of aging.

Previous cross-sectional research has identified varying effects of preclinical AD on different domains of cognitive functioning (Bäckman et al., 2005). Although cross-sectional approaches offer insight into between-group differences, individual differences in within-person change can only be evaluated through longitudinal data and analysis. A longitudinal evaluation of the preclinical period has offered insight into when older adults undergo a *change point* over the course of cognitive aging, indicating an acceleration in the rate of cognitive decline preceding diagnosis (i.e., MCI or dementia) or death (i.e., terminal decline/drop; Palmore & Cleveland, 1976; Siegler, 1975). These change points often appear years before diagnosis or death, providing insight into the sensitivity of different indicators exhibiting the earliest onset of accelerated decline.

Originally pioneered by researchers on HIV/AIDS (Kiuchi, Hartigan, Holford, Rubinstein, & Stevens, 1995; Lange, Carlin, & Gelfand, 1992), change point studies are not unique to cognitive aging research, but they have become increasingly popular within the field of aging since first applied to detect the onset of accelerated change in years prior to dementia (Hall, Lipton, Sliwinski, & Stewart, 2000; Joseph et al., 1999). The published literature on preclinical and terminal decline change points has grown extensively, analyzing data of multiple international cohorts from Australia (Batterham, Mackinnon, & Christensen, 2011), Canada (MacDonald, Hultsch, & Dixon, 2011), France (Jacqmin-Gadda, Commenges, & Dartigues, 2006), Sweden (Laukka, MacDonald, Fratiglioni, & Backman, 2012), the United Kingdom (Muniz-Terrera, van den Hout, Piccinin, Matthews, & Hofer, 2013; Muniz Terrera, Minett, Brayne, & Matthews, 2014), and the United States (Grober et al., 2008; Hall et al., 2000, 2001; Hall, Ying, Kuo, & Lipton, 2003; Wilson, Beckett, Bienias, Evans, & Bennett, 2003; Wilson, Beck, Bienias, & Bennett, 2007; Wilson, Leurgans, Boyle, & Bennett, 2011; Wilson, Leurgans, Boyle, Schneider, & Bennett, 2010; Wilson et al., 2012a; Wilson, Segawa, Hizek, Boyle, & Bennett, 2012b; Yu & Ghosh, 2010). The international focus on change points aligns with the global scientific goal to identify the earliest possible biomarkers of neurodegenerative processes and modifiable risk factors associated with the

onset or rate of cognitive decline (Alzheimer's Association, 2017). In turn, change point studies have focused not just on the acceleration of cognitive decline, but also the acceleration of neurological changes (Carlson, 2008; Silbert et al., 2012) and variables that may delay or slow preclinical or terminal decline (e.g., education, cognitive activity; Hall et al., 2007; Hall et al., 2009; Muniz Terrera et al., 2014).

Despite the coherent mission of researchers to identify biomarkers and modifiable risk factors, change point studies vary considerably with respect to design, statistical model, inclusion of covariates, and the outcomes used as dependent variables. As such, there is a lack of consensus regarding the order in which different neurological and cognitive domains decline and the factors that are associated with the onset and rate of decline in later age. Anticipating that researchers will continue to conduct change point analyses on longitudinal datasets of older adults, the current literature must be reviewed to determine common and disparate findings across studies, informing future researchers about appropriate analytical practices, which covariates to include in their models, and evidence for differential sensitivity of particular cognitive and neurological measures to detect within-person change and change points. In turn, the current systematic review focused on cognitive change occurring during the latter stages of life, either preceding an age-related disease process or death. Both preclinical and terminal decline are relevant to researchers examining longitudinal data of aging cohorts, and both have been extensively considered in the context of aging research (Sliwinski, Hofer, & Hall, 2003; Sliwinski, Hofer, Hall, Bushke, & Lipton, 2003). To synthesize the many studies examining cognitive or neurological decline among older adults, the current systematic review aimed to summarize the published literature on change point models indicating the onset of accelerated decline in relation to MCI, dementia, and death, identifying (a) the order in which cognitive and neurological outcomes accelerate in their rate of decline preceding each clinical endpoint and (b) factors that modify the onset or rate of decline.

## Method

The report for this systematic review was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher, Liberati, Tetzlaff, Altman, & the PRISMA Group, 2009).

### Literature search

The key words, subject headings and index terms used in the electronic search protocol included terms associated with MCI and dementia, terminal decline, cognitive and neurological outcomes, longitudinal methods, and change point analyses. The full list of search terms is provided in the supplementary materials. The electronic search involved four databases (i.e., CINHAHL Complete, MedLine with Full Text, PSYCInfo, and PSYCArticles) and was conducted in March 2017, with no filters placed on the search findings. Two reviewers independently reviewed the electronic search results to ensure no eligible studies were missed (Edwards et al., 2002). A manual search was also conducted, inclusive of reference lists, targeted journals not indexed in psychological and biomedical databases (i.e., Journal of Applied Statistics, Computational Statistics and Data Analysis),

and articles known by the authors but not detected by the electronic search strategy. A post-hoc search using the statistics-oriented database, *The Current Index to Statistics*, was also conducted as part of the manual search strategy, using multiple combinations of the term “change point” and cognition or dementia-related search terms.

### Eligibility criteria

For inclusion in the systematic review, authors needed to (a) report a longitudinal study involving four or more measurement waves and (b) test a change point model for (c) either a cognitive or neurological outcome. The researchers needed to (d) test a model with a pre-clinical or terminal decline change point, modeled in relation to MCI onset, dementia onset, or death (i.e., models using age or time-in-study as the time metric were ineligible). Participants included in analyses (e) needed to be free of concurrent neurological disorders other than dementia that could contribute to cognitive decline (e.g., Parkinson’s disease, stroke). If a small subsample ( $n < 5\%$  of the sample) of participants were diagnosed with a concurrent neurological condition at baseline or during the course of the study, this study was included in the systematic review; however, if a majority of the sample was diagnosed with a concurrent neurological condition at baseline (e.g., Parkinson’s disease; Aarsland, Muniz, & Matthews, 2011; Johnson, Langford, Garnier-Villarreal, Morris, & Galvin, 2016), the study was deemed ineligible. Further, (f) studies reporting samples with the majority experiencing early-onset dementia (i.e., mean age at onset  $< 65$ ) were also deemed ineligible (Aguirre-Acevedo et al., 2016). Eligible articles needed to (g) be published in an academic journal or book and (h) be written in the English language.

### Data extraction

Two reviewers separately examined articles identified through the literature review to determine their eligibility for inclusion in the research synthesis. For all eligible studies, two reviewers independently extracted information following a common data collection instrument. The extracted data included participant characteristics, study characteristics, and quantitative results. The participant characteristics included the sample size of participants that were included in the change point analysis, the baseline demographics of the sample (i.e., mean age, gender composition, years of education, ethnicity, and the percent with an apoE  $\epsilon 4$  allele, *APOE*  $\epsilon 4$ ), and the operational definition of MCI or dementia used for the sample. Study characteristics included the study duration in years, maximum number of measurement waves completed by any participant included in the analysis, the mean number of measurement waves completed by all participants included in the analysis, the mean number of years follow-up for all participants included in the analysis, and the interval duration between measurement occasions. Model information was recorded, including whether the estimation approach was Bayesian or frequentist and what covariates were included in the analysis. The names of the cognitive and neurological outcomes included in change point analyses were also extracted along with the change points for each outcome in relation to diagnosis or death along with a 95% Confidence or Credible Interval.

### Individual and across study bias

The risk of bias within individual studies was not easily operationalized, as the criteria typically used to assess individual study bias and study quality are often written for

intervention studies involving randomized controlled trials (Sanderson, Tatt, & Higgins, 2007; Vandenbroucke et al., 2007). Although certain recommendations for quality reporting in observational longitudinal analyses have been previously proposed (Tooth, Ware, Bain, Purdie, & Dobson, 2005), no study quality instrument designed for longitudinal change point analyses exists. Although individual study bias was not quantified, certain study characteristics (e.g., mean number of measurement waves in combination with study duration and maximum number of measurement waves) gave a proxy for attrition bias, with these findings qualitatively interpreted in aggregate within the discussion. As well, bias across studies was not quantified, but certain types of across study bias (e.g., publication bias, selective reporting) was covered in the discussion as potentially affecting the interpretation of results.

## Results

### Literature Search

Figure 1 provides a flow diagram of the systematic review process. Among the 81 articles originally identified through electronic and manual search strategies, a total of 35 articles ultimately met eligibility criteria for inclusion in the systematic review. References for full text articles that were reviewed by the authors, but did not ultimately meet inclusion criteria are provided in the supplementary materials and sorted by their reason for exclusion. Among these 35 articles, 4 evaluated change points in relation to MCI diagnosis, 13 evaluated change points in relation to dementia diagnosis, one evaluated change points in relation to both MCI and dementia diagnosis, and 17 evaluated change points in relation to death. A total of 16 different longitudinal cohorts were represented across the articles, including the Alzheimer's Disease Centers Neuropsychological Database Initiative (Ji, Xiong, & Grundman, 2003), Bronx Aging Study (BAS; Hall et al., 2000, 2001, 2003, 2007, 2009; Sliwinski et al., 2006), Baltimore Longitudinal Study of Aging (Grober et al., 2008), Cambridge City over 75 Cohort Study (CC75C; Muniz-Terrera et al., 2013, 2014; van den Hout, Muniz-Terrera, & Matthews, 2011), Canberra Longitudinal Study (Batterham et al., 2011), Gerontological and Geriatric Population Study (H70; Thorvaldsson et al., 2008; Thorvaldsson et al., 2011), Honolulu Asia Aging Study (Yu & Ghosh, 2010), Kungsholmen Project (KP; Laukka et al., 2012; Thorvaldsson et al., 2011), Monongahela Valley Independent Elders Survey (Dodge, Wang, Chang, & Ganguli, 2011), Oregon Brain Aging Study (OBAS; Buracchio, Dodge, Howieson, Wasserman, & Kaye, 2010; Carlson, 2008; Howieson et al., 2008; Silbert et al., 2012), Origins of Variance in the Old-old Study (van den Hout, Muniz-Terrera, & Matthews, 2013), Paquid Project (Jacqmin-Gadda et al., 2006), Religious Orders Study/Memory and Aging Project (ROS/MAP; Boyle et al., 2013; Li, Dowling, & Chappell, 2015; Wilson et al., 2003, 2007, 2010, 2011, 2012a, 2012b, 2015; Yu et al., 2013), Victoria Longitudinal Study (MacDonald et al., 2011), and lastly a cohort from the Washington University School of Medicine Alzheimer's Disease Research Center (Johnson, Storandt, Morris, & Galvin, 2009).

The following sections will discuss the findings of change point studies based on their clinical endpoint: MCI, dementia, or death. Each section will cover the demographic information of the samples evaluated, discuss study design characteristics, and summarize

the findings of the change point analyses, including the effects of moderating variables that influenced either the location of the change point in relation to diagnosis or death or the rate of decline before or after the change point. For MCI, dementia, and terminal decline change point studies, respectively, Tables 1-3 summarize the demographic information for the participants included in each analysis, and Tables 4-6 summarize the design characteristics and reported change points.

### Preclinical MCI Change Point Studies

**Demographic characteristics**—Five studies examined change points in relation to the diagnosis of MCI, with four analyzing participant data from the OBAS (Buracchio et al., 2010; Carlson, 2008; Howieson et al., 2008; Silbert et al., 2012) and one analyzing participant data from the ROS/MAP cohorts (Wilson et al., 2011). For the OBAS, MCI was defined as having two or more consecutive scores of  $\geq 0.5$  on the Clinical Dementia Rating Scale (Morris, 1993) along with no functional impairment. For the ROS/MAP cohorts, participants were classified as having MCI if they did not meet criteria for dementia, but presented with impairment in one of five domains of cognitive functioning (i.e., orientation, attention, memory, language, and visuospatial ability) based on educationally adjusted cutoff scores for 11 individual cognitive tests and the judgement of a neuropsychologist. The ROS/MAP MCI sample was subdivided into amnesic and non-amnesic subtypes. The sample sizes with MCI ranged from 37 to 742 across studies, with a baseline age of 78.1 years for ROS/MAP and about 84 years for the OBAS studies. The ROS/MAP sample was majority female (i.e., 71.0%) and well-educated (i.e., 16.6 years). The OBAS sample was predominantly female (~60-65%), White (~98%) and well-educated, with participants having about 13 to 14 years of education on average. Roughly 20-25% of OBAS participants were carriers of the *APOE*  $\epsilon 4$  allele.

**Design characteristics**—The ROS/MAP and OBAS studies involved samples with up to 16 years and 20 years of follow-up, respectively. Both studies had annual neuropsychological assessments, while just the OBAS had annual neurological assessments. The average number of years follow-up ranged from 6.3 to 10.5 depending on the sample used for each study. The modeling approach for both the ROS/MAP and OBAS data was entirely based on profile likelihood methods with fixed change points (Hall et al., 2000).

**Summary of findings**—Figure 2 provides a forest plot of change points for the MCI studies, organized by the type of outcome evaluated (i.e., motor, neurological, and cognitive). On three measures of motor function (i.e., gait speed and finger tapping for each hand), men showed an earlier decline than women. The onset of decline in finger tapping occurred near or even after MCI diagnosis, while gait speed showed the earliest change point for any outcome:  $-6.0$  years (95% CI:  $-9.5, -4.6$ ) and  $-14.2$  years (Unknown,  $-8.7$ ) before diagnosis for men and women, respectively. In comparison to change point analyses in relation to dementia or terminal decline, only MCI studies explored preclinical change points for neurological outcomes. As shown visually in Figure 2, motor and neurological change points were on average earlier than cognitive change points; however, the 95% CIs around change points for cognitive and neurological outcomes were far broader than those observed for cognitive outcomes. The participants with MCI from the ROS/MAP were

subdivided into amnesic and non-amnesic MCI. For a global cognitive composite score, the onset of decline for amnesic MCI participants (i.e., -6.67 years) preceded the onset of decline for non-amnesic MCI participants by about 1.5 years.

