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Abstract

Objective: We describe and compare the expected performance trajectories of older adults on the Mini Mental Status Exam (MMSE) across six independent studies from four countries in the context of a collaborative network of longitudinal studies of aging. A coordinated analysis approach is used to compare patterns of change conditional on sample composition differences related to age, sex, and education. Such coordination accelerates evaluation of particular hypotheses. In particular, we focus on the effect of educational attainment on cognitive decline.

Method: Regular and Tobit mixed models were fit to MMSE scores from each study separately. The effects of age, sex and education were examined based on more than one centering point.

Results: Findings were relatively consistent across studies. On average, MMSE scores were lower for older individuals and declined over time. Education predicted MMSE score, but, with two exceptions, was not associated with decline in MMSE over time.

Conclusion: A straightforward association between educational attainment and rate of cognitive decline was not supported. Thoughtful consideration is needed when synthesizing evidence across studies, as methodologies adopted and sample characteristics, such as educational attainment, invariably differ.

Key Terms: Cognitive, Longitudinal, Coordinated Analysis, Education, Mental Status Exam, Mixed Model, Meta-analysis

Although the number of longitudinal studies of aging is rapidly growing, there are still few in existence relative to those with cross-sectional designs. Combined with the broad multidisciplinary range of research on aging and the complexity of longitudinal analyses, the ensuing literature has been distributed in such a way that it is often difficult to compare results and conclusions across published reports.

In response to this situation, the Integrative Analysis of Longitudinal Studies on Aging network (IALSA: http://web.uvic.ca/~ilife) was established as an international collaborative of researchers, data and methods focused on the simultaneous evaluation of longitudinal data. Of the more than 30 studies currently in the network, some offer public access data, and most include direct involvement of the principal investigator. The network objective is to test new hypotheses (and settle old debates), with coordinated replications, and to extend prior findings from both the cross-sectional and longitudinal literatures. Rather than pooling data to obtain a single result, the IALSA research process emphasizes replication of research and the comparability of results across samples (e.g., countries, birth cohorts, selection strategies), variables (within and across constructs), designs (e.g., length and spacing of follow-up) and analyses (Piccinin & Hofer, 2008; Hofer & Piccinin, 2009, 2010). This approach involves interactive development of the research protocol, with the aim of maximizing each study's data value while enhancing the comparability of results across a variety of samples and designs. In addition to including the same predictors in the same analysis for each study, these predictors are centered at a common value across studies so that interpretation of the parameter estimates is conditional on the same level of the predictor (i.e., the "centercept"; Wainer, 2000). Centering of this type has attracted significant attention in multilevel models, due

to their necessary involvement in interaction terms (Enders & Tofighi, 2007). Thorough reporting of results permits direct comparison across studies and variations in models.

An underlying goal of the current paper is to report initial proof-of-concept work to demonstrate implementation of the coordinated approach described in Hofer and Piccinin (2009). Although not ideal as a measure of cognitive function, the Folstein Mini Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975) was chosen for this initial analysis because it is available in many of the IALSA affiliated studies. A small number of additional measures are relatively common across studies, but much of the coordination will occur at the construct level, which will be demonstrated in a subsequent manuscript.

Given the MMSE's status as a screening measure, it has been used in both clinical and research settings, including longitudinal evaluation of cognitive change. Its widespread use facilitates comparability across studies, and can provide a consistent proxy indicator for dementia when formal diagnostic information is not available. Since diagnosis of dementia is predicated on decline in functioning from a previous level, there is substantial interest in the extent to which MMSE scores decline in older adults, and particularly whether individuals with fewer years of formal education are likely to decline more rapidly (e.g. Muniz-Terrera, Matthews, Dening, Huppert, Brayne and CC75C Group, 2009). In a study of normative cognitive aging it would be reasonable to expect little decline on this measure – between the maximum score of 30 and around Folstein's suggested cut-off of 24 to indicate impairment – and for those of above average ability declines may be obscured by ceiling effects, which we address with a Tobit model, described below.

Analysis of change in the Mini-Mental Status Exam

Given recent interest in cognitive reserve (Stern, 2002, 2009), a second goal is to address, using similar methods and covariates in multiple studies, the question of whether education is related to rate of decline in cognitive function, as measured by the MMSE. Extensive discussions of longitudinal research on cognitive reserve based on other measures of cognition are available elsewhere (e.g., Christensen, Anstey, Parslow, Maller, Mackinnon & Sachdev, 2007; Tucker-Drob, Johnson & Jones, 2009; Zahodne, Glymour, Sparks, Bontempo, Dixon, MacDonald & Manly, 2011).

In their review addressing the impact of a number of predictors, including education, on cognitive change, Anstey and Christensen (2000) point to difficulties in making direct comparisons across studies, due to the use of different designs, measures, and methods of analysis, but report that education generally appears to protect against declines in mental status scores over time despite the fact that mental status measures are not intended to measure cognitive function at the upper end of the distribution. Except for Jacqmin-Gadda, Fabrigoule, Commenges & Dartigues (1997), however, reports from prior to 2006 modeled change in MMSE over only two occasions. In addition, many of these adjusted for baseline cognitive status, a practice that can seriously bias results (Glymour, Weuve, Berkman, Kawachi, & Robins, 2005). More recent publications, employing growth models based on 3-5 occasions of measurement have, with some exceptions (Wilson, et al., 2009; Muniz-Terrera, Brayne, & Matthews, 2010) more often found that change in MMSE is not related to education (Laukka, MacDonald, & Bäckman, 2006; Van Dijk et al., 2008; Muniz-Terrera et al., 2009).

Table 1 lists details regarding previous studies addressing the association between education and MMSE performance. As with the publications reviewed by Anstey and Christensen (2000), it is worth considering implementation differences in these models.

One characteristic of most gerontological research is a heterogeneous initial age range. As a result, information is available on both (cross-sectional) age differences between persons and (longitudinal) age changes within persons. Depending on the type of analysis used, estimates of average change in scores over time may be confounded by this baseline age heterogeneity. To focus on longitudinal changes, it is essential that initial between-person age differences are accounted for. This can be accomplished by including baseline age as a covariate of both the intercept and the slope of the estimated outcome trajectories. Different between-person (BP) and within-person (WP) slopes are expected, and can result from cohort differences and population selection and mortality. The older individuals in a sample are no longer representative of the entire birth cohort from which they originate, but are an increasingly select subset of survivors (Hofer & Sliwinski, 2006). This is a key methodological issue in the developmental aging literature. In addition to demonstrating the feasibility and utility of coordinated analysis, and evaluating the association between education and change in MMSE, a third goal of the current paper is, therefore, to explicitly evaluate the similarity of initial between person age differences and subsequent within-person age changes (Sliwinski, Hoffman & Hofer, 2010).

Another feature complicating research is the inclusion of different predictors in the various reports. Reported associations between education and change in MMSE represent values conditional on the included covariates. To the extent that these

additional covariates are correlated with the predictors of interest, the meanings of parameter estimates from models containing different sets of covariates are not necessarily comparable.

In addition, different model specifications produce different conditional estimates of change in MMSE and associations of this change with covariates such as education. For example, Van Dijk and colleagues (2008) found a non-significant linear rate of change in MMSE over six years in a linear mixed-model analysis of three waves of data with a time in study metric and age, sex, education, and indices of mental and physical health as covariates. They also reported a non-significant education by (linear) time interaction and concluded that education did not protect against cognitive decline in the MMSE. Both of these findings (no decline and no association with education), however, must be interpreted in the context of a (non-significant) quadratic time term that was included in the model: they are based on relations with the instantaneous rate of change at baseline, rather than an index of the overall rate of change during the data collection period.