### Preclinical Dementia Change Point Studies

**Demographic characteristics**—Fourteen studies examined change points in cognitive functioning in relation to dementia diagnosis. A total of ten cohorts were evaluated in these analyses, with two of these cohorts combined and evaluated as a single sample in two studies (i.e., ROS/MAP; Li et al., 2015; Wilson et al., 2011). Taking the largest sample size reported by a study for each cohort, a total of 1,994 participants that progressed to dementia during follow-up were represented in the systematic review. The mean baseline age of participants across studies ranged from 70 to 82 years. Three cohorts reported ethnicity data: the BAS sample was over 90% White (Hall et al., 2007; Hall et al., 2009), the ROS/MAP sample was 87.9% White (Wilson et al., 2011), and the Honolulu Asia Aging Study was entirely Japanese-American (Yu & Ghosh, 2010). Three samples reported the percent prevalence of the *APOE* ε4 allele in their sample, with values of 18.0% (Yu & Ghosh, 2010), 27.0% (Johnson et al., 2009) and 29.6% (Li et al., 2015). The education of the samples varied substantially, from samples where most participants had some college education (Grober et al., 2008; Ji et al., 2003; Johnson et al., 2009) to samples where most participants had equal to or fewer than 12 years (Hall et al., 2007; Li et al., 2015), fewer than 8 years (Laukka et al., 2012), and fewer than 6 years (Thorvaldsson et al., 2011). The majority of participants from one sample did not complete primary school (Jacqmin-Gadda et al., 2006).

In terms of dementia diagnosis, six cohorts used criteria from the Diagnostic and Statistical Manual for Mental Disorders, Third Edition (DSM-III; American Psychiatric Association, 1980) or Third Edition, Revised (DSM-III-R; American Psychiatric Association, 1987). One study considered alternative criteria for dementia (Cummings & Benson, 1992; White et al., 1996) in combination with the DSM-III-R criteria (Yu & Ghosh, 2010). In terms of subtypes of dementia, five studies (Grober et al., 2008; Hall et al., 2000; Laukka et al., 2012; Li et al., 2015; Wilson et al., 2011) cited specific criteria to define AD (McKhann et al., 1984), while two other studies (Hall et al., 2000; Laukka et al., 2012) cited criteria to define Vascular Dementia (Román et al., 1993) or Multi-Infarct Dementia (Rosen, Terry, Fuld, Katzman, & Peck, 1980). Two studies did not cite established criteria for diagnosing AD, but instead provided their own criteria (Johnson et al., 2009) or asserted the sample had an AD diagnosis without offering an operational definition (Ji et al., 2003).

**Design characteristics**—The cohorts used to estimate preclinical dementia change points ranged in years of follow-up from 9 years to up to 30 years. The interval between measurement waves varied by cohort from annual assessments to assessments occurring every three years. The average years of follow-up or number of measurement waves completed was not consistently reported across cohorts. In terms of analytical approach, most studies took a frequentist estimation approach with a fixed change point; however, one study applied a Bayesian approach (Yu & Ghosh, 2010) and two studies applied both Bayesian and frequentist approaches, calculating both fixed and random change points (Hall

et al., 2003; Hall et al., 2001). One frequentist study calculated a random change point (Jacqmin- Gadda et al., 2006) and another conducted a quantile regression with a change point (Li et al., 2015).

**Summary of findings**—Among the dementia change point studies, a few different moderators were evaluated to determine their influence on components of the change point model (i.e., the change point and the slopes before and after the change point). These moderators included demographics (e.g., gender, education), frequency of engagement in cognitive activities, dementia subtype, genetic risk (i.e., presence of *APOE ε4*), and the cognitive construct evaluated.

**Demographics:** One study evaluated the effects of both gender and education on model components (Li et al., 2015). These researchers reported no gender or education-related differences for the change point, and further reported no gender differences for the rate of change before or after the change point. The effect of education on slopes before and after the change point was not discussed. Although no other studies evaluated the relationship between gender and model components, three additional studies examined the effect of education. Among the BAS cohort, participants experienced a delay in their verbal memory change point, as measured by the Buschke Selective Reminding Test (BSRT), of roughly 2 months (i.e., 0.21 years) for each year of additional education; and while there were no significant education-related differences in the rate of decline prior to the change point, the rate of decline following the change point was faster for individuals with more years of education (Hall et al., 2007).

An additional study that explored the effects of education on preclinical change found a similar pattern of results (Jacqmin- Gadda et al., 2006). The change point was delayed for participants with more education, where individuals with at least a primary school diploma had a median onset of accelerated decline at 90.3 years (89.3, 91.4) and individuals with either no education or without a primary school diploma had a median onset of accelerated decline at 69.7 years (65.0, 74.6). Following the change point, the rate of decline was more rapid for participants with a higher level of education, which meant that the median distance between the change point and dementia diagnosis was smaller for participants with more education (e.g., for a change point at 65 years, the age at dementia diagnosis was a median of 73.1 and 83.4 years for participants with high and low educational backgrounds, respectively). Another study found the same results (Yu & Ghosh, 2010), where participants with more than 10 years of education underwent a change point around 12 years later than participants with 10 or fewer years of education; however, those participants with more education declined more rapidly following the change point.

**Frequency of cognitive activities:** In the BAS, participants were queried at baseline for the frequency at which they engaged in cognitively engaging leisure activities (i.e., reading, writing, crossword puzzles, board/card games, group discussions, and playing music; Hall et al., 2009). For each additional day of cognitive activity (i.e., participation in one cognitively engaging activity for one day in a week), the change point for the BSRT tasks was delayed by a little more than 2 months (i.e., 0.18 years), but following the change point, preclinical decline occurred more rapidly for participants engaged in more cognitive activities. This



pattern was observed for participants progressing to dementia and was replicated for a subsample of participants progressing to AD specifically. When education was added to the model, fit did not improve and an interaction between education and cognitive activity was non-significant, although both remained uniquely predictive of a delayed change point and a more rapid rate of preclinical decline.

**Dementia subtype:** Two studies evaluated the KP dataset (Laukka et al., 2012; Thorvaldsson et al., 2011). The first evaluation identified change points for different cognitive constructs in relation to dementia diagnosis in general (Thorvaldsson et al., 2011), whereas the second study explored differences in the location of the change point in relation to diagnosis for two different dementia types: AD and VaD (Laukka et al., 2012). These authors found that for every cognitive test except for Clock Reading, the onset of preclinical decline occurred earlier for AD than VaD by approximately two to four years. When AD and VaD samples were combined, the change points for the Block Design and Word Recall tasks were  $-8.3$  years (Unknown,  $-5.4$ ) and  $-8.6$  years (Unknown,  $-6.2$ ), respectively (Thorvaldsson et al., 2011); however, the change points for these tests were different when the sample was sub-divided based on dementia subtype. The earliest change point observed for AD patients involved the Block Design task (i.e.,  $-9.6$  years [Unknown,  $-6.8$ ]), and the earliest change point observed for VaD involved Word Recall (i.e.,  $-6.5$  years [Unknown,  $-3.1$ ]).

**Genetic risk:** Only one study evaluated the effect of genetic risk on the change point model parameters, using a quantile regression approach to determine the effect of moderators at different quantiles of performance on a composite measure of verbal memory (Li et al., 2015). The presence of an *APOE*  $\epsilon 4$  allele did not affect the location of the change point in relation to AD diagnosis, but it did lower the intercept (i.e., level of verbal memory at age 65) for participants in the 20<sup>th</sup> and 50<sup>th</sup> percentiles. *APOE*  $\epsilon 4$  allele carriers in the 20<sup>th</sup> percentile also had a slower rate of decline, which was likely a consequence of a lower starting point in comparison to individuals without genetic risk.

**Cognitive construct:** In terms of dementia cohorts in general, the earliest observed change point was for a measure of processing speed (i.e., Figure Identification), occurring  $-10.9$  years ( $-14.4$ ,  $-7.5$ ) before diagnosis (Thorvaldsson et al., 2011); however, the earliest change point for AD-only samples was observed for Block Design, a measure of visuospatial ability, with a change point of  $-9.6$  years (Unknown,  $-6.8$ ; Laukka et al., 2012). The most commonly measured domain was verbal memory, with change points for dementia ranging from  $-1.0$  years to  $-8.6$  years (Unknown,  $-6.2$ ; Thorvaldsson et al., 2011) before diagnosis. The latest cognitive ability to decline was verbal IQ as measured by a test of reading ability. The change point was  $-0.4$  years ( $-1.1$ ,  $0.1$ ) before diagnosis with a 95% CI inclusive of possible values after the diagnosis of AD (Grober et al., 2008).

Figure 3 provides a forest plot of change points for AD-only sample coded in years to diagnosis with 95% CIs when reported by the authors. The change points were categorized in terms of the cognitive construct evaluated by the test used to calculate the change point, as determined by the authors of this review. The decision to only include AD samples in the forest plot was to ensure the change points were as comparable as possible across studies,

assuming a common pathological pathway underlying the cognitive changes observed for each sample. As shown visually in Figure 3, substantial variability in change points were observed both within and between cognitive constructs. An exact sequence of decline based on cognitive construct could not be determined, considering the substantial scatter among change point estimates for the same cognitive constructs, the limited data points reported for some cognitive constructs, and the overlap between the CIs around different change points.

### Terminal Decline Change Point Studies

**Demographic characteristics**—Seventeen studies examined change points in cognitive functioning prior to death. A total of nine cohorts were evaluated in these analyses, with two of these cohorts combined and evaluated as a single sample in three studies (i.e., ROS/MAP; Boyle et al., 2013; Wilson et al., 2015; Yu et al., 2013), but kept separate in five other studies (i.e., MAP-only; Wilson et al., 2007); ROS-only (Wilson et al., 2003, 2010, 2012a, 2012b). Taking the largest sample size reported by a study for each cohort, a total of 5,613 participants that passed away during follow-up were represented in the systematic review, with 37% of these participants coming from a single cohort (i.e., CC75C,  $N = 2,078$ ; Muniz Terrera et al., 2014). The mean baseline age of participants across studies ranged from 72.7 to 88.9 years. The only cohorts with ethnicity data were the MAP-only (Wilson et al., 2007), ROS-only (Wilson et al., 2010, 2012b), and ROS/MAP combined cohorts (Boyle et al., 2013), reporting samples that were over 90% White. The percent prevalence of the *APOE*  $\epsilon 4$  allele was reported for two samples: the MAP-only (29.5%; Wilson et al., 2007) and ROS/MAP combined cohorts (23.8%; Yu et al., 2013). The education of the samples ranged from means of 11.4 years (Batterham et al., 2011) to 18.3 years (Wilson et al., 2003). Two samples described the educational backgrounds of their samples categorically. One study described a sample where the majority had completed at least high school education (i.e., 54.3%; Dodge et al., 2011), while the other study reported that participants left formal education on average at 14.8 years of age (Muniz Terrera et al., 2014).

**Design characteristics**—The cohorts used to determine change points for the onset of terminal decline ranged in years of follow-up from 8 years to up to 30 years. The intervals between measurement waves varied by cohort from annual assessments, to assessments occurring every three years, to irregular assessments occurring every two to five years. As with dementia studies, terminal decline studies inconsistently reported the average years of follow-up or number of measurement waves completed across cohorts. The mean number of measurement waves completed by participants ranged from 2 waves (Batterham et al., 2011; MacDonald et al., 2011) to 10.9 waves (Wilson et al., 2012a). The number of measurement waves completed differed from the average number of years follow-up, which ranged from 5.7 years (Sliwinski et al., 2006) to 10.7 years (Wilson et al., 2015). In terms of analytical approach, eight studies took a frequentist approach with a fixed change point, while one study also took a frequentist approach, but included a random change point (van den Hout et al., 2013). A total of eight studies conducted a Bayesian analysis with a random change point.

**Summary of findings**—In comparison to the dementia change point studies, far more moderators were evaluated in the terminal decline studies. These studies determined the

influence of moderators on the change point (i.e., the onset of terminal decline) along with the slope before the change point (i.e., the rate of age-related cognitive decline) and the slope after the change point (i.e., the rate of terminal decline). These moderators included demographics (e.g., age, gender, education), physical impairment, cognitive impairment, genetic risk, neuropathology, personality, practice effects, and cognitive construct.

**Demographics:** The demographics examined as potential moderators included age at baseline or death, gender, and educational background. One study identified that participants older at baseline declined at a slightly faster rate before the change point, but declined at a slower rate following the change point (Muniz-Terrera et al., 2013), while another study found no relationship between age and the rate of terminal decline (Wilson et al., 2007). Participants older at death declined at slower rates prior to the change point than those who died younger; however, after the change point, those who died later had more rapid change than those who died younger (Muniz-Terrera et al., 2013, 2014).

Gender was evaluated twice using the same cohort (i.e., CC75C), but was associated with different results across studies. One study found that women declined at the same rate as men before the change point, but at a faster rate than men after the change point (Muniz-Terrera et al., 2013); while another study found that women declined at a faster rate than men before the change point, but at a slower rate than men after the change point (Muniz-Terrera et al., 2014).