It is relevant to consider that, as a screening measure, the purpose of the MMSE is to identify individuals with cognitive impairment, and so it contains items focused at the lower end of cognitive function. A score of 30/30, therefore, should be attainable by any non-impaired adult of average intelligence across most of the lifespan (Colsher & Wallace, 1991b). As a result, true cognitive ability for a large portion of a population is at a level above the ceiling for this measure, and the earliest stages of a dementing illness are inevitably hidden for these individuals. This may relate to the findings of faster decline in demented individuals with higher education (e.g., Farmer, Kittner, Rae, Bartko,

& Regier, 1995; Geerlings et al., 2000; Hall et al., 2007): by the time the MMSE registers decline in these individuals (i.e., their scores have dropped below the maximum score of 30) they may be much farther along in the dementia process. This has led to attempts to develop MMSE-based tests with a higher ceiling (e.g., the CAMCOG, Roth et al., 1986; and 3MS, Teng & Chui, 1987).

In studying rate of change in MMSE over time, it is advisable to address the fact that some individuals exceed the ceiling of the test. One strategy for dealing with this artifact may be a recently described Tobit growth curve model (Glymour et al., 2005; Wang, Zhang, McArdle, & Salthouse, 2008), designed to address the analysis of censored data. This may, in particular, be relevant to estimation of the association of education with cognitive change, which may have been underestimated due to ceiling effects.

Given the differences in modeling strategies, including baseline adjustment and choice of covariates across published results, it is difficult to determine whether previous results are consistent. Implementing a common analytic protocol across studies from the Integrative Analysis of Longitudinal Studies on Aging (IALSA; Hofer & Piccinin, 2009) network, the current paper compares associations between education and change in MMSE across six studies, adjusting for ceiling effects, and obtaining parameter estimates based on the same model and covariates.

Method

Samples.

For the current set of analyses, participating studies from the IALSA network are the Canberra Longitudinal Study (CLS), the Gerontological and Geriatric Population

Studies in Gothenburg, Sweden (H-70), The Healthy Older Person Edinburgh (HOPE), the Octogenarian Twins Study (OCTO-Twin), the Longitudinal Aging Study Amsterdam (LASA) and the Swedish Adoption/Twin Study of Aging (SATSA). Geographically, one is Australian, three Swedish, one Dutch and one British.

These studies were mainly initiated in the early 1990s except for SATSA, initiated in 1984, and H-70, started in 1971, but in which MMSE collection did not begin until 1986 (MMSE was not yet published in 1971). Age differences across the samples, therefore, mainly represent cohort differences, and period differences might be minimal.

H-70 has both the oldest (age 85) and earliest measured (1986) sample, representing the 1901-1902 birth cohort. Within sample birth cohort differences also exist (except for H-70, which is single-aged), and these range mainly from 1901 to 1936. OCTO-Twin and H-70 samples are the oldest, and also have the lowest median education level. SATSA, also Swedish, has the youngest sample, on average, but an education distribution similar to OCTO-Twin and H-70.

Descriptive statistics on sample characteristics and MMSE scores are provided in Table 3. Sample size and percent of sample retained at each wave are listed in Table 4. OCTO-Twin has the highest participant retention at wave 2; SATSA is highest for waves 3 and 4. Note that all individuals in H-70 were 85 years of age at wave 1. In both text and tables, studies are ordered according to mean age at the first wave of measurement.

Swedish Adoption/Twin Study of Aging (SATSA).

This sample, drawn from the population-based Swedish Twin Registry (Pedersen, Lichtenstein, & Svedberg, 2002), started in 1984 with a survey completed by 2019 individuals aged 26 to 93 years of age (Pedersen et al, 1991; Finkel & Pedersen, 2004).

In-person testing (IPT) sessions, begun in 1985, focused on initially intact twin pairs aged 50 years and older. The current analyses included up to 632 IPT1 participants with available MMSE scores at baseline or later waves who reached 50 years of age or older during the period of data collection. Subsequent samples were drawn in later waves, but in order to match more closely the design of the other studies, only the original IPT1 sample was analyzed here. The data from this study include five occasions of cognitive testing (IPT1-3, IPT5-6), spaced at three year intervals (i.e., up to 15 years of follow-up) with the exception of a gap at IPT4 which only included a telephone interview.

Longitudinal Aging Study Amsterdam (LASA). Municipal registries formed the sampling frame for this study, and specific efforts were made to reflect culturally distinct geographical areas and the national distribution of urbanization and population density. In order to balance mortality-related attrition, the initial sample (N=3017) was also weighted according to expected mortality at mid-term within each sex and age group (5-year bands between 55 and 85) (Huisman et al., 2011). Data are available on five occasions of measurement, starting in 1992, spaced at 3 year intervals, for up to 12 years of follow-up. Years of education were estimated based on categories from original data collection.

Healthy Older Person Edinburgh Study (HOPE). Individuals 70 years and older were identified from the registers of 67 general medical practitioners in the city of Edinburgh, Scotland. Out of over 10,000 case notes, and home interview of 1467 individuals, 603 (237 men, 366 women) were found to have no health problems and to be on no regular medications (Starr, Whalley, Inch, & Shering, 1992). Representing six percent of the target population, this sample is highly selected on health status. Data are available on four occasions of measurement, starting in 1990, spaced at four year

intervals, for up to 12 years of follow-up. The minimum MMSE score at the first

occasion is 20. The sample is well-educated: only 5% had less than the standard 9 years

of full-time education.

Canberra Longitudinal Study (CLS). A probability sample of 897 people aged 70

years and older was drawn from compulsory electoral rolls for Canberra and

Queanbeyan, Australia. The sample is predominantly native English speaking (86%) and

Caucasian, representative of people living in the region (Australian Bureau of Statistics,

1989). Four occasions of measurement were obtained, the first completed in 1991, with

an average between-occasion span of 3.5 years, for up to 11 years of follow-up. Further

demographic, diversity and dispersion data are published elsewhere (Christensen et al.,

2004).

Origins of Variance in the Oldest-Old: Octogenarian Twins (OCTO-Twin). The

sample was drawn from the oldest cohort of the Swedish Twin Registry (Cederlöf &

Lorich, 1978; Pedersen, Lichtenstein, & Svedberg, 2002) which was comprised of all

intact twin pairs, born 1913 and earlier, who were, or became, 80 years of age during the

three year period of data collection that started in 1991 (737 pairs in 1474 individuals).

Of these, some were excluded because one or both members of the pair were deceased

before they were scheduled for examination (188 pairs), or because one or both declined

participation in the study for other reasons (198 pairs). The total number of participants

for this study was 702 individuals from 351 complete twin pairs (149 identical

(monozygotic) pairs and 202 same-sex fraternal (dizygotic)). Other than for reasons of

death, the pairwise cooperation rate at the initiation of this study was 65%, and the

sample can be considered representative of Swedish octogenarian twins. Participants

were assessed up to five times at 2-year intervals providing up to eight years of follow-up. For the present analyses, all available individuals from the twin sample with MMSE data on one or more occasions were included. Substantial efforts were made to retain demented and dementing individuals in this sample.

Gerontological and Geriatric Population Studies in Gothenburg (H-70). A representative sample of individuals aged 70 (both community residing and institutionalized, born 1st July 1901 through 30th June, 1902), living and registered for census purposes in Gothenburg, Sweden, was recruited in 1971 (85% response rate; Rinder, Roupe, Steen, & Svanborg, 1975; Svanborg, 1977). A second representative sample of the same cohort was added in 1986 (Skoog et al., 1993) and since that date both samples have been examined at 2 or 3 year intervals (earlier intervals were either 2, 3, or 5 years). MMSE administration began on a systematic subsample in 1986, when all participants were 85 years of age (Aevarsson & Skoog, 2000). The current analyses include 396 individuals. Data are available for up to six waves, however, N=9 at the sixth wave of MMSE data collection, as this wave represents 99 years of age for this cohort. The average age of death was 91.93 (SD=3.93).

Measures.

The Mini Mental Status Exam (MMSE; Folstein, et al., 1975) is a measure of global mental status consisting of 11 (mainly multi-part) questions addressing orientation (time and place), immediate and delayed recall of three object names, understanding simple commands, naming, simple arithmetic or spelling, and constructional praxis. In all of the studies, total score out of 30 was used. Two of the studies administered the

measure in English, three in Swedish and one in Dutch. Additional variations in MMSE administration across the six studies are detailed in Table 3. There is evidence that modifications implemented to "translate" the measure into different cultures can impact scores: naming one's county in the UK, for example, is more difficult than naming one's state in the US (Gibbons et al., 2002). Similarly, use of serial 7s, spelling 'WORLD' backwards, or the more successfully completed of the two, is also likely to impact scores. Co-calibration across studies(Crane et al., 2008) was not attempted, however, as this was not the purpose of this manuscript. Variability in administration was taken as representative of the likely variation across other reports in the literature.

Statistical Analysis.

A growth curve modeling approach was used. Conceptually, growth curve analysis involves estimating within-individual regressions of performance on time and on expected predictors of these individual regression parameters (i.e., individual performance at baseline and change over time). All models were estimated using Mplus (version 5.21, Muthen & Muthen, 2009).

Time was specified as "Individual specific time since baseline", and baseline age was included as a covariate to clearly separate the effects of age (between person age differences) and time (within person age changes)(Ware, 1985). All covariates were incorporated for both level (intercept) and linear slope regressions using simultaneous entry. For each study, in addition to the unconditional model, a model regressing longitudinal trajectory intercept and linear slope on main effects of baseline age, sex and

education and a model adding interaction terms among these three covariates were estimated. Specifically, the conditional model fit to the data was:

$$Y_{it} = \left(\alpha_{00} + \beta_0^0 BP_{age_i} + \beta_0^1 sex_i + \beta_0^2 educ_i + u_{0i} \right) +$$

$$\left(\alpha_{11} + \beta_1^0 BP_{age_i} + \beta_1^1 sex_i + \beta_1^2 educ_i + u_{1i} \right) Time_{it} + \varepsilon_{it}$$

Coding of Education Variable. There were marked country and birth cohort differences in educational attainment. In the HOPE sample, nine years of education was the median value, as many people left school at age 14. In the Swedish studies with older birth cohorts (e.g., H-70; OCTO-Twin, SATSA) it was common for young people to get only the basic six years of "folkskola". LASA study participants also had a median of six years of education. CLS, consisting largely of public servants in the capital region of Canberra in the mid-1900s, had a median education of 11 years.

Other population comparison studies (Huisman et al., 2004) have categorized education into low, middle, and high following the conventions described by the International Standard Classification of Education (ISCED; UNESCO, 1997). These categories correspond to ISCED 0-2 (pre-primary, primary, and lower secondary education); 3 (upper secondary education), and 4-6 (post-secondary education). However, this classification standard was developed for comparing current educational attainment, and does not map as directly on to the educational systems for birth cohorts ranging from the early 1900s to the mid-1930s. Considering the median and range for each study, the approach here was to code education as a continuous variable, with the exception of H-70 (already coded 6 versus > 6 years) and SATSA (with four categories, rescored to match

H-70). Mean education is reported in Table 3 and Figure 1 contains the distribution of education for the studies with education measured in years.

Sensitivity to Ceiling Effects. Since the MMSE is less sensitive to change at high levels of function, and many people may score at or near ceiling, a Tobit model (e.g., Wang, et al., 2008) was considered. Implementation of this model involved specifying the MMSE as being "censored above" in Mplus (in this case, above the maximum score of 30). In the studies considered here, the percentage of people at ceiling averaged over all waves ranged between 12.2% (LASA) and 18.5% (HOPE) (or between 6.7% (H-70) and 19.9% (HOPE) at the most extreme waves) of the individual study samples. Whereas these percentages are rather variable across time and study, they are lower than the maximum of 40% considered by Wang et al. (2008), who suggest that the Tobit model will be particularly appropriate when more than 20% of cases are at ceiling for at least one occasion.

Centering of covariates. Two sets of models were estimated in which the covariates were centered at different values in order to illustrate the impact of covariate centering on the interpretation of the growth model intercept and linear slope. First, the study specific medians for age and education were subtracted from the baseline value for each individual. This centered the covariates so that the intercept and linear slope terms would be interpreted as the expected value for an individual at the median age and with the median level of education for the sample. Second, all studies were centered at 83 years of age and 7 years of education in order to have a common centering that would overlap with the oldest sample, for which the youngest participants were 80 years of age, and the median years of education was 6. Exceptions to this coding scheme were required

for initial age in H-70, a single-age cohort study, in which all participants are age 85 at the first MMSE measurement and for education in H-70 and SATSA, as noted above. Similar coding across studies was also used for sex (male=0, female=1) to effectively "center" it at "male", thereby establishing a common interpretation of the corresponding parameters in each study. Reported estimates represent the expected values for 83 year old men with seven years of education. The value for "Female" represents the average differences for intercept and slope between women and men.

Combining Estimates

The results from multiple studies can be robustly combined to obtain a variance-weighted average effect using meta-analytic techniques (DerSimonian & Laird 1986). Unlike a typical meta-analysis of existing literature, our "integrative analysis" is not susceptible to publication bias. We used fixed-effects meta-analysis in STATA 11 to combine our independently obtained estimates and I^2 to test for heterogeneity among them. Since the samples differ substantially in size, we use standardized estimates. Sensitivity to model assumptions was considered by replicating this analysis using random-effects estimates, which did not change our estimates.

Results

Given that the covariate interactions models did not yield consistently better Akaike or Bayesian Information Criteria (AIC and BIC) values, results presented here are based on the covariate main effect models. On average, at age 80 years with seven years of education, men scored between 25 and 27 on the MMSE and declined about 0.3 points per year. Consistent with this, older individuals tended to score lower initially (0.1 to 0.2

points per year), and decline at a faster rate (0.01 to 0.08 points more decline per year).

Sex differences are more apparent in some studies: the women in LASA and CLS score almost a half a point higher than the men in these samples; H-70 and SATSA women show more decline than men.

Level and Rate of Change in MMSE with Respect to Education

In each of the six samples considered here, MMSE performance was associated positively with level of educational attainment, controlling for sex and age. Focusing on studies with similarly coded education, higher educated participants have higher initial scores (0.2 to 0.4 points per additional year of education). Change in MMSE, on the other hand, was associated with education only in the full OCTO-Twin sample (b=0.08, p=0.03). Meta-analysis supports such a conclusion, suggesting that while educational attainment was associated with intercepts (Fig. 2.1: Standardized Effect Size (ZES)= 0.27; 95% Confidence Interval = [0.25, 0.30]), educational attainment was not related to within-person changes in MMSE score (Fig. 2.2: ZES=0.01, n.s.). Non-significant I^2 estimates suggest that these associations, or lack thereof, are stable.

Figure 3 shows expected trajectories, based on the Tobit model, for men with six years of formal education who were recruited at the median age for each study, based on the parameter estimates from the independent analyses. As sex and education were not significant predictors of rate of change, they were not included here. Scatterplots of education by change in MMSE are provided in Figure 4, however, to visually illustrate the (lack of) association between these two variables.

Impact of Ceiling Effect

In comparing the Tobit and Standard Model Results, the AIC and BIC indicate better model fit for the models based on the Tobit link function than for those with a standard Identity link function, except for CLS. However, except for variance estimates (i.e., random effects) for the Intercept and Residual terms, the parameter estimates for the standard and Tobit adjusted growth models differed very little. Therefore, results of the Tobit growth model analysis for each of the six studies are presented (Table 6), as well as, for comparison, the AIC, BIC and intercept, slope and residual variances for the standard model.