In terms of education, four studies evaluated the effect of education on change point models examining terminal decline on the MMSE (Batterham et al., 2011; Muniz-Terrera et al., 2013, 2014; Wilson et al., 2007). In an analysis of two groups stratified at 11 years of education (i.e., <11 years or ≥11 years), the low education group had a later change point than the high education group on the MMSE: -2.6 years (-3.8, -2.1) and -8.6 years (-10.1, -7.7), respectively (Batterham et al., 2011). However, the rates of preterminal and terminal decline on the MMSE were greater for the low education group when compared to the high education group (Batterham et al., 2011). Another study also using the MMSE as the outcome measure observed a different effect of education on the location of the change point. This study (Muniz-Terrera et al., 2014) had education coded as the age at which participants left formal schooling. Leaving school at a later age delayed the change point by 4.8 months per additional year of education, and thus participants with more education had a later onset of slightly faster decline. And yet another study examining the MMSE found a different pattern, where participants with more education experienced a faster decline on the MMSE prior to the change point in comparison to individuals with less education; however, following the onset of terminal decline, this pattern was reversed, where more educated participants declined at a slower rate than those participants with less education (Muniz-Terrera et al., 2013). Although not examining the MMSE, a different study (Wilson et al., 2007) found that the rate of terminal decline on a global composite measure of cognitive function did not vary by education.

Only one study examined the effect of education on change point models of specific cognitive constructs (Batterham et al., 2011). As noted earlier, these authors provided point estimates of change points for low and high education groups (i.e., <11 years or ≥11 years,

respectively). Because the confidence intervals for the change point estimates overlapped, the authors suggested that education did not modify the onset of terminal decline in processing speed or episodic memory tests. Interestingly, the Episodic Memory score had very similar change points for the low education (i.e., -5.5 years [-8.3, -2.8]) and high education (i.e., -6.6 years [-6.9, -5.5]) groups; however, the point estimates for the Symbol-Letters Modalities Test (SLMT), a measure of processing speed, were further apart for low and high education groups: -11.3 years (<-17, -4.8) and -7.8 (-9.3, -6.8). For both the MMSE and Episodic Memory score, the low education group had a later change point than the high education group; however, for the processing speed task, participants with less education showed an earlier change point estimate. There was no difference based on education in preterminal decline for the SLMT, but the high education group showed faster terminal decline for this construct (i.e., potentially later onset, but faster decline). In an opposite pattern, there were no education-based differences in terminal decline for Episodic Memory scores; however, the high education group showed faster preterminal decline than the low education group for this outcome.

**Physical impairment and health problems:** The effects of physical impairment on rates of cognitive decline did not reach significance either before or after the change point (Muniz-Terrera et al., 2013; Muniz-Terrera et al., 2014). Another study (Wilson et al., 2003) did not report significant changes in their model upon controlling for baseline medical conditions and physical disability. A different study that explored physical health as a moderator found no association between vascular risk factors (i.e., diabetes, smoking and hypertension) and terminal decline, but did find that the presence of vascular conditions (i.e., heart attack, stroke, claudication, congestive heart failure) was related to terminal decline, in that terminal decline was absent when an individual had a vascular condition (Wilson et al., 2007). Another study examining vascular risk factors and conditions found that risk factors were marginally associated with a delay in the onset of terminal decline, while vascular conditions were not associated with any components of the change point model (Wilson et al., 2012a).

**Cognitive impairment:** The effect of cognitive impairment on components of the change point models varied across studies. One study found that participants with baseline cognitive impairment declined more rapidly both before and after the change point (Muniz-Terrera et al., 2014), while another study found that participants with baseline cognitive impairment declined at a slower rate before the change point and a faster rate after the change point (Muniz-Terrera et al., 2013). In one study, the removal of participants with MCI at baseline from analysis resulted in a very slight delay in the onset of terminal decline (Wilson et al., 2012a). Yet another study found no association between the presence of mild cognitive impairment and the rate of terminal decline (Wilson et al., 2007).

Two studies specifically evaluated the effects of participants with dementia on components of their change point models. For one study, participants with dementia had a lower baseline performance, but did not differ from participants without dementia in their rate of cognitive decline before the change point; however, they experienced a faster rate of decline following the change point (Sliwinski et al., 2006). In contrast, for another cohort, the exclusion of participants with a dementia diagnosis did not substantially affect the location of the change

point or the rates of preterminal or terminal decline (Batterham et al., 2011). For the ROS cohort, dementia diagnosis occurred about a year before the change point for terminal decline in motor functioning, and about the same time as the change point for terminal decline in cognitive functioning (Wilson et al., 2012a).

**Genetic risk:** Two studies examined the relationship between the presence of the *APOE*  $\epsilon 4$  allele and components of their change points models, one examining the combined ROS/MAP cohorts (Yu et al., 2013) and another examining just the MAP cohort (Wilson et al., 2007). When evaluating the associations between *APOE*  $\epsilon 4$  status and the components of the change point model, one study identified an earlier change point for *APOE*  $\epsilon 4$  carriers by roughly 9 months (Yu et al., 2013). In terms of rates of cognitive decline before and after the change point, *APOE*  $\epsilon 4$  carriers had a 75% faster rate of preterminal decline and a 40% faster rate of terminal decline compared to non-carriers. In contrast, a different study found that the presence of an *APOE*  $\epsilon 4$  allele was associated with a more rapid terminal decline, but was unassociated with the rate of preterminal decline (Wilson et al., 2007). The study examining the combined cohorts also explored the potential protective effects of possessing an *APOE*  $\epsilon 2$  allele, but found no evidence that the presence of the  $\epsilon 2$  allele was associated with any component of the change point model (Yu et al., 2013).

**Neuropathology:** A set of studies analyzing the ROS/MAP combined cohorts examined the effects of different indicators of neuropathology and genetic risk on the components of their change point models for a global cognition composite score (Boyle et al., 2013; Wilson et al., 2015; Yu et al., 2013). One of these studies further examined the relationship between conscientiousness and neuropathology (Wilson et al., 2015), with the findings of these researchers explained under the personality subsection below. Three additional studies analyzing just the ROS cohort further examined the relationship between neuropathologic indices and decline in motor functioning (Wilson et al., 2012a) or specific cognitive constructs (Wilson et al., 2010, 2012b). The indices of neuropathology evaluated included neurofibrillary tangle density (hereafter referred to as tangles) and amyloid plaque burden (hereafter referred to as amyloid), along with the presence of micro-infarcts, gross infarcts, neocortical Lewy bodies or hippocampal sclerosis. Global AD pathology was also derived as an average of the summary scores given for tangles, neuritic plaques, and diffuse plaques.

In a study that included all neuropathologic indices in the same model, these indices accounted for 25% of variation in the change point, 32% of variation in the rate of change before the change point, and 21% of variation in the rate of change after the change point (Boyle et al., 2013). The location of the change point was associated with global AD pathology, tangles, and the presence of gross infarcts, micro-infarcts and neocortical Lewy bodies; the rate preterminal decline was associated with global AD pathology, tangle density, and the presence of gross infarcts and Lewy bodies; and lastly, the rate of terminal decline was associated with tangles and the presence Lewy bodies. Notably, amyloid was not associated with any component of the change point model, potentially due to the inclusion of Global AD pathology as a covariate (i.e., these two variables correlated at  $r = 0.78$ ). In another study (Wilson et al., 2015), tangles and the presence of Lewy bodies, gross infarcts and hippocampal sclerosis were included as covariates in a change point model, identifying

associations between the preterminal slope and three neuropathologic indices (i.e., tangles, Lewy bodies and hippocampal sclerosis, accounting for 25.9% of variation) and the terminal slope and two neuropathologic indices (i.e., Lewy bodies and gross infarcts, accounting for 13.2% of variation).

One study evaluated the relationship between neuropathologic indices and specific cognitive constructs in addition to global cognition (Wilson et al., 2010). These researchers identified that higher tangle density was associated with faster preterminal and terminal decline in global cognition as well as all cognitive domains evaluated (i.e., perceptual speed and episodic, semantic, and working memory). Gross and micro-infarcts were associated with faster preterminal decline in global cognition, and more specifically, episodic and working memory. While micro-infarcts were associated with preterminal decline in semantic memory, gross infarcts were associated with terminal decline in this same construct. Neocortical Lewy bodies were related to increased rates of preterminal decline in perceptual speed, and terminal decline in global cognition along with episodic, semantic, and working memory; however, nigral and limbic Lewy bodies were not associated with any components of the change point model.

Another study involving random change points found that greater plaques and tangles, but not Lewy bodies or infarcts, were associated with an earlier onset of terminal decline for both motor and cognitive functioning; however, all neuropathologic indices were associated with both preterminal and terminal rates of decline (Wilson et al., 2012a). An additional study involved a random change point for each of the aforementioned cognitive domains, and found that Global AD pathology was also associated with earlier change points for each cognitive domain (Wilson et al., 2012b). While these researchers found an association between AD pathology and greater rates of preterminal decline in episodic and semantic memory, they found no relationship between AD pathology and rates of terminal decline.

Another group of researchers (Yu et al., 2013) examined the same neuropathologic indices, but evaluated their association with components of the change point model after accounting for variance attributable to the presence of an *APOE*  $\epsilon 4$  allele. The relationship between *APOE*  $\epsilon 4$  status and components of the change point model were discussed above in the genetic risk subsection. When included in the model, AD pathology was associated with an earlier change point and faster rates of decline before and after the change point. The associations between *APOE*  $\epsilon 4$  status and all components of the change point model were all attenuated by the inclusion of AD pathology and became non-significant, albeit the association between the rate of terminal decline and *APOE*  $\epsilon 4$  status remained marginally significant. When examining tangles and amyloid separately, both were associated with an earlier change point and more rapid rates of preterminal and terminal decline, although the association between amyloid and terminal decline was only a trend. When controlling for amyloid burden, the presence of an *APOE*  $\epsilon 4$  allele was still significantly associated with all three components of the change point model. When controlling for tangles, the presence of an *APOE*  $\epsilon 4$  allele was no longer significantly associated with the rate of preterminal decline or the location of the change point, but maintained a modest association with the rate of terminal decline. When controlling for both amyloid and tangles simultaneously, *APOE*  $\epsilon 4$  was not associated with any component of the model, amyloid was only associated with

an earlier change point, and tangle density was still associated with all components of the change point model.

Gross infarcts were not associated with the location of the change point, but were associated with faster rates of preterminal and terminal decline. In contrast, microscopic infarcts were associated with an earlier change point, but not the rates of decline (Yu et al., 2013). The relationships between *APOE*  $\epsilon 4$  status and components of the change point model were unaffected when controlling for the presence of infarcts. A final model run by these authors accounted for global AD pathology, infarcts, Lewy bodies and *APOE*  $\epsilon 4$  status simultaneously. This model found that AD pathology and microscopic infarcts were associated with an earlier change point, while AD pathology, macroscopic infarcts and Lewy bodies were associated with faster rates of cognitive decline before and after the change point. Upon accounting for all neuropathologic indices, the presence of an *APOE*  $\epsilon 4$  allele was not associated with any component of the change point model.

**Personality:** One study (Wilson et al., 2015) involved a series of models evaluating the relationship between personality and cognitive decline. The first model evaluated just the relationship between conscientiousness and the components of the change point model, finding that conscientiousness was not associated with the location of the change point. Higher conscientiousness was associated with a slower rate cognitive decline following the change point, but not before the change point. This relationship (i.e., higher traits leading to slower terminal decline) was true for all facets of conscientiousness (i.e., orderliness, goal striving, and dependability) and all domains of cognition evaluated (i.e., global, episodic, semantic, and working memory), except for perceptual speed and visuospatial ability. In contrast to conscientiousness, neuroticism, baseline depressive symptoms, and the personality facets of negative affect and self-reproach were not associated with any component of the change point model. When included in a model with neuropathologic indices (i.e., tangles and the presence of Lewy bodies, gross infarcts or hippocampal sclerosis), conscientiousness was still associated with a slower rate of decline following the change point, accounting for 4.0% of additional variance in the terminal slope. When an interaction between conscientiousness and various neuropathologic indices were included in the model, an association was observed between conscientiousness, Lewy bodies and the terminal slope, where the relationship between Lewy bodies and the terminal slope was attenuated at higher levels of conscientiousness. In a closer examination of the stages of Lewy body disease (i.e., nigral, limbic, and neocortical), the researchers observed that conscientiousness specifically modified the association between terminal slope and neocortical Lewy body disease.

**Practice effects:** A single group of researchers (Dodge et al., 2011) ran change points models with and without adjusting for practice effects (i.e., using dummy variables for the number of assessments), and identified that change points shifted further from death for three constructs (i.e., learning, memory, language) when practice effects were considered in the model. There was no shift in the change point for executive functions after controlling for practice effects, and a slight shift for the psychomotor speed change point (i.e., ~1 year earlier).

**Cognitive construct:** Figure 4 provides a forest plot of change points preceding terminal decline coded in years to diagnosis with 95% CIs presented when reported by the authors. The change points are organized in terms of the cognitive construct evaluated, as categorized by the authors of this review, and substantial variability in change points was observed both within and between most cognitive constructs. The most commonly measured domain was memory and learning, which includes tasks measuring learning and verbal or visual memory. Change points for this domain ranged from –2.6 years (Wilson et al., 2012b) to –8.4 years (–9.8, –7.1; Sliwinski et al., 2006) before diagnosis. When excluding the earliest change points from the ROS cohort (Wilson et al., 2012a, 2012b), the change points within this domain were fairly comparable, with the lower bound for this range moving to –6.6 years before death (Batterham et al., 2011).

As with dementia cohorts, the earliest observed change point was for a measure of processing speed (i.e., Figure Identification) among the H70 cohort, with the change point preceding death by –14.8 years (–16.6, –10.8; Thorvaldsson et al., 2008). In terms of the latest cognitive ability to decline, change points for various domains using the ROS dataset were very similar for global cognition, processing speed, memory and learning, executive function, and language (range: –2.3 to –4.3; Wilson et al., 2003, 2010, 2012a, 2012b). The ROS cohort experienced a later onset of decline across most cognitive domains in comparison to other cohorts, as displayed visually in Figure 4. Interestingly, as a cognitive domain, processing speed had both the earliest and one of the latest change points observed across samples, with processing speed presenting with close to the latest change point for the ROS cohort. Unlike for the dementia cohorts, verbal IQ, as measured by a test of vocabulary and semantic knowledge, did not have the latest change point. Instead, this construct began declining around –6.4 to –8.2 years before death (MacDonald et al., 2011), which was comparable to change point estimates for other domains. The relationship between rates of change across constructs was also evaluated among the ROS cohort to determine whether dedifferentiation of cognitive abilities occurs in the context of terminal decline; and while the correlations between rates of change were moderate during preterminal decline (i.e., range:  $r = 0.25$  to  $0.46$ ), the correlations were quite large during upon the onset of terminal decline (i.e., range:  $r = 0.83$  to  $0.89$ ; Wilson et al., 2012b). In addition to different cognitive constructs, terminal decline in motor functioning was specifically evaluated in one study (Wilson et al., 2012a), identifying decline in global motor functioning about two years before death, about a half year later than global cognitive decline. Three specific measures of motor functioning (i.e., manual strength, manual dexterity, and gait), all underwent accelerated decline within about two and a half years of death.

Not displayed visually in Figure 4, one study could not reliably estimate change points on tests of word reading (i.e., the National Adult Reading Test), verbal fluency, face recognition, and word recognition (Batterham et al., 2011). For many constructs, there were few change points estimates reported in the literature overall (e.g., visuospatial ability, executive function, language). As with the dementia cohorts, an exact sequence of decline for cognitive constructs could not be determined based on the current findings, considering variability within cognitive constructs, limited data points for some cognitive constructs, and the overlap between the confidence/credible intervals around different change points.



## Discussion

Since the first application of change point modeling in dementia populations (Joseph et al., 1999), the research within this area has steadily progressed, with 35 eligible studies evaluated in the current review. Among these studies, change points were examined in relation to MCI, dementia, and death, with researchers modeling numerous motor, neurological, and cognitive outcomes. The primary aims of this systematic review included identifying the order in which different neurological and cognitive outcomes decline in relation to diagnosis or death, and the determination of factors that modify the rate of decline or the location of the change point for each of these outcomes. In terms of the first aim, as detailed through the summary of results, the findings do not provide a clear and definitive temporal sequence by which different domains decline in the years preceding MCI or death, but offered some indication of a sequence preceding AD.

### Temporal Sequence of Cognitive Decline

Only studies examining MCI explored change points in neurological outcomes, and although these researchers identified early change points for gait speed and white matter hyperintensities, this examination of pre-MCI change points has derived almost entirely from one cohort (i.e., OBAS) with very small sample sizes (i.e.,  $N$  range: 37 to 134) and an unidentified lower bound of the CI surrounding their change points (Buracchio et al., 2010; Carlson, 2008; Howieson et al., 2008; Silbert et al., 2012). If you only consider the pre-MCI change points with estimates for both upper and lower bounds of their CIs, all outcomes (i.e., both cognitive and neurological) occur within the five years preceding diagnosis, apart from finger tapping, which occurs after diagnosis (see Figure 2). One study examining pre-MCI change points for the ROS cohort (Wilson et al., 2011) found earlier change points for both amnesic and non-amnesic MCI (i.e.,  $-6.7$  and  $-5.2$  years pre-diagnosis, respectively), but the researchers did not report confidence intervals for these estimates. Nonetheless, based on a single study, MCI with memory impairment onset earlier than MCI without memory impairment; however, for the OBAS cohort, change points did not differ between cognitive constructs (Howieson et al., 2008).

In regard to dementia, there was more evidence to suggest a sequence of decline preceding AD. A visual examination of Figure 3 appears to indicate an early decline in verbal memory, followed by visuospatial ability, then fluency and executive functions, and lastly verbal IQ. This interpretation is debatable, as this trend was not quantitatively determined, but rather based on a qualitative interpretation of the change points reported across studies. Many of the observed change points have either no reported CI or a very wide CI, overlapping with the intervals for other constructs. Further, some of the estimates for these domains (e.g., verbal IQ, executive functions) derive from just one to three studies (Grober et al., 2008; Johnson et al., 2009; Wilson et al., 2011), and have consequently not been critically evaluated through either direct or conceptual replications. In turn, while there is some evidence for a trend, this conclusion is a tentative one at best. Nonetheless, it does align with previous reviews of cross-sectional research evaluating cognitive deficits associated with preclinical AD (Bäckman et al., 2005; Han, Nguyen, Stricker, & Nation, 2017). One construct sensitive to preclinical AD based on these reviews (i.e., processing speed) was only evaluated by one AD-only study (Wilson et al., 2011) and one general dementia study

(Thorvaldsson et al., 2011). In the context of general dementia, it was the earliest observed change point across studies. Future researchers should consider including processing speed outcomes in future change point analyses of preclinical AD, considering its relationship to white matter integrity (Gunning-Dixon & Raz, 2000) and the early increase of white matter intensities preceding MCI (Silbert et al., 2012).

In contrast to pre-dementia change points, terminal change point studies did not provide evidence of a temporal sequence in cognitive decline preceding death. With the exception of three studies on the ROS cohort finding change points across cognitive domains within five years of death (Wilson et al., 2003, 2012a, 2012b), most all change points were identified as occurring within five to ten years of death. Even typical hold tests tapping into Verbal IQ, which appear to decline last in dementia (Grober et al., 2008), declined within this five-year window, evidencing a global decline in cognitive functioning across domains preceding death.

Although the temporal sequence of cognitive decline was interpreted separately for MCI, AD, and terminal decline, these three endpoints can have shared etiology explaining the cognitive decline that precedes them. Individuals with a diagnosis of MCI will not necessarily develop AD or dementia, but some participants included in the pre-MCI change point studies likely present with an underlying AD or neurodegenerative pathology. Notably, previous researchers have suggested that an amnesic MCI presentation may be better defined as prodromal AD (Dubois & Albert, 2004), and performances on cognitive measures have very good predictive accuracy at determining which participants with MCI will progress to AD (Belleville, Fouquet, Hudon, Zomahoun, & Croteau, 2017). Further, over the course of terminal decline, many older adults will eventually qualify for a dementia diagnosis, and the cause for terminal decline among a subset of participants included in these studies may be an underlying AD or dementia process. Nonetheless, despite their overlap, the division of these three endpoints offers a cleaner framework for interpreting change points findings in aggregate, because in research and clinical practice, MCI, dementia, and terminal decline are often treated as separate but related processes among older adults.

Although few pre-MCI change point studies were identified, the AD literature offers some evidence for a temporal sequence of decline. From the perspective of a systematic review, one aim of aggregating the current findings is to identify typical longitudinal cognitive profiles based on a disease process, where declines observed in specific cognitive domains at retest are indicative of a specific stage of an underlying AD pathology (e.g., while decline in verbal memory may precede a diagnosis by many years, declines in executive function may be more proximal to diagnosis). The reviewed studies show consistent evidence for non-linear preclinical decline that varies by cognitive domain, and they demonstrate the utility of measuring cognitive functioning longitudinally in clinical practice, where observed declines in certain domains could serve as early predictors of a future AD diagnosis. An understanding of the empirical research on longitudinal cognitive change can be informative when differentiating AD from normal cognitive aging and potentially different dementia types.

When clinicians evaluate older adults for AD at a single timepoint, they often compare neuropsychological test performances to cross-sectional normative datasets of age-matched samples, identifying lower than expected performances within cognitive domains that are often reduced in the context of preclinical AD (Bäckman et al., 2005; Han et al., 2017). However, the certainty of a probable AD diagnosis can be enhanced with evidence of documented decline (McKhann et al., 2011); and in the context of a re-evaluation, an understanding of the expected onset and rate of decline preceding diagnosis can improve early detection, where individuals likely to develop AD are identified prior to presenting with impaired cognitive performances based on normative comparisons. However, although this systematic review of change point analyses offers some clarification of the preclinical course of AD, this interpretation was tentative, and the findings are not easily translatable into clinical practice.

### **Variables Modifying the Onset and Rate of Cognitive Decline**

The second aim focused on determining factors that modify the location of a change point in relation to MCI, dementia, or death along with the rates of change both before and after the change point. The MCI studies involved limited focus on covariates, considering there were few of them, and all but one involved the analysis of the OBAS cohort. They found some effects of gender on motor outcomes, where earlier change points for gait speed and finger tapping were observed for men than women. Similarly, few modifying variables were evaluated for dementia studies overall, but some showed a meaningful effect of the change point or rate of change. With more years of education, the change point was delayed, but once accelerated change began, it occurred at a more rapid rate for individuals with more education (Hall et al., 2007; Jacquemin-Gadda et al., 2006). Participants involved more frequently in cognitively engaging activities (e.g., reading, crossword puzzles, playing music) also experienced a delay in the onset of a faster rate of decline (Hall et al., 2009). In terms of dementia type, decline occurred earlier among participants with AD than VaD (Laukka et al., 2012). Dementia type was only evaluated as a change point modifier in one study; while in all other studies, participants were either grouped as a single dementia cohort or the subgroup with AD diagnoses were separately evaluated.

The number of covariates evaluated in the terminal decline studies far exceeded those evaluated among either the MCI or dementia cohorts. For some covariates there were discrepant findings. While one study found no effect of gender decline before the change point (Muniz-Terrera et al., 2013), another found that women declined faster before the change point (Muniz-Terrera et al., 2014); and while one study found women decline at a faster rate following the change point (Muniz-Terrera et al., 2013), another found that women declined at a slower rate following the change point (Muniz-Terrera et al., 2014). Education as a covariate produced similarly discrepant findings, where two studies found that more education delayed the change point (Batterham et al., 2011; Muniz-Terrera et al., 2014), but the rate of accelerated decline was either faster with more education (Muniz-Terrera et al., 2014), faster with less education (Batterham et al., 2011; Muniz-Terrera et al., 2013), or education had no effect at all (Wilson et al., 2007). Personality was also explored as a covariate, where one study determined that higher levels of conscientiousness was not

associated with the location of the change point, but did lead to a slower rate of terminal decline (Wilson et al., 2015).

Aside from demographic characteristics, genetic risk and neuropathology were also explored. The presence of an *APOE*  $\epsilon 4$  allele was related to an earlier change point and a more rapid rate of terminal decline (Wilson et al., 2007; Yu et al., 2013); however, AD neuropathology explained the relationship between *APOE*  $\epsilon 4$  and components of the change point model, as the relationship between *APOE*  $\epsilon 4$  and model components became non-significant with the inclusion of AD neuropathologic indices as covariates in the model (Yu et al., 2013). Multiple neuropathologic indices of AD were evaluated as covariates (e.g., tangles, neuritic plaques, neocortical Lewy bodies, etc.), explaining a substantial amount of variance in the change point along with the pre-terminal and terminal rates of decline (Boyle et al., 2013; Wilson et al., 2015).

### Limitations

The studies reviewed herein were variable in terms of their research designs, cognitive measurements, and analytic approaches, limiting the conclusions that can be drawn from the current systematic review. Among the many longitudinal cohort studies evaluated, the study durations, number of completed measurement waves, and intervals between measurement waves varied substantially. Studies ranged in duration from 10 years (Jacqmin-Gadda et al., 2006; Laukka et al., 2012) to 30 years (Thorvaldsson et al., 2008; Thorvaldsson et al., 2011). The number of completed measurement waves varied from 2 (for a study with up to five waves; MacDonald et al., 2011) to 10.9 (for a study with up to 16 waves; Wilson et al., 2012a). Attrition is not uncommon for longitudinal research, especially among older adults who experience dementia or death during follow-up; however, for some cohorts, many participants completed just a small number of measurement waves on average. The inter-test intervals ranged from annual (which was the most common) to up to five years (Muniz-Terrera et al., 2013; Muniz Terrera et al., 2014; van den Hout et al., 2011). Studies with long intervals between measurement waves may fail to detect the precise onset of change. If a participant undergoes a change point within months of their last measurement, but must wait years till their next assessment, the analysis would misestimate the temporal onset of accelerated decline, biasing the change point estimates calculated for these participants. Comparing change points for studies with such variable intervals may be a reason for the inconsistent findings across studies, where variability in change point estimation may be a consequence of discrepant research designs.

In addition to research designs, the cognitive measures used were also highly variable across studies, with very little overlap. Many tests were assumed to measure the same construct, but they all have unique psychometric characteristics, including different methods of scoring (e.g., total correct, time-to-completion), different reliability estimates, and different evidence for validity. The psychometric qualities of each outcome were not evaluated in the current review, but measurement may influence the variability in change points estimated across studies. For example, the MMSE has a well-known ceiling effect, where most all healthy participants obtain either the highest possible score, or close to the highest possible score. In the context of detecting a change point, older adults may begin accelerated decline years

before this decline is detected by the MMSE, with the change points reported in published studies representing an end of the ceiling effect rather than the true onset of accelerated cognitive decline.