Impact of Common Covariate Centering

Comparing the sample specific (Table 6) to the common covariate centering models, all parameter estimates were essentially equivalent except those for the intercept, and linear slope means, reported in this paragraph. It is noteworthy that while the younger samples with more education had higher intercept and slower decline estimates than the OCTO-Twin sample, once common age (83 years) and education (7 years) centering was specified, intercepts for the other studies were lower (CLS: 24.20; HOPE: 26.14; LASA: 25.25; OCTO-Twin: 26.38), and the slope estimates, while still quite modest relative to OCTO-Twin (likely due to the greater proportion of dementing individuals in this sample), moved toward the OCTO-Twin estimate (CLS: -0.42; HOPE: -0.26; LASA: -0.39; OCTO-Twin: -1.20). Regression estimates for the covariates and model fit statistics, as they should, remained unchanged. Models with common centering were not estimated in H-70 and SATSA data, as their education variables were not readily re-centered, and H-70 is a single age cohort study.

Between Person Age Differences versus Within Person Age Changes

Where median values for age and education in each study were used for centering of covariates, the between-person age differences and within-person age changes were quite similar. However, in the models with covariate centering at 83 years of age and 7 years of education (common values), age change estimates (-0.26 to -1.20 [or -0.48 without the dementing participants in OCTO-Twin]) were notably larger than were age difference estimates (-0.12 to -0.19).

Follow-up Analyses

    Non-linear impact of education. Considering the low and skewed education distribution in the OCTO-Twin sample, whether the impact of an additional year of education was stronger at lower levels of education was explored by introducing a squared education term in the model for all samples except H-70 and SATSA, for which education was a dichotomous variable. As in Wilson and colleagues (Wilson et al., 2009), education squared was a statistically significant predictor of change in MMSE scores (b=-0.06, p=0.04) for the CLS dataset, but this was not the case for HOPE, LASA, or OCTO-Twin samples.

    Impact of Proportion of Dementing Participants. Given the strikingly different rate of change, known differences in sampling and maintenance of contact, and availability of diagnostic information in the OCTO-Twin study (consensus diagnosis based on DSM-III-R and NINCDS-AIREN criteria), the impact of inclusion of individuals known to be dementing on estimates of change was evaluated in a follow-up to the main analysis. Excluding individuals who were demented at the first occasion (analysis n=604), estimated yearly decline reduced to -1.005 (SE=.108). Excluding both demented and dementing individuals from the OCTO-Twin analysis (analysis n=477)

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resulted in an estimated yearly change of -0.447 (SE=.088), much less than in the full sample. In addition, education-related differences in rate of change became non-significant (0.033 (SE=.021).

Discussion

The current paper is a demonstration of the coordinated analysis approach advocated by Piccinin and Hofer (2008; Hofer & Piccinin, 2009, 2010). Based on a measure commonly available in longitudinal studies of aging and the cognitive reserve hypothesis, we implemented parallel models in six longitudinal studies to demonstrate a way to assess the consistency of findings relating to the association between education and cognitive decline, for which comparable analyses in the literature are few. We found relative consistency across the available studies, with greater average declines in the older samples that may, as our follow-up analyses suggest, reflect greater prevalence of dementia at the older ages. While this consistency is visible in the raw estimates, the conclusions based on significance levels, and the plot of average trajectories by study, we demonstrate that it can also be summarized using meta-analytic methods.

It is important to consider the role of operational definitions in such replications. Although, at the conceptual level, similar predictors were used in these analyses, differences in information collected across the studies required that education was coded dichotomously for some of the analyses. Had we conducted a pooled analysis, it would have been necessary to either drop the studies that did not have age/year of completion or to dichotomize education for all of the studies. The coordinated approach allows flexible use of a mix of measures and models to address the questions of interest and to follow-up on hypotheses generated in the initial analyses.

Level and Rate of Change in MMSE with Respect to Education

In general, we observed an absence of association between education and change in MMSE. This is generally in agreement with recent growth curve analyses of multi-occasion data rather than the earlier two-occasion change score analyses. With respect to discrepancies in the previous literature, therefore, the current analyses do not provide evidence to support the cognitive reserve hypothesis, at least as indexed by years of education.

However, there were two hints that education-related differences may have more impact at lower as compared with higher levels of education. A positive time*education term was observed in the OCTO-Twin sample, which had lower average education, though this association disappeared once demented and dementing individuals were excluded in a follow-up analysis. Also in follow-up analyses, a positive time*education term, paired with a significant negative time*education[2] term was observed in CLS (but not the other samples), indicating less decline with additional years of education near the median (11 years), but diminishing returns for additional years.

It may be that the critical aspect of education is completion of the minimum mandatory standard. Although in older birth cohorts lack of school completion may be related to family needs for an additional breadwinner, if students with below average school performance are more likely to drop out of school early, lacking the minimum standard may represent lifelong limitations in cognitive function or poor development of cognitive reserve (Mehta et al., 2009). Minimum mandatory schooling standards have also increased markedly over the range of birth cohorts studied here. Careful cross-referencing of age by such standards may allow more appropriate operationalization of

education in the future (Glymour, Kawachi, Jencks, & Berkman, 2008). Measures of education quality (e.g., Glymour & Manly, 2008; Manly et al., 2002; Richards & Hatch, 2011), unavailable for our analyses, would further enhance research on the role of education in cognitive aging.

Self-rating of literacy (e.g., Kavé, Shrira, Palgi, Palter, Ben-Ezra & Shmotkin, 2012) and self-evaluation of school performance (Mehta et al., 2009) are additional measures of "education" that have recently been associated with late life cognition and Alzheimer's disease. Although also not available for the current analyses, they may provide a reasonably straightforward addition to the complicated processes of gauging schooling quality and standards.

It is also likely that associations between educational attainment and declines in cognitive functioning, if they exist, are more complex. Higher education may result in reduced (or delayed) decline in the pre-clinical stages (or absence) of dementia, but accelerated decline once pathology has advanced beyond the level at which higher education/ability individuals are able to compensate (Hall, et al., 2007) . It may also interact with other characteristics such as declining health (Meijer et al., 2009; Piccinin, Muniz, Sparks & Bontempo, 2011).

Impact of Ceiling Effect

Given that ceiling effects may bias results when dementia screening measures are used as an index of cognitive function, it was important to first evaluate the potential impact on the conclusions of having used the MMSE. In this case, based on the comparison of typical versus Tobit models, it seems that our results were not markedly affected. In terms of deciding to specify a Tobit model, the percent of individuals at

ceiling is a relevant factor. In the samples studied here, between 4.1 and 19.9 percent of individuals scored at ceiling at any one occasion, considerably fewer than the maximum of 40% considered by Wang and colleagues (Wang, et al., 2008), who suggested that the Tobit model will be particularly appropriate when more than 20% of cases are at ceiling for at least one occasion. Although the AIC suggested that the Tobit models fit better than the standard models, and the estimated variance components were larger for these models, the Tobit model estimates did not result in different conclusions regarding the trajectories or the covariates. In particular, it had no impact on estimates of the association between education and cognitive decline.

Impact of Common Covariate Centering

Including the same set of covariates across analysis of the different samples is a first step toward obtaining equivalent interpretations for the parameter estimates conditioned upon them. While sampling differences may in some cases suggest, or require, inclusion of additional covariates in order to compare results, including the same covariates in this way is a straightforward approach to maximize the utility of comparisons. The coordinated analysis approach employed here facilitated this comparability.

A further step toward comparability of parameter estimates can be attained through centering predictors at the same value so that the parameter estimates represent the expected values at the same, meaningful, value of the predictors. In the analysis of these six studies, different centering of the covariates influenced the trajectory parameter estimates, but not their estimated associations with the covariates themselves. In other words, interpretation of the average level and rate of change in performance was affected (for example, average decline was greater for older reference ages and the estimates were

more similar when the same reference age was used), but, again, not the conclusions regarding the covariates such as the association between education and cognitive decline, at least for the centering choices considered here. Attention to such differences, through either pre- or post-analysis centering is recommended as a way of appropriately comparing results across studies.