The problem of ceiling effects is endemic in screening measures that are not designed to differentiate between participants across the full spectrum of cognitive ability. Aside from the many studies analyzing change in MMSE scores (Batterham et al., 2011; Ji et al., 2003; Muniz-Terrera et al., 2013, 2014; van den Hout et al., 2011), just one additional study analyzed change through use of a different dementia screening measure (i.e., Cognitive Abilities Screening Instrument; Yu & Ghosh, 2010), and these researchers elected to log-transform the scores on this measure to adjust for the skewness of its distribution. When selecting measures to detect the onset of change in a longitudinal design, researchers must be mindful to select measures that have neither a ceiling nor a floor effect, to ensure change in ability levels is readily detectable by the dependent variable. Some researchers have discussed the psychometric rationale for using specific cognitive tests in their models, emphasizing the normal distributions of scores, sensitivity and specificity of the test at detecting dementia, and lack of floor and ceiling effects (e.g., Hall et al., 2000, 2003).

Another key issue in change point modeling is the relationship between the diagnosis of MCI or dementia and the tests used to detect the change point. In some studies, the same tests that are used to define cognitive impairment in the context of MCI or dementia (e.g., Boyle et al., 2013; Li, Dowling, & Chappell, 2015; Wilson et al., 2003, 2007, 2010, 2011, 2012a, 2012b, 2015; Yu et al., 2013; Yu & Ghosh, 2010) are those that are modeled as dependent variables. This confound makes the clinical endpoint directly contingent on preclinical change in the outcome of interest. This confound may affect the generalizability of research findings to contexts in which different measures are used to diagnose MCI or dementia; however, this contingency also aligns with dementia detection in clinical practice, where the same neuropsychological measures may be used repeatedly until cognitive impairment is detected.

Aside from cognitive measurement, the operationalization of MCI or dementia diagnosis was also variable across studies. While there was some consistency in defining dementia in general (i.e., most studies used DSM-III or DSM-III-R criteria; American Psychiatric Association, 1980, 1987), there was more heterogeneity in defining AD. Most studies used the same standard criteria for AD (McKhann et al., 1984), but some studies used either their own criteria (Johnson et al., 2009) or provided no criteria (Ji et al., 2003). In terms of MCI studies, all but one article evaluated the OBAS cohort, and used two or more consecutive Clinical Dementia Rating Scale scores  $\geq 0.5$  as their psychometric criterion for diagnosis, coupled with the absence of functional impairment (Buracchio et al., 2010; Carlson, 2008; Howieson et al., 2008; Silbert et al., 2012). This same psychometric criterion was used to diagnose dementia in a separate article (Johnson et al., 2009), although it was combined with a more comprehensive assessment (e.g., semi-structured history interview, neurological examination). The presence of functional impairment is a key differential between MCI and dementia diagnosis. Nonetheless, these similarities in diagnostic criteria between MCI and dementia challenge the notion of distinguishing between pre-MCI and pre-dementia change points. However, despite some evidence of overlap in operational definitions between MCI

and AD, no studies used the exact same criteria to define the disorders, and these clinical endpoints were treated as distinct in the current review.

Lastly, the analytical approaches taken by previous researchers also showed substantial inconsistency. An important finding of this review is that change point modelling in cognitive aging includes a wide range of models with many fundamental differences. For instance, some models include both cases (i.e., participants who develop MCI or dementia) and non-cases (i.e., participants who remain healthy throughout follow-up), while others only include participants who ultimately receive a diagnosis at follow-up. Other studies continue to evaluate participants following a dementia diagnosis, while other do not. There is no consensus on the best modeling or estimation approach when detecting change points, and models varied regarding whether they included random effects and whether they used frequentist or Bayesian estimation. Further, the variable inclusion or exclusion of covariates across studies blurs the inferences that can be drawn from the literature in aggregate. There was no common inclusion of covariates across studies, which is likely why some predictors varied in their significance across studies. Considering between-study differences in the significance of covariates, there is also a risk of selective reporting, where covariates that were found to be non-significant were not reported in published findings. This review did not involve a formal evaluation of this type of bias across studies, but such bias could have affected the representation of different covariates in the published literature on preclinical and terminal change points among older adults.

### Future Directions

Change point modeling in aging research is a new and promising avenue for detecting the onset of preclinical and terminal accelerations in cognitive and neurological decline. These models have been extensively used in other research areas as well, including economics (Bardsley, Horvath, Kokoszka, & Young, 2017), climate science (Reeves, Chen, Wang, Lund, & Lu, 2007), and biostatistics (Erdman & Emerson, 2008). Many applications of change points modeling in other fields involve far denser data than the cohort data available in longitudinal aging research; however, the onset of new technologies into longitudinal aging research (e.g., mobile cognitive testing) may bridge the methods used across fields. In the context of studies on cognitive aging, the most commonly used formulation of change point models estimates two linear phases with an abrupt change, alternative formulations also exist that could provide smooth change points (van den Hout et al., 2011) or multiple change points (Grober et al., 2008) and offer more realistic descriptions of late-life cognitive and neurological changes.

To date, the change point research on cognitive aging has evidenced the clear preclinical or terminal change points that occur years before diagnosis or death; and – based on the evaluation of covariates – it is also clear that demographic, genetic, and neuropathologic factors are associated with the onset and rate of decline. However, inference around these modifying variables is clouded by the inconsistent inclusion of covariates across studies. Considering the discrepancies across studies in terms of the estimation approach, cognitive measurements, statistical modeling, and the inclusion or exclusion of covariates, a coordinated analysis of multiple datasets may provide an improved method of drawing

inference on change point studies across cohorts (Hofer & Piccinin, 2009). It is clear based on the current findings that gender and education are both commonly measured and have some effect on components of change point models; and these demographic features should likely be included as covariates across future models to promote comparability. Baseline age is also a candidate for a common covariate in future analyses, as most all studies reported this demographic, but only one evaluated its significance (Muniz-Terrera et al., 2013). Through analytical coordination, the results of future change point models could be as comparable as possible, allowing for stronger inferences to be drawn about the time at which accelerated change begins and the variables that modify the onset and rates of change.

The identification of modifying variables is likely the most useful research finding that can be drawn from change point research. Although meaningful at a population level, the average onset of preclinical decline is of little meaning at the individual patient level unless clinicians know both when to predict decline and how to delay or slow its acceleration. Demographic features, genetic data, and neuroimaging results would support prediction, but modifying the onset and rate of decline requires either behavioral change or intervention. Change point analysis could be useful in future intervention research, where the experimental condition could serve as a covariate, determining the delay in decline attributable to treatment. However, change point analysis may be most useful when determining the interaction between patient characteristics (e.g., age, gender, *APOE ε4* status, white matter hyperintensities) and the effectiveness of a given intervention. Such advances in “precision health” are particularly important in research on dementia, with its long prodromal period and current limitations of clinical detection of neurological impairment, and where signs and symptoms may emerge clearly only years after neuropathological change has accumulated in the brain. Improvement in change point estimation and individualized risk models will provide information to support a precision health approach to the design of effective interventions to delay the onset or slow the rate of decline caused by dementia and related disorders.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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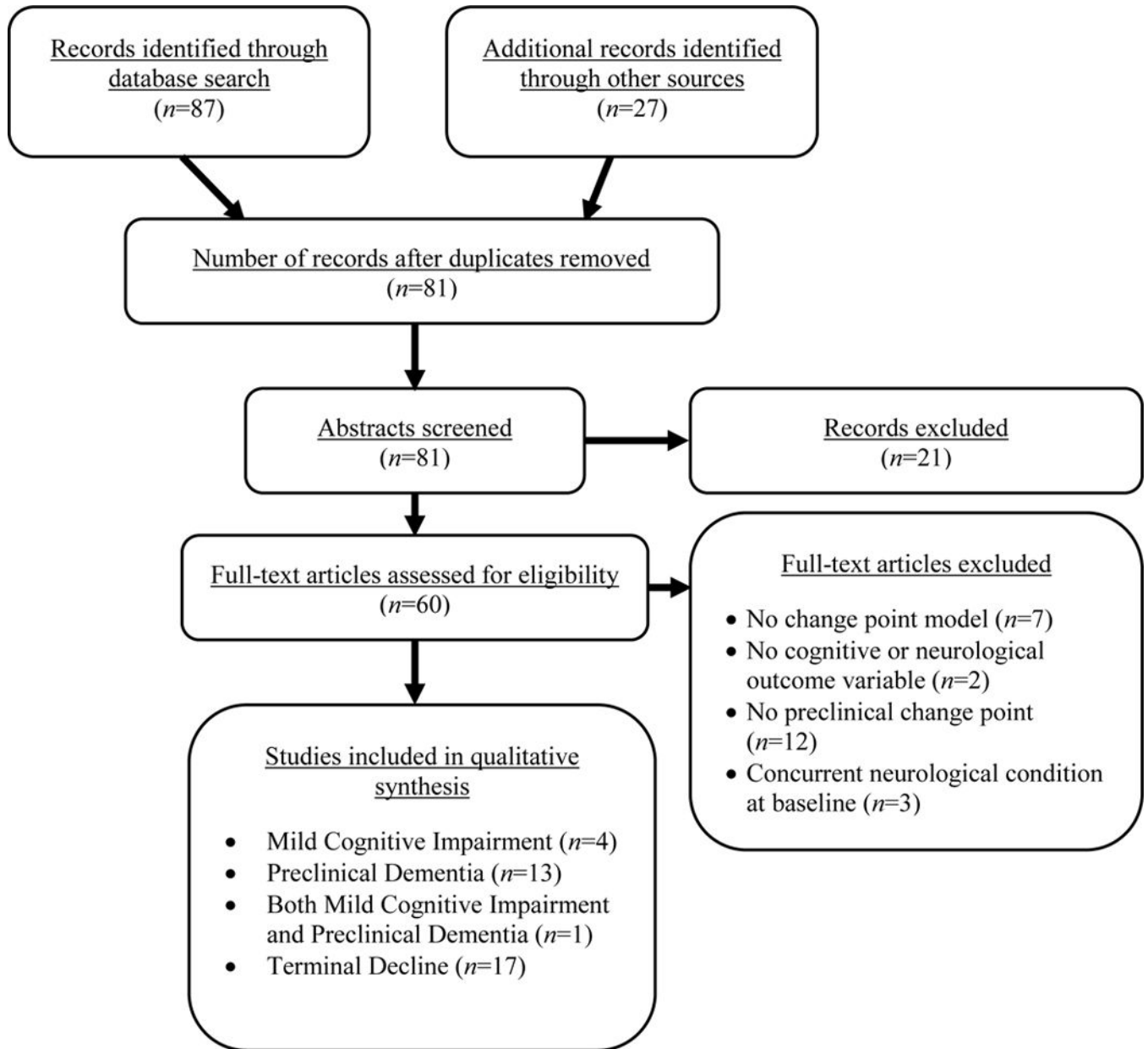
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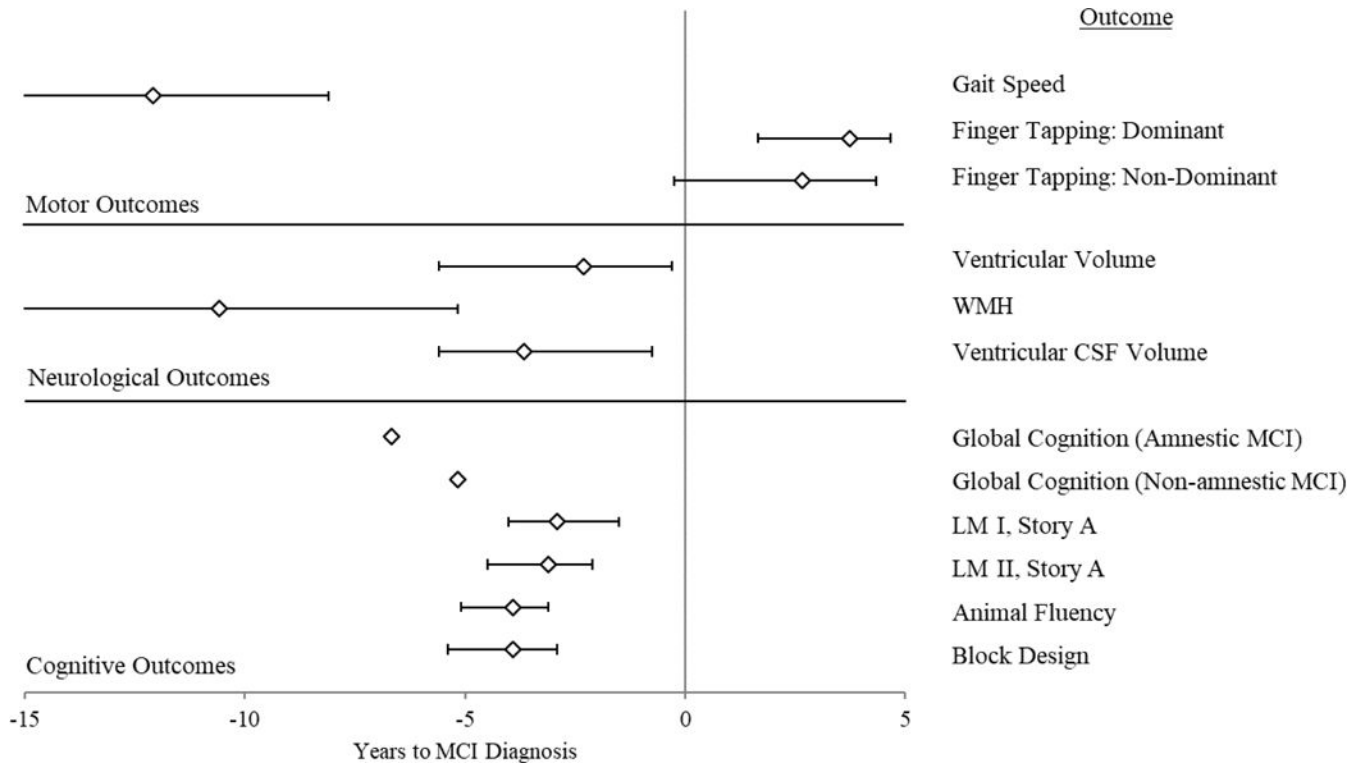
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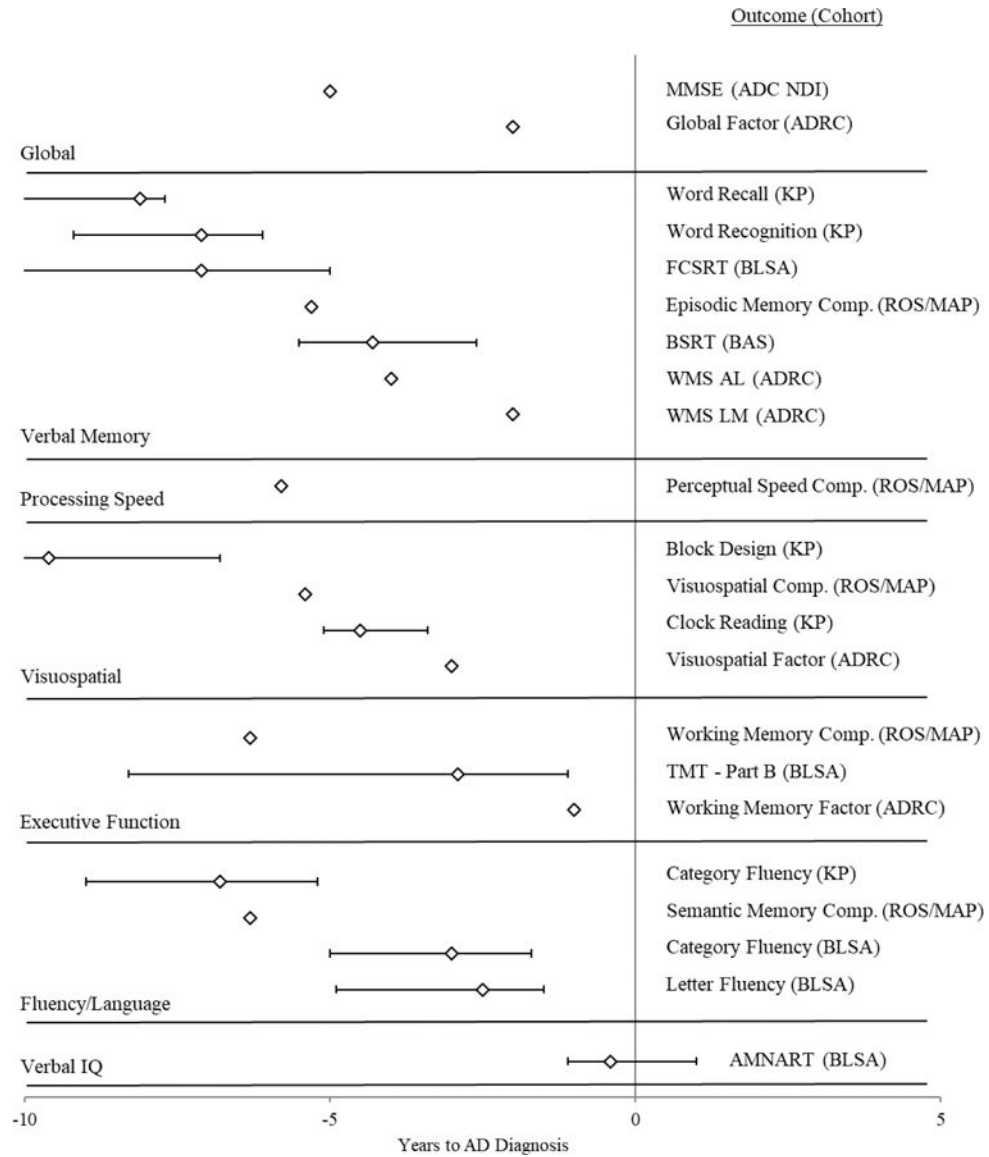


**Figure 1.**  
Flowchart of Systematic Review



**Figure 2. Change Point Estimates with 95% Confidence Intervals for MCI Studies by Outcome Type**

*Note.* All change point estimates derive from the Oregon Brain Aging Study (Buracchio et al., 2010; Carlson, 2008; Howieson et al., 2008; Silbert et al., 2012), except for both Global Cognition change points, which derive from the Religious Orders Study and Memory and Aging Project (Wilson et al., 2011). CSF = Cerebrospinal Fluid; LM = Logical Memory; MCI = Mild Cognitive Impairment; WMH = White Matter Hyperintensities. Lower end confidence intervals for Gait Speed and WMH were unknown. All change points for motor outcomes come from the full sample (Men and Women; Buracchio et al., 2010).



**Figure 3. Change Point Estimates with 95% Confidence/Credible Intervals for Alzheimer's Disease Studies by Cognitive Construct**

*Note.* ADC NDI = Alzheimer's Disease Centers Neuropsychological Database Initiative; ADRC = Washington University School of Medicine Alzheimer's Disease Research Center; AL = Associate Learning; AMNART = American Version of the Nelson Adult Reading Test; BAS = Bronx Aging Study; BLSA = Baltimore Longitudinal Study of Aging; BSRT = Buschke Selective Reminding Test; Comp. = Composite; FCSRT = Free and Cued Selective Reminding Test; H70 = Gerontological and Geriatric Population Study; KP = Kungsholmen Project; LM = Logical Memory; MAP = Memory and Aging Project; MMSE = Mini Mental Status Examination; ROS = Religious Orders Study; TMT = Trail Making Test; WMS = Wechsler Memory Scale. For the Bronx Aging Study, the only change point listed above is for the AD-only sample (Hall et al., 2000). One study (Johnson et al., 2009) reported a change point for a Verbal Memory factor, and separate change points for the tests that composed this Verbal Memory factor. The change points included in the figure above came



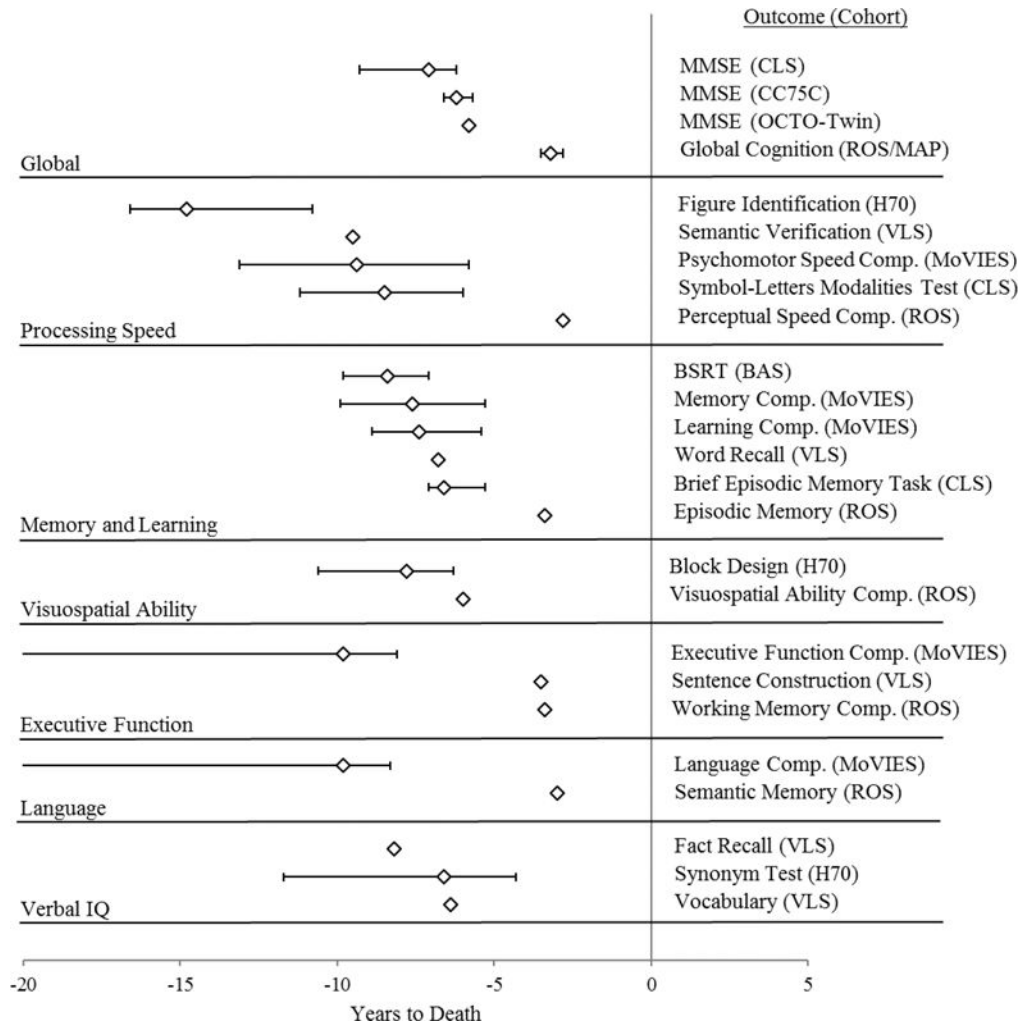
from the individual tests and not the factor. Another study (Grober et al., 2008) provided two change points for the Free and Cued Selective Reminding Test. Only the first, earlier change point is displayed on the figure. Two studies reported change points for the ROS/MAP cohort (Li et al., 2015; Wilson et al., 2011), and only the change points from the study that reported estimates for multiple constructs are displayed above (Wilson et al., 2011).

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**Figure 4. Change Point Estimates with 95% Confidence/Credible Intervals for Terminal Decline Studies by Cognitive Construct**

*Note.* BAS = Bronx Aging Study; BSRT = Buschke Selective Reminding Test; CC75C = Cambridge City over 75 Cohort Study; CLS = Canberra Longitudinal Study; H70 = Gerontological and Geriatric Population Study; MMSE = Mini Mental Status Examination; MoVIES = Monongahela Valley Independent Elders Survey; OCTO-Twin = Origins of Variance in the Old-old Study; MAP = Memory and Aging Project; ROS = Religious Orders Study; VLS = Victoria Longitudinal Study. Three studies (Muniz-Terrera et al., 2013; Muniz-Terrera et al., 2014; van den Hout et al., 2013) all reported change points for the MMSE using CC75C data, but only the change point for one study (Muniz-Terrera et al., 2014) is displayed above. Eight studies (Boyle et al., 2013; Wilson et al., 2003, 2007, 2010, 2012a, 2012b, 2015; Yu et al., 2013) provided change points for a Global Cognition Summary Measure using data from the ROS and/or MAP, but only the change point from one study (Wilson et al., 2015) is displayed above. Three studies provided estimates for ROS data based on cognitive construct (Wilson et al., 2003, 2012a, 2012b), and only the change points from one study (Wilson et al., 2003) is displayed above.

**Table 1**

**MCI Change Point Studies: Participant Characteristics**

Cohort	Study	n*	$\bar{x}$ Age (SD)	Age Range	% Male	Education ( $\bar{x}$ years)	% White	% APOE $\epsilon 4+$	MCI Definition
OBAS	Buracchio et al. (2010)	95	83.5 (7.0)	65-98	39.0	14.7	-	27.7	2 consecutive CDRs $\leq$ 0.5; No functional impairment
	Carlson et al. (2008)	37	84.8 (6.9)	66-97	35.1	13.8	-	24.3	Same as above
	Howieson et al. (2008)	68	84.9 (5.0)	65-110	33.8	14.6	98.1 <sup>†</sup>	-	Same as above
ROS/MAP	Silbert et al. (2012)	134	84.8 (5.9)	65-102	38.8	14.2	-	20.9	Same as above
	Wilson et al. (2011)	742	78.1	-	29.0	16.6	90.7 <sup>†</sup>	-	Cognitive impairment was determined by educational adjusted cutoff scores and a neuropsychologist. Participants with cognitive impairment, but not meeting criteria for dementia, were classified as MCI, and divided into amnesic and non-amnesic subtypes

Note. % APOE  $\epsilon 4+$  = Percent positive for the Apolipoprotein E  $\epsilon 4$  allele; CDR = Clinical Dementia Rating Scale; Educ. = Education; MCI = Mild Cognitive Impairment; OBAS = Oregon Brain Aging Study; ROS/MAP = Religious Orders Study/Memory and Aging Project

\* n values correspond to the sample size of participants that ultimately received an MCI diagnosis and were included in analysis.

<sup>†</sup> Value derived from the full sample, rather than just the sub-sample developing MCI.