Between Person Age Differences versus Within Person Age Changes

On average, in all the samples, MMSE scores were lower in older individuals, they declined over time, and the between and within person effects were similar at the sample age medians. However, larger age changes than age differences were generally observed by the ninth decade. This discrepancy points to the likely existence of selection or healthy participant (Mendes de Leon, 2007) effects in studies of aging with age heterogeneous initial samples, where initial performance may be overestimated at older ages due to the lower probability of enrollment of ill or frail individuals. In this situation, longitudinal declines may also be overestimated due to regression to the mean or to capturing change associated with changes in health that did not lead to attrition.

Impact of Proportion of Dementing Participants

The impact of dementia was not a specific focus in the current study, but the very different sampling strategies across the samples are likely to have resulted in distinct selection patterns. For example, HOPE participants were limited to healthy individuals with a minimum MMSE score above 19 at baseline. OCTO-Twin, on the other hand, while limited to intact twin pairs (i.e., both twins alive), made a special effort to retain demented individuals. These differences may be reflected in the generally lower age difference and age change estimates for HOPE and generally higher estimates for OCTO-

Twin, relative to the other studies. HOPE had similar change versus difference estimates, but OCTO-Twin change estimates were strikingly larger. When dementing individuals were omitted from the OCTO-Twin analysis, estimates of change in MMSE were much reduced (b= -0.479). When the sample was restricted to individuals who were not demented at the first measurement, estimated change in MMSE fell between the other two estimates (b= -1.005). Accounting for dementia will be an important additional factor relevant to both estimating rate of change and characterizing the role of education and other inter-individual covariates in cognitive change in late life. In this regard, it is interesting to note the trajectory similarity between studies with more similarly aged participants, and to consider the extent to which dementia incidence may influence estimates of rate of decline.

Summary and Conclusions

Coordinated analysis is a collaborative approach for estimating parallel models in multiple datasets. We find a general lack of linear association between reported years of education in non-dementing individuals and their change in MMSE performance over time. We also find similar age and time effects (accounting for age) across the different studies, including similar within person age declines and between person age differences until after 80 years of age.

Understanding the generalizability of the impact of birth cohort and national differences in education, socio-economic status and health gradients motivated this coordinated analysis of longitudinal studies on aging, providing an opportunity for simultaneous evaluation of longitudinal data to test, replicate, and extend prior findings on aging-related change (Hofer & Piccinin, 2009, 2010). A coordinated approach for

cross-study comparison of results using identical statistical models permits direct

comparison of results and opportunities to understand why results might differ. Attention

to sampling differences may play a key role in such endeavours.

Word Count: ~~4586~~ ~~5913~~ 6337

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Table 1. Methods and Findings from Previous Studies of Education and Rate of Change in MMSE

MSS	Ed-cog change assoc?	education measure	cognitive measure	Method	Conclusion	n at T1	Age	Study length (years)	# waves	sample	Bpage as covariate	Conditioned on Baseline performance
Colsher & Wallace, 1991	(Y) NO	<9, 9-12, >12	SPMSQ	Sex specific RMANOVA	Women with less education declined more between T1 and T2, but overall did not have a greater rate of decline	1953	62+	6	3	Iowa 65+ Rural Health Study	Y	N
Evans et al., 1993	Y	years	SPMSQ	Regression of normalized change scores on education and other covariates	Fewer years formal education, greater declines in cognitive function	2273	65+	3	2	East Boston EPESE	Y	Y
Farmer, et al., 1995	Y	0-9 v 10-12 & some college+	MMSE	Logistic regression (3+ point decline in 1 year)	Decline more likely in lower education group with MMSE >23 (not for MMSE <=23).	14,883	18+	1	2	NIMH ECA	Y	Y
Butler, Ashford, & Snowdon, 1996	Y	<bachelors v bachelors	MMSE	Annualized change; compared top 3 T1MMSE categories (20-23, 24-26, 27-30) for 2 levels education and 2 age groups (ANOVA)	75-84 years: bachelors less decline; 85+ years: bachelors more decline	575	75-102	1.6	2	NUN	Groups*	Y
Christensen, Korten, Jorm, & Henderson, 1997	Y	years; and <10, 10-13, 14+	MMSE	Change scores regressed on predictors	Lower education predictive of decline	617	70+	3.5	2	Canberra Longitudinal Study	Y	Y

Study		Education groups	Measure	Analysis	Findings	N	Age			Study		
Lyketsos, Chen, & Anthony, 1999	Y	5 groups: 0-8 (reference), 9-11, 12, 13-15, 16	MMSE	T3-T2 Change scores regressed on predictors	More decline in those with ≤8 years education with and without adjusting for age (group).	1488	18-75+	2	5	Baltimore ECA	Groups*	Y
Aevarsson & Skoog, 2000	Y	6 v >6	MMSE	change score	More decline in non-demented women with less education	102	85	3	2	Gothenburg	NA (single age sample)	Y
Jacqmin-Gadda, et al., 1997	Y (for SQRT MMSE errors)	5 groups: none, < primary, primary, high school, university; in educ x time analysis: < v > high school	Square root of MMSE errors	Time based growth model	Less decline with more education	2792	65+	5	4	PAQUID	Y	N
Nguyen, Black, Ray, Espino, & Markides, 2002	Y	<5, 5-11, >11	MMSE	Logistic Regression	Significant Odds Ratio for <5 years of education relative to >11 years.	1759	65+	5	2	Hispanic EPESE	Y	N
Laukka, MacDonald, & Bäckman, 2006	N	years	MMSE	Multilevel Growth Model - years to event	Education predicted MMSE 3 years pre-"event", but not rate of change	1475	75+	9	4	Kungholmen Project (KP)	Y	N

Alley, Suthers, & Crimmins, 2007	Y	years	TICS	age based growth model with age^2	age2*ed positive and significant: less acceleration in people with more education	6651	70-103	7	5	AHEAD	N	N
Van Dijk, et al., 2008	N	low v high	MMSE	Time-based growth model	No effect of education on cognitive change over time	872	49-81	6	3	Maastricht (MAAS)	Y	N
Wilson, et al., 2009	Y & N	years	MMSE part of composite	Time-based growth model with quadratic time and education squared	No linear association of education and rate of cognitive change;	6533	mean=72	14; mean=6.5	mean=3	Chicago Health and Aging Project	Y	N
Muniz-Terrera et al., 2009	N	<14 v ≥15 years of age	MMSE	Age-based joint growth model and logistic model for death and dropout	No education difference in rate of change	2053	75+	9	4	Cambrige City 75 Cohort (CC75C)	≤85 v >85	N
Muniz-Terrera, Brayne, & Matthews, 2010	Y & N	<14 v ≥15 years of age	MMSE	Age-based joint growth mixture model and logistic model for death and dropout	Education difference in rate of change only for class with high performance and little decline	2043	75+	9	4	CC75C	≤85 v >85	N

*Groups: Age was treated as a grouping variable, rather than as a continuous covariate.