**Table 2**

**Dementia Change Point Studies: Participant Characteristics**

Cohort	Study	n*	$\bar{x}$ Age (SD)	Age Range	% Male	Educ. ( $\bar{x}$ yrs. or specified)	% White	% APOE e4+	MCI/Dementia Definition
ADC NDI	Ji et al. (2003)	92	76.9 (9.4)	-	-	14.1	-	-	No definition provided, but sample described as having a definitive AD diagnosis
ADRC	Johnson et al. (2009)	134	80.4 (8.9)	60-101	34.0	14.1	-	27.0	CDR = 0.5 → Uncertain Dementia; CDR 0.5 → AD; based on semi-structured interviews with participants/collateral sources, health history, medication/depression inventories, aphasia assessment, and neurologic examination
BLSA	Grober et al. (2008)	92	79.8 (6.9)	-	48.0	16.5	-	-	Dementia (APA, 1980); Probable/Possible AD (McKhann et al., 1984)
BAS †	Hall et al. (2000)	125 (71 w/AD)	80.5 (3.3)	75-85	35.5	Mode of 7 <sup>th</sup> -9 <sup>th</sup> Grade	90	-	Dementia (APA, 1980); Probable AD (McKhann et al., 1984); MID based on clinical features and modified Hachinski ischemic score (Rosen et al., 1980)
H70	Thorvaldsson et al. (2011)	127	70	70-70	34.0	Same as above	-	-	>8 on Blessed Information Memory Concentration Test
HAAS	Yu & Ghosh (2010)	299	-	71	-	59% >10 years	0	18.0	Dementia (APA, 1987; Cummings & Benson, 1992); detailed description of diagnostic process reported elsewhere (White et al., 1996)
KP	Laukka et al. (2012)	286 w/AD	82.5 (4.7)	-	14.3	56.6% <8 years	-	-	Dementia (APA, 1980) AD (McKhann et al., 1984)
		63 w/VaD	82.1 (4.9)	-	23.8	52.4% <8 years	-	-	Dementia (APA, 1980) VaD (Román et al., 1993)
PP	Thorvaldsson et al. (2011)	279	82	75	18.0	43% >7 years	-	-	Dementia (APA, 1987)
	Jacquin-Gadda et al. (2006)	314	-	65	-	43.3% w/out primary school	-	-	Dementia (APA, 1987)
ROS/MAP	Li et al. (2015)	429	81.5 (6.6)	64-102	26.8	79.3% 12 years	-	29.6	AD (McKhann et al., 1984)
	Wilson et al. (2011)	462	81.3	-	27.3	16.4	87.9 <sup>‡</sup>	-	AD (McKhann et al., 1984)

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Note. % *APOE* ε4+ = Percent positive for the Apolipoprotein E ε4 allele; AD = Alzheimer’s disease; ADCNDI = Alzheimer’s Disease Centers Neuropsychological Database Initiative; ADRC = Washington University School of Medicine Alzheimer’s Disease Research Center; APA = American Psychiatric Association; BAS = Bronx Aging Study; BLSA = Baltimore Longitudinal Study of Aging; CDR = Clinical Dementia Rating Scale; Educ. = Education; H70 = Gerontological and Geriatric Population Study; HAAS = Honolulu Asia Aging Study; KP = Kungsholmen Project; PP = Paquid Project; MAP = Memory and Aging Project; MID = Multi-infarct Dementia; ROS = Religious Orders Study; VaD = Vascular Dementia.

\* *n* values correspond to the sample size of participants that ultimately received a dementia diagnosis or died over the course of the study and were included in analysis.

<sup>†</sup>For Hall et al. (2001, 2001), demographic characteristics for the BAS sample and the diagnostic criteria for dementia and Alzheimer’s disease were pulled from another article (Katzman et al., 1989).

<sup>‡</sup>Value derived from the full sample, rather than just the sub-sample developing dementia.

**Table 3**  
Terminal Decline Change Point Studies: Sample Size Included in Analysis and Baseline Participant Characteristics

Cohort	Study	<i>n</i> <sup>*</sup>	$\bar{x}$ Age (SD)	Age Range	% Male	Educ. ( $\bar{x}$ years or specified)	% White	% APOE e4+
BAS	Slivinski et al. (2006)	445	79.3 (3.1)	75-85	-	-	-	-
CC75C	Muniz-Terrera et al. (2013)	1,896	81	75	35.0	-	-	-
	Muniz-Terrera et al. (2014)	2,078 <sup>†</sup>	81	75	35.0	Left school at $\bar{x}$ age 14.8 years	-	-
	van den Hout et al. (2011)	156	81.6	75	-	-	-	-
CLS	Batterham et al. (2011)	687	77.3 (5.1)	70	50.9 <sup>‡</sup>	11.4	-	-
H70	Thorvaldsson et al. (2008)	288	70	All 70	43.8	-	-	-
MoVIES	Dodge et al. (2011)	613	74.3 (6.0)	64-95	49.8	54.3% w/high school or more	-	-
MAP	Wilson et al. (2007)	115	83.7 (5.1)	-	41.7	14.7	91.6 <sup>§</sup>	29.5
OCTO-Twin	van den Hout et al. (2013)	656	-	80	-	-	-	-
ROS	Wilson et al. (2003)	122	80.5 (6.3)	-	48.4	18.3	-	-
	Wilson et al. (2010)	354	-	-	41.0	-	94.4	-
	Wilson et al. (2012a)	124	77.7 (6.3)	65-93	37.9	18.0	-	-
	Wilson et al. (2012b)	174	78.2 (6.1)	-	38.5	18.1	96.6	-
ROS/MAP	Boyle et al. (2013)	573	-	-	36.0 <sup>§</sup>	16.5 <sup>¶</sup>	95 <sup>¶¶</sup>	-
	Wilson et al. (2015)	309	-	50	35.3	18.2	-	-
	Yu et al. (2013)	581	88.9 (6.5)	71-108	34.4	-	-	23.8
VLS	MacDonald et al. (2011)	265	72.7 (6.4)	55-85 <sup>#</sup>	-	-	-	-

Note. % APOE e4 = Percent positive for the Apolipoprotein E e4 allele; BAS = Bronx Aging Study; CC75C = Cambridge City over 75 Cohort Study; CLS = Canberra Longitudinal Study; Educ. = Education; H70 = Gerontological and Geriatric Population Study; MoVIES = Monongahela Valley Independent Elders Survey; OCTO-Twin = Origins of Variance in the Old-old Study; MAP = Memory and Aging Project; ROS = Religious Orders Study; VLS = Victoria Longitudinal Study.

<sup>\*</sup> *n* values correspond to the sample size of participants that ultimately died over the course of the study and were included in analysis.

<sup>†</sup> Muniz-Terrera et al. (2014) specified that only five participants from the baseline cohort were alive at the time of analysis. It is not clear from the article whether the *n* value reported was the sample size included in analysis and whether this value is inclusive of participants that did not pass away during follow-up.

<sup>‡</sup> Percent Male for Batterham et al. (2011) derived from the full sample, not just participants dying during follow-up.

<sup>§</sup> Percent White for Wilson et al. (2007) derived from the full sample, not just participants dying during follow-up.

<sup>¶</sup> Values taken from full sample reported in manuscript, although only subsample of participants used in change point analysis.

#For MacDonald et al. (2011), the age range was provided for all participants in the VLS, not just those dying at follow-up.

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MCI Change Point Studies: Study Design Characteristics, Outcomes and Change Points

Table 4

Cohort	Authors (Year)	Duration (Years)	Max # MWS	# MWS: $\bar{x}$ (SD)	Years Follow-up: $\bar{x}$ (SD)	Interval Duration (Years)	Bayesian/Frequentist; Random/Fixed CP	Covariates	Outcome	Construct	CP (95% CI) in Years to Dx
OBAS	Buracchio et al. (2010)	20	20	–	10.5 (4.0)	1	Frequentist; Fixed CP	Age, education, sex, <i>APOE</i> ε4 status, baseline speed, stroke, and depression	Gait Speed	Motor	Men/Women: –12.1 (Unknown to –8.1) Men: –14.2 (Unknown to –8.7) Women: –6.0 (–9.5 to –4.6)
	Carlson et al. (2008)	15	12	6.0 (3.3)	6.3 (3.6)	1	Frequentist; Fixed CP	–	Finger Tapping: Dominant Hand	Motor	Men/Women: 3.8 (1.7 to 4.7) Men: –5.9 (–10.0 to 6.5) Women: –3.0 (0.2 to 4.9)
	Howieson et al. (2008)	–	–	–	8.0 (2.8)	1	Frequentist; Fixed CP	–	Finger Tapping: Non-Dominant Hand	Motor	Men/Women: 2.7 (–0.3 to 4.3) Men: 6.2 (–7.7 to 6.8) Women: 0.4 (–1.8 to 2.9)
	Silbert et al. (2012)	19.6	15	<i>M</i> = 4.0	10.4 (4.1)	1	Frequentist; Fixed CP	Age, gender, <i>APOE</i> ε4 status, diabetes, HTN, smoking, stroke/TIA, and baseline intracranial and hippocampal volume	Ventricular Volume	Neurological	–2.3 (–5.6 to –0.3)
									LM I, Story A	Verbal Memory	–2.9 (–4.0 to –1.5)
									LM II, Story A	Verbal Memory	–3.1 (–4.5 to –2.1)
									Animal Fluency	Verbal Memory	–3.9 (–5.1 to –3.1)
									Block Design	Visuospatial Ability	–3.9 (–5.4 to –2.9)
									WMH	Neurological	–10.6 (Unknown to –5.2)
ROS/MAP	Wilson et al. (2011)	16*	–	–	7.8 (3.9)*	1	Frequentist; Fixed CP	Age, sex, and education	Ventricular CSF Volume	Neurological	–3.7 (–5.6 to –0.8)
									Global Composite	Global	Amnesic MCI: –6.7 Non-amnesic MCI: –5.2

Note.

\* Values based on full sample, not just MCI sub-sample. *APOE*ε4 = Apolipoprotein E ε4 allele; CI = Confidence or Credible Interval; CLS = Canberra Longitudinal Study; CP = Change Point; CSF = Cerebrospinal Fluid; HTN = Hypertension; LM = Logical Memory; MWS = Measurement Waves; OBAS = Oregon Brain Aging Study; ROS/MAP = Religious Orders Study/Memory and Aging Project; WMH = White Matter Hyperintensities.



Table 5

Dementia Change Point Studies: Study Design Characteristics, Outcomes and Change Points

Cohort	Authors (Year)	Duration (Years)	Max # MWS	# MWS: $\bar{x}$ (SD)	Years Follow-up $\bar{x}$ (SD)	Interval Duration (Years)	Bayesian/Frequentist; Random/Fixed CP	Covariates	Outcome	Construct	CP (95% CI) in Years to Dx
ADC NDI	Ji et al. (2003)	12	-	-	-	-	Frequentist; Fixed CP	-	MMSE	Global	AD-Only: -5
WUSM ADRC	Johnson et al. (2009)	25.7	-	7.1*	5.9 (5.3)	1	Frequentist; Fixed CP	Age, education	Global Factor Verbal Memory Factor WMS Associate Learning Memory WMS Logical Memory Visuospatial Factor Working Memory Factor	Global Verbal Memory Memory Verbal Memory Verbal Memory Memory Visuospatial Executive Function	AD-Only: -2 AD-Only: -1 AD-Only: -4 AD-Only: -2 AD-Only: -3 AD-Only: -1
BLSA	Grober et al. (2008)	15	-	-	4.6	2.4	Frequentist; Fixed CP	-	FCSRT Category Fluency Letter Fluency Trail Making Test Part B AMNART	Verbal Memory Fluency Fluency Executive Function Verbal IQ	Two Change Points Reported: AD-Only: -7.1 (Unknown to -5) AD-Only: -2.6 (CI Not Reported) AD-Only: -3 (-5.0 to -1.7) AD-Only: -2.5 (-4.9 to -1.5) AD-Only: -2.9 (-8.3 to -1.1) AD-Only: -0.4 (-1.1 to 0.1)
BAS	Hall et al. (2000)	18	10	-	-	1	Frequentist; Fixed CP	-	BSRT	Verbal Memory	Dementia: -5.1 (-6.1 to -4.2) AD-Only: -4.3 (-5.5 to -2.6)
	Hall et al. (2001) <sup>†</sup>	19	-	-	1-1.5	1-1.5	Bayesian & Frequentist; Random & Fixed CPs	-	BSRT	Verbal Memory	Dementia: -7.3 (-9.0 to -3.1)
	Hall et al. (2003)	20	-	-	1	1	Bayesian & Frequentist; Random & Fixed CPs	-	WAIS-III PIQ	Visuospatial Ability	Dementia: -3.0 (-4.1 to -1.6)
	Hall et al. (2007)	27	-	2.7; 3.6; 4.2 <sup>‡</sup>	~1.5 <sup>‡</sup>	-	Frequentist; Fixed CP	Education	BSRT	Verbal Memory	Dementia: -7.96 (-9.9 to -1.2)
	Hall et al. (2009)	28	-	3.5 <sup>§</sup>	5.0 <sup>§</sup>	1-1.5	Frequentist; Fixed CP	Cognitive activity, education	BSRT	Verbal Memory	Dementia: -5.5 (-7.0 to -4.2)
H70	Thorvaldsson et al. (2011)	30	12	-	~2.5	~2.5	Frequentist; Fixed CP	-	Synonym Test Block Design Figure Identification Cognitive Abilities Screening Instrument	Verbal IQ Visuospatial Ability Processing Speed Global	Dementia: -5.5 (-7.1 to -4.0) Dementia: -5.9 (-7.1 to -4.6) Dementia: -8.6 (-11.6 to -5.6) Dementia: -10.9 (-14.4 to -7.5)
HAAS	Yu & Ghosh (2010)	9	4	-	-	3	Bayesian; Random CP	Education, hypertension, APOE e4 status	-	-	-