Table 2. Variations in Administration across the Six Studies

Original MMSE Items	SATSA	LASA	HOPE	CLS	OCTO-Twin & H-70
STATE	**Country/Land**	Province	**Country**	State	**Country**
COUNTY	County	**Address**	County	**Country**	County
CITY/TOWN	City/Town	Municipality	City	Town	City/Town; **Place**
HOSPITAL	**District** (municipal)/Institution	**Two main streets in neighbourhood**	**Residence**	**Residence**	**District/Institution**
FLOOR OF BLDG	**Address/Department**	Floor of building	Floor	Floor	**Street/ward**/floor
APPLE TABLE PENNY	**nykel, tandborste, lampa (Key, toothbrush, lamp)**	**Appel Tafel Stuiver**	**Lemon key ball**	Apple table penny	**Key, toothbrush, lamp**
SERIAL 7s	Serial 7s	Serial 7s	**WORLD backward**	Serial 7s	Serial 7s (H-70 alt) **KONST**[2] backward
		(alt) DORST backward	**(alt) Serial 7s**	(alt) WORLD backward	
PENCIL IDENTIFIED	**pen**[1]	pencil	pencil	pencil	pencil
'NO IFS....' REPEATED	**"burned down two-family house"**	"No ifs..." ("Geen als en of maar")	"No ifs…" repeated	"No ifs…" repeated	**"burned down two-family house"**
Right Hand	**Hand**	Right Hand	Right hand	Right hand	**Hand**
Put it on the floor	Put it on your lap	Put it on **your lap**	Put it on the floor	Put it on **your lap**	Put it on the floor **/ chair**
CLOSED EYES	**Point at the door**[2]	Closed eyes	Closed eyes	Closed eyes	**Point at the door**[3]
Additional scoring details:		*Best of* Serial 7s / World Backward Two versions of memory test to reduce practice effect		*Best of* Serial 7s/ World Backward	*(H-70) Best of* Serial 7s/ Konst Backward
Language of administration:	Swedish	Dutch	English	English	Swedish

Note: Differences printed in bold font. [1]Not usually distinguished from "pencil" in daily language; [2]Swedish word for art; [3]or window (based on home environment)

Table 3. Observed Means (SDs) of MMSE Scores, Initial Age, Educational Attainment, and Gender Distribution by Study

	SATSA	LASA	HOPE	CLS	OCTO	H-70
Initial Age	65.66	70.74	75.70	76.52	83.48	85.48
	(8.40)	(8.75)	(4.22)	(4.90)	(3.08)	(0.11)
Education	*	8.76	10.92	11.37	7.13	*
		(3.32)	(2.60)	(2.56)	(2.29)	
MMSE 1	27.81	26.82	28.02	27.31	25.65	25.12
	(2.05)	(3.18)	(1.75)	(2.78)	(5.02)	(6.25)
MMSE 2	28.23	26.76	27.89	27.12	24.26	20.88
	(1.54)	(3.31)	(2.30)	(2.83)	(6.97)	(8.86)
MMSE 3	27.57	26.84	27.82	26.57	23.71	22.77
	(2.46)	(3.29)	(3.08)	(3.65)	(7.76)	(7.55)
MMSE 4	26.47	26.81	27.64	27.44	22.87	21.75
	(3.61)	(3.41)	(2.29)	(2.93)	(8.10)	(8.30)
MMSE 5	26.67	26.83	---	---	21.24	20.24
	(3.61)	(3.13)			(8.31)	(9.09)
MMSE 6	---	---	---	---	---	18.00
						(13.64)
% Female	59.0	51.64	60.57	48.7	64.3	72.3

* Elementary = 60%; Vocational, `gymnasium`, university or higher = 40%.

CLS = Canberra Longitudinal Study; HOPE = Healthy Older Person Edinburgh Study;
LASA = Longitudinal Aging Study Amsterdam; OCTO-T = Origins of Variance in the
Oldest-Old Octogenarians Twins; H70 = Gerontological and Geriatric Population
Studies; SATSA = Swedish Adoption/Twin Study of Aging.

Table 4. N and % Retention at each Wave

Wave	SATSA		LASA		HOPE		CLS		OCTO		H-70	
	N	% of W1	N	% of W1	N	% of W1	N	% of W1	N	% of W1	N	% of W1
1	588	93*	3083		601		883		619		396	
2	493	78	2289	74	386	64	592	67	508	82	197	50
3	462	73	1870	61	288	48	365	41	382	62	134	34
4	343	54	1468	48	201	33	204	23	273	44	122	31
5	272	43	1043	34		---		---	189	31	75	19
6		---		---		---		---		---	9	2

Note: N based on number of individuals with at least one MMSE score and non-missing covariate values (age, sex and education). *A total of 632 SATSA twins participated in IPT1 and had at least one MMSE score across one of the five testing waves.

CLS = Canberra Longitudinal Study; HOPE = Healthy Older Person Edinburgh Study; LASA = Longitudinal Aging Study Amsterdam; OCTO-T = Origins of Variance in the Oldest-Old Octogenarians Twins; H70 = Gerontological and Geriatric Population Studies; SATSA = Swedish Adoption/Twin Study of Aging.

Table 5. Percent of individuals at MMSE Ceiling at each Wave and Overall.

Wave	SATSA	LASA	HOPE	CLS	OCTO	H-70
1	12.76	12.26	18.64	13.44	12.28	14.14
2	15.01	12.23	17.88	15.71	15.52	4.06
3	11.47	12.09	18.06	11.51	18.80	6.71
4	9.62	12.13	19.90	19.12	14.91	7.37
5	9.93	12.56	--	--	7.94	9.33
6	---	---	---	---	---	11.11
All Waves	12.14	12.23	18.50	14.28	14.33	9.65

CLS = Canberra Longitudinal Study; HOPE = Healthy Older Person Edinburgh Study;
LASA = Longitudinal Aging Study Amsterdam; OCTO-T = Origins of Variance in the
Oldest-Old Octogenarians Twins; H70 = Gerontological and Geriatric Population
Studies; SATSA = Swedish Adoption/Twin Study of Aging.

Table 6. Parameter Estimates (and Standard Errors) from Tobit Growth Curve Models, by Study, for Time-in-study Metric, with baseline age and education centered at study-specific median values

	SATSA	LASA	HOPE	CLS	OCTO-T	H-70
Fixed Effects						
Intercept	28.195** (.133)	27.437** (.074)	27.844** (.127)	27.075** (.137)	25.897** (.366)	25.207** (.539)
Time	-0.117** (.021)	-0.190** (.013)	-0.159** (.040)	-0.221** (.033)	-1.272** (.125)	-1.119** (.202)
Baseline Age	-0.072** (.011)	-0.125** (.007)	-0.129** (.022)	-0.132** (.024)	-0.297** (.062)	n/a
Female	0.022 (.151)	0.396* (.113)	0.311 (.163)	0.467* (.182)	0.258 (.436)	-0.260 (.625)
Education	0.817** (.140)	0.283** (.018)	0.274** (.035)	0.226** (.034)	0.490** (.076)	3.244** (.622)
Time * Age	-0.008** (.002)	-0.015** (.001)	-0.022* (.008)	-0.027** (.005)	-0.084** (.023)	n/a
Time * Female	-0.077* (.025)	0.004 (.015)	0.027 (.051)	0.025 (.036)	0.144 (.139)	-0.413* (.182)
Time * Educ	-0.001 (.027)	0.001 (.002)	-0.018 (.011)	0.008 (.008)	0.077* (.027)	0.209 (.177)
Variance Components and Fit Indices						
Intercept	1.796** (.413)	6.139** (.517)	0.877* (.368)	3.798** (.802)	22.070** (3.327)	32.226** (5.602)
Slope	0.051** (.014)	0.039** (.007)	0.092 (.060)	0.077** (.023)	1.244** (.194)	1.115** (.195)
Cov(IS)	-0.018 (.054)	0.074 (.051)	0.164 (.090)	0.058 (.103)	3.005** (.561)	3.617** (.806)
Residual	2.797** (.329)	4.103** (.152)	3.166** (.336)	3.449** (.309)	12.306** (1.061)	8.766** (.961)
AIC	9041.668	44259.453	5953.143	9781.348	11070.583	5601.338
BIC	9109.791	44345.677	6016.708	9848.785	11137.643	5649.647

Table 6. Parameter Estimates (and Standard Errors) from Tobit Growth Curve Models by Study for Time-in-study Metric, with baseline age and education centered at study-specific median values (cont'd)

Variance Components and Fit Indices for Standard Growth Curve Models

Intercept	1.521** (.389)	5.586** (.490)	0.695* (.279)	3.792** (.798)	18.674** (2.922)	26.247** (4.786)
Slope	0.054** (.015)	0.040** (.007)	0.100 (.056)	0.075** (.023)	1.293** (.192)	1.250** (.213)
Residual	2.166** (.273)	3.166** (.121)	2.117** (.251)	3.434** (.307)	9.398** (.846)	7.283** (.792)
AIC	9276.931	45949.942	6217.217	9781.371	11875.847	5858.704
BIC	9345.054	46036.166	6280.782	9848.808	11942.907	5907.013

*P<.05; **P<=.001; CLS = Canberra Longitudinal Study (median age=76, education=11 years); HOPE = Healthy Older Person Edinburgh Study (median age=76, education=10); LASA = Longitudinal Aging Study Amsterdam (median age=70, education=9); OCTO-T = Origins of Variance in the Oldest-Old Octogenarians Twins (median age=83, education=6); H70 = Gerontological and Geriatric Population Studies (age=85, education dichotomized <=6 v. >6) and SATSA = Swedish Adoption/Twin Study of Aging (median age=64, education dichotomized <=6 v. >6).

Figure Captions

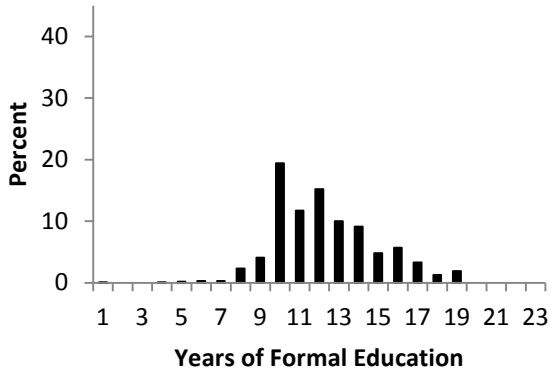*Figure 1.* Education distribution (%) by study

(Note: H-70 and SATSA: 60% completed elementary school or less, 40% completed more than elementary school).

Figure 2. Meta-analysis using estimated age-distributed between-person differences (Education) and within-person change (Education * Time) results for six studies.
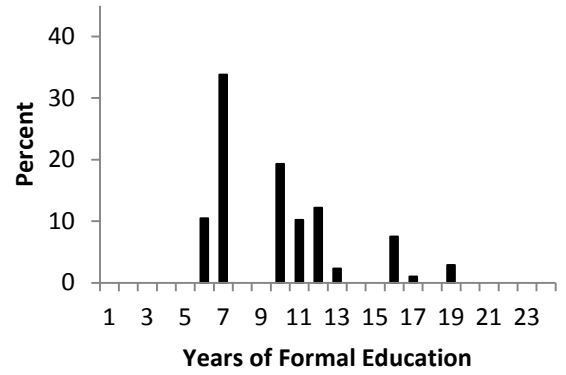
Figure 3. Predicted MMSE scores over time for a hypothetical man enrolling at the median age and years of education for each study and for OCTO-Twin including and excluding individuals diagnosed with dementia.

Figure 4. Scatterplots of years of formal education by individual fitted linear slope for each study and for OCTO-Twin including and excluding individuals diagnosed with dementia.

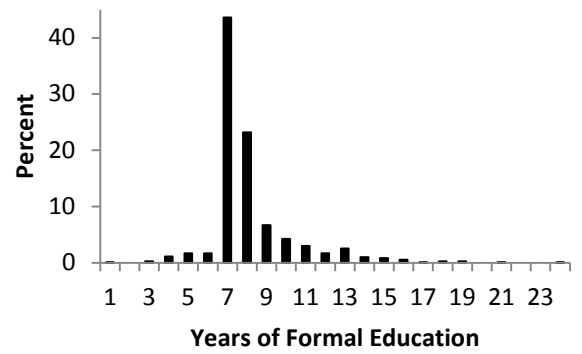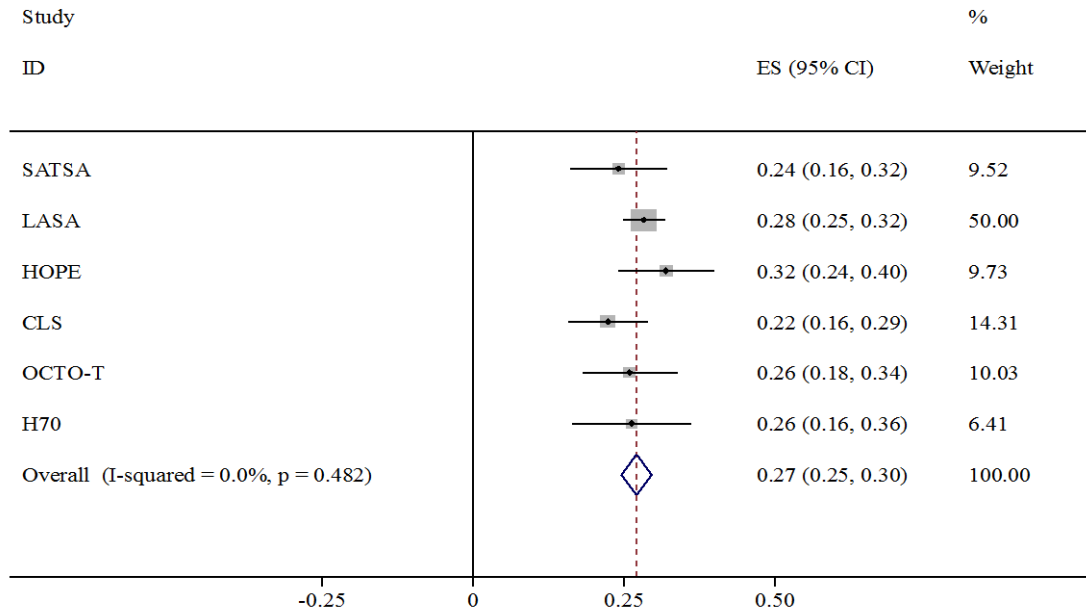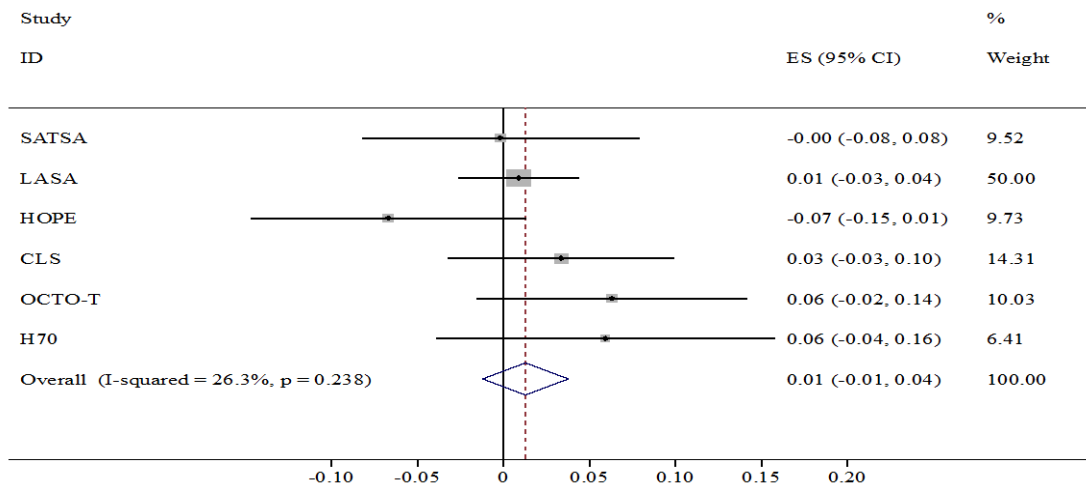## CLS
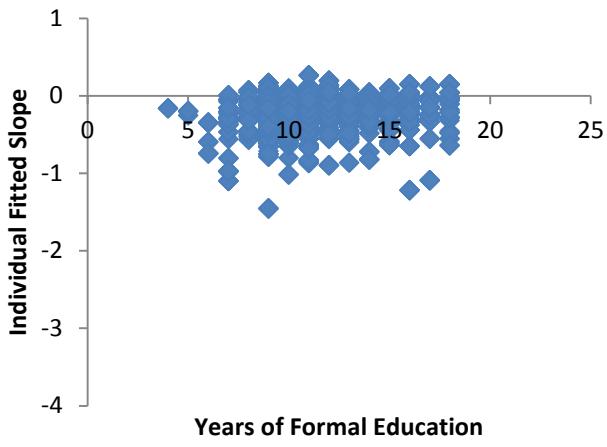