Cohort	Authors (Year)	Duration (Years)	Max # MWS	# MWS: $\bar{x}$ (SD)	Years Follow-up $\bar{x}$ (SD)	Interval Duration (Years)	Bayesian/Frequentist/Random/Fixed CP	Covariates	Outcome	Construct	CP (95% CI) in Years to Dx
KP	Laukka et al. (2012)	10	4	2.8 (1.0)	-	3	Frequentist; Fixed CP		Word Recall Word Recognition Block Design Category Fluency Clock Reading	Verbal Memory Verbal Memory Memory Visuospatial Ability Fluency Visuospatial Ability	AD-Only: -8.1 (Unknown to -7.7) VaD-Only: -6.5 (Unknown to -3.1) AD-Only: -7.1 (-9.2 to -6.1) VaD-Only: -4.8 (-6.8 to -3.3) AD-Only: -9.6 (Unknown to -6.8) VaD-Only: -5.3 (Unknown to -3.7) AD-Only: -6.8 (-9.0 to -5.2) VaD-Only: -4.4 (-5.7 to -3.1) AD-Only: -4.5 (-5.1 to -3.4) VaD-Only: -4.8 (-7.2 to -3.4)
PP	Thorvaldsson et al. (2011)	13	4	-	-	3	Frequentist; Fixed CP	Baseline Age	Word Recall Block Design Category Fluency Clock Reading	Verbal Memory Visuospatial Ability Fluency Visuospatial Ability	Dementia: -8.6 (Unknown to -6.2) Dementia: -8.3 (Unknown to -5.4) Dementia: -4.6 (-6.5 to -3.5) Dementia: -4.1 (-5.9 to -2.8)
ROS/MAP	Jacquin-Gadda et al. (2006) <sup>f</sup> Li et al. (2015)	10 -	6 12	- 7.1 (2.8)	- -	~2 1	Frequentist; Random CP Quantile Regression w/CP	Education Gender, education, <i>APOE</i> e4 status	BVRT Episodic Memory Composite <sup>#</sup>	Visual Memory Verbal Memory	- AD-Only: -4.6 (-5.0 to -4.1)**
	Wilson et al. (2011)	16		7.4 (3.8)	7.0 (4.0)	1	Frequentist; Fixed CP	Age, sex, education	Global Composite Episodic Memory Semantic Memory Working Memory Perceptual Speed Visuospatial Ability	Global Verbal Memory Language Executive Function Processing Speed Visuospatial Ability	AD-Only: -5.4 AD-Only (w/o baseline MCI): -4.5 AD-Only: -5.3 AD-Only: -6.3 AD-Only: -6.3 AD-Only: -5.8 AD-Only: -5.4

Note. AD = Alzheimer's disease; *APOE* e4 = Apolipoprotein E e4 allele; ADC NDI = Alzheimer's Disease Centers Neuropsychological Database Initiative; AMNART = American Version of the Nelson Adult Reading Test; BAS = Bronx Aging Study; BLSA = Baltimore Longitudinal Study of Aging; BSRT = Buschke Selective Reminding Test; BVRT = Benton Visual Retention Test; CI = Confidence or Credible Interval; CP = Change Point; FCSRT = Free and Cued Selective Reminding Test; H70 = Gerontological and Geriatric Population Study; KP = Kungsholmen Project; MCI = Mild Cognitive Impairment; MMSE = Mini Mental Status Examination; MWS = Measurement Waves; PP = Paquid Project; MAP = Memory and Aging Project; ROS = Religious Orders Study; VaD = Vascular Dementia; WAIS-III PIQ = Wechsler Adult Intelligence Scale, Third Edition, Performance IQ; WMS = Wechsler Memory Scale; WUSM ADRC = Washington University School of Medicine Alzheimer's Disease Research Center.

<sup>\*</sup> For Johnson et al. (2009), the average number of observations was calculated by dividing the total assessments for participants progressing to AD (i.e., 957) by the number of participants progressing to AD (n = 134)

<sup>f</sup> For Hall et al. (2001), the change points provided are for full models, but the authors also reported two reduced models with similar results.

<sup>g</sup> For Hall et al. (2007), the mean number of visits before dementia diagnosis was broken down by three groups, displayed in the following order within the table: Education 7 years; 8-11 years; 12 years (No significant difference was observed between groups for this variable). The mean testing interval durations were also divided by education level for this study, but they were all approximately 1.5 years.

<sup>h</sup> For Hall et al. (2009), the average number of years follow-up was calculated by dividing the total number of person-years reported (i.e., 505) by the number of participants in the analysis (i.e., 101). The average number of visits was calculated by dividing the total number of clinic visits (i.e., 351) by the number of participants (i.e., 101).

Jacqmin-Gadda et al. (2006) included a random change point and did not report a mean or modal change point in relation to dementia diagnosis for the sample evaluated.

#Tests included in composite provided in Wilson et al. (2002).

\*\*Li et al. (2015) reported a quantile regression with change points reported for the 20<sup>th</sup>, 50<sup>th</sup>, and 80<sup>th</sup> percentile. The change point provided here is the one for the 50<sup>th</sup> percentile.

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**Table 6**

Terminal Decline Change Point Studies: Study Design Characteristics, Outcomes and Change Points

Cohort	Authors (Year)	Duration (Years)	Max # MWS	# MWS: $\bar{x}$ (SD)	Years Follow-up $\bar{x}$ (SD)	Interval Duration (Years)	Bayesian/Frequentist; Random/Fixed CP	Covariates	Outcome	Construct	CP (95% CI) in Years to Death
BAS	Slivinski et al. (2006)	-	-	-	5.7	-	Frequentist; Fixed CP	Dementia diagnosis	BSRT	Verbal Memory	-8.4 (-9.8 to -7.1)
CC75C	Muniz-Terrera et al. (2013)	17	7	-	-	-	Bayesian; Both	Education, gender, age at death, baseline physical and cognitive impairment	MMSE	Global	-7.7 (-8.1 to -7.2)*
CLS	Muniz-Terrera et al. (2014)	21	7	-	-	2-5	Bayesian; Random CP	Education, gender, age at death, baseline physical and cognitive impairment	MMSE	Global	-6.2 (-6.6 to -5.7)
	van den Hout et al. (2011)	21	7	-	-	2-5	Bayesian; Random CP	-	MMSE	Global	-6.1
	Batterham et al. (2011)	12	4	2.0 <sup>†</sup>	-	-	Frequentist; Fixed CP	Education, gender, heart attack/hypertension, grip strength, smoking, functional ability, disease count, and depression	MMSE	Global	-7.1 (-9.3 to -6.2)
H70	Thorvaldsson et al. (2008)	30	12	-	-	~2.5	Frequentist; Fixed CP	-	Symbol-Letters Modalities Test	Processing Speed Memory	-8.5 (-11.2 to -6.0)
									Brief Episodic Memory Tasks <sup>‡</sup>	Verbal IQ	-6.6 (-11.7 to -4.3)
MoVIES	Dodge et al. (2011) <sup>§</sup>	14	9	-	6.8 (4.0)	1.5	Frequentist; Fixed CP	Education, sex, sampling group, and practice effects	Learning Memory Composite	Learning Memory	-7.4 (-8.9 to -5.4)
									Psychomotor Speed Composite	Psychomotor Speed	-7.6 (-9.9 to -5.3)
									Executive Function Composite	Executive Function	-9.4 (-13.1 to -5.8)
MAP	Wilson et al. (2007)	9	9	4.0	-	1	Frequentist; Fixed CP	Education, age, sex	Language Composite	Language	-9.8 (Unknown to -8.1)
									Global Composite	Global	-3.5 <sup>¶</sup>
OCTO-Twin	van den Hout et al. (2011)	10	5	3.1 <sup>#</sup>	-	2	Frequentist; Random CP	-	MMSE	Global	-5.8
ROS	Wilson et al. (2003)**	8	9	5.6	-	1	Frequentist; Fixed CP	Age, sex, education, medical conditions, disability	Global Composite	Global	-3.6

Cohort	Authors (Year)	Duration (Years)	Max # MWs	# MWs: $\bar{x}$ (SD)	Years Follow-up $\bar{x}$ (SD)	Interval Duration (Years)	Bayesian/Frequentist; Random/Fixed CP	Covariates	Outcome	Construct	CP (95% CI) in Years to Death
			14	-	6.4 (3.2)	1	Frequentist; Fixed CP	-	Perceptual Speed Episodic Memory Semantic Memory Working Memory Visuospatial Ability	Processing Speed Verbal Memory Language Executive Function Visuospatial Ability	-2.8 -3.4 -3.3 -3.8 -6.0
	Wilson et al. (2010)	13							Global Cognition Summary Measure	Global	-4.3
	Wilson et al. (2012a)		16	10.9 (1.8)		1	Bayesian; Random CP	Age at death, vascular risk factors and conditions, plaques/tangles, Lewy bodies, cerebral infarcts	Global Cognition Summary Measure	Global	-2.8 (-3.2 to -2.4)
									Episodic Memory Semantic Memory Working Memory Perceptual Speed Motor Function Summary Measure Manual Strength Manual Dexterity Gait	Verbal Memory Language Executive Function Visuospatial Ability Motor Motor Motor	-3.1 (-3.6 to -2.6) -2.7 (-3.1 to -2.3) -2.8 (-3.5 to -2.4) -3.2 (-3.8 to -2.7) -2.5 (-2.9 to -2.1) -2.5 (-3.0 to -2.1) -2.4 (-2.7 to -2.1) -2.5 (-2.8 to -2.1)
	Wilson et al. (2012b)	-	16	10.2 (2.0)	-	1	Bayesian; Random CP	Age at death, sex, and education	Episodic Memory Semantic Memory Working Memory Perceptual Speed	Verbal Memory Language Executive Function Visuospatial Ability	-2.6 -2.3 -2.4 -2.6
ROS/MAP	Boyle et al. (2013)	18	18	8.6 (3.0)	-	1	Bayesian; Random CP	Global AD pathology, amyloid, tangles, gross and micro infarcts, Lewy bodies	Global Cognition Summary Measure	Global	-3.0 (-3.2 to -2.8)
	Wilson et al. (2015)	-	-	-	10.7 (4.0)	1	Bayesian; Random CP	Age at death, sex, education, conscientiousness, neuroticism, depressive symptoms, tangles, gross and micro infarcts, Lewy bodies, hippocampal sclerosis	Global Cognition Summary Measure	Global	-3.2 (-3.6 to -2.8)
	Yu et al. (2013)	17	-	-	8.0	1	Bayesian; Random CP	Age, sex, education, APOE $\epsilon$ 4 status, global AD pathology, amyloid, tangles, gross and micro infarcts, Lewy bodies	Global Cognition Summary Measure	Global	APOE $\epsilon$ 4+/-: -3.2 (-3.5 to -2.9) APOE $\epsilon$ 4+/-: -4.0 (-4.7 to -3.2)††

Cohort	Authors (Year)	Duration (Years)	Max # MWs	# MWs: $\bar{x}$ (SD)	Years Follow-up $\bar{x}$ (SD)	Interval Duration (Years)	Bayesian/Frequentist; Random/Fixed CP	Covariates	Outcome	Construct	CP (95% CI) in Years to Death
VLS	MacDonald et al. (2011)	12	5	2.0 <sup>††</sup>	8.1	3	Frequentist; Fixed CP	Age at death	Semantic Verification Sentence Construction Word Recall Fact Recall Vocabulary	Processing Speed Executive Function Verbal Memory Verbal IQ Verbal IQ	-9.5 -3.5 -6.8 -8.2 -6.4

Note. AD = Alzheimer's disease; ADC NDI = Alzheimer's Disease Centers Neuropsychological Database Initiative; AMNART = American Version of the Nelson Adult Reading Test; *APOE*  $\epsilon 4$  = Apolipoprotein E  $\epsilon 4$  allele; BAS = Bronx Aging Study; BLSA = Baltimore Longitudinal Study of Aging; BSRT = Buschke Selective Reminding Test; BVRT = Benton Visual Retention Test; CC75C = Cambridge City over 75 Cohort Study; CDR = Clinical Dementia Rating Scale; CI = Confidence or Credible Interval; CLS = Canberra Longitudinal Study; CSF = Cerebrospinal Fluid; FCSRT = Free and Cued Selective Reminding Test; H70 = Gerontological and Geriatric Population Study; KP = Kungsholmen Project; LM = Logical Memory; MMSE = Mini Mental Status Examination; MoVIES = Monongahela Valley Independent Elders Survey; MWs = Measurement Waves; OBAS = Oregon Brain Aging Study; OCTO-Twin = Origins of Variance in the Old-old Study; PP = Paquid Project; MAP = Memory and Aging Project; ROS = Religious Orders Study; VaD = Vascular Dementia; VLS = Victoria Longitudinal Study; WAIS-III PIQ = Wechsler Adult Intelligence Scale, Third Edition, Performance IQ; WMH = White Matter Hyperintensities; WMS = Wechsler Memory Scale; WUSM ADRC = Washington University School of Medicine Alzheimer's Disease Research Center.

<sup>\*</sup> Muniz-Terrera et al. (2013) reported a change point of -5.66 (-6.08 to -5.24), but subtracted 2 years from this value because time zero was coded as two years to death.

<sup>†</sup> For Batterham et al. (2011), the average number of visits was calculated by dividing the total number of observations (i.e., 1406) by the number of participants (i.e., 687).

<sup>‡</sup> Brief episodic memory tasks included both visual and verbal recall (e.g., word, face, name, and address recall; and figure reproduction)

<sup>§</sup> Dodge et al. (2011) reported change points with and without controlling for practice effects. Those reported here are the change points controlling for practice effects.

<sup>¶</sup> Wilson et al. (2007) did test change points for other domains, but either did not find a difference between the global change point and the construct-specific change points or found the identification of a change point ambiguous based on profile likelihood values.

<sup>¶¶</sup> For van den Hout et al. (2011), the mean number of observations was calculated by dividing the number of records (i.e., 2024) by the number of participants (i.e., 656).

<sup>#</sup> For Wilson et al. (2007), the longitudinal design data were taken for the full sample, not just those dying at follow-up.

<sup>††</sup> For Yu et al. (2013), the change point for *APOE*  $\epsilon 4$  carriers was calculated by adding the additional burden for carriers reported by the authors to the change point and 95% CI reported for non-carriers.

<sup>†††</sup> For MacDonald et al. (2011), the mean number of observations was calculated by summing the number of measurement waves completed by participants and dividing that sum by the total number of participants.