LASA

HOPE
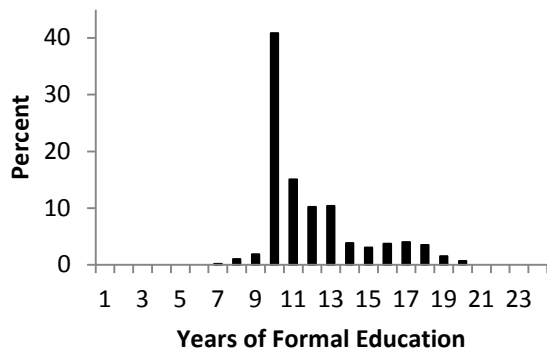
OCTO-Twin

Panel 1: Educational Attainment Intercepts

Study ID	ES (95% CI)	% Weight
SATSA	0.24 (0.16, 0.32)	9.52
LASA	0.28 (0.25, 0.32)	50.00
HOPE	0.32 (0.24, 0.40)	9.73
CLS	0.22 (0.16, 0.29)	14.31
OCTO-T	0.26 (0.18, 0.34)	10.03
H70	0.26 (0.16, 0.36)	6.41
Overall (I-squared = 0.0%, p = 0.482)	0.27 (0.25, 0.30)	100.00

Panel 2: Education * Time

| Study ID	ES (95% CI)	% Weight
SATSA	-0.00 (-0.08, 0.08)	9.52
LASA	0.01 (-0.03, 0.04)	50.00
HOPE	-0.07 (-0.15, 0.01)	9.73
CLS	0.03 (-0.03, 0.10)	14.31
OCTO-T	0.06 (-0.02, 0.14)	10.03
H70	0.06 (-0.04, 0.16)	6.41
Overall (I-squared = 26.3%, p = 0.238)	0.01 (-0.01, 0.04)	100.00

NB: Estimates have been standardized to account for sample size heterogeneity. Panel 2 uses non-demented estimates for change in educational attainment in the OCTO-Twin study.
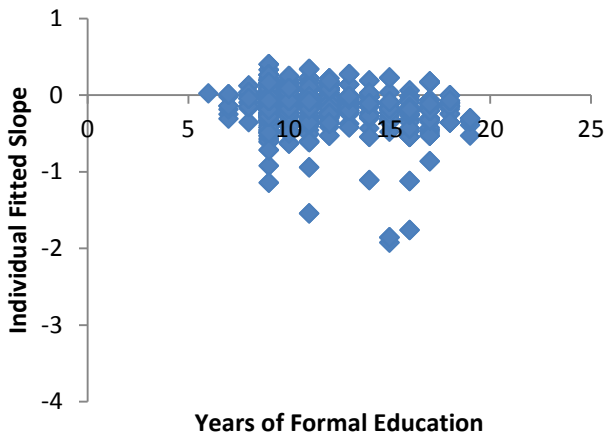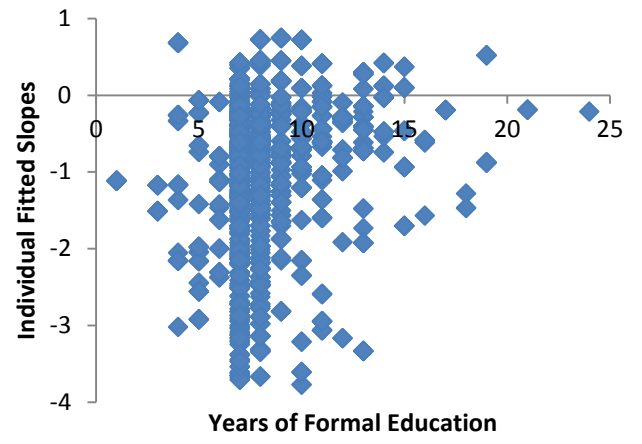
CLS
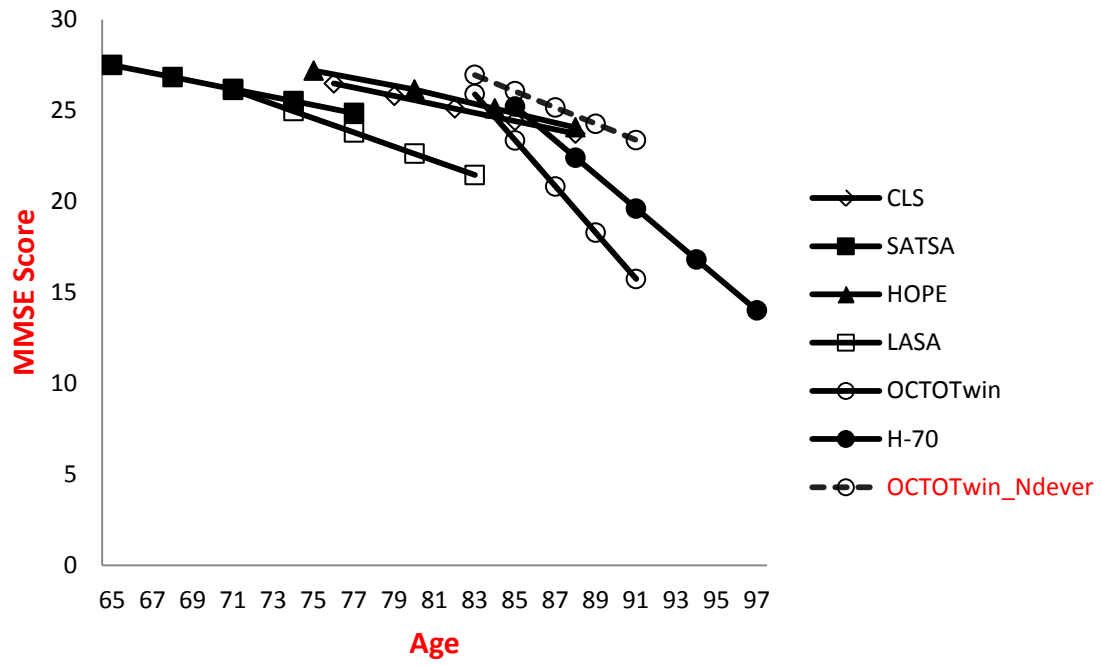
LASA
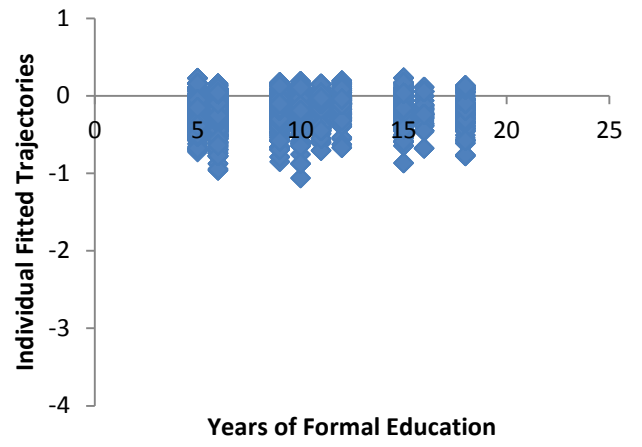
HOPE

OCTO-Twin

OCTO-Twin Never Demented