Coordinated Analysis of Age, Sex, and Education Effects on Change in MMSE Scores


1Department of Psychology, University of Victoria, British Columbia, Canada. 2MRC Unit for Lifelong Health and Ageing, London. 3Department of Psychology, University of California, Riverside. 4Department of Psychology, University of Gothenburg, Sweden. 5Department of Psychology, University of Edinburgh. 6EMGO Institute for Health and Care Research, VU University Medical Centre/LASA, Amsterdam, The Netherlands. 7Centre for Youth Mental Health Research, University of Melbourne, Australia. 8Normative Aging Study, VA Boston Healthcare System, Boston, MA. 9Alzheimer Scotland Dementia Research Centre, University of Edinburgh. 10Neuropsychiatric Epidemiology, University of Gothenburg, Sweden.

Objectives. We describe and compare the expected performance trajectories of older adults on the Mini-Mental Status Examination (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 Words: Cognitive—Coordinated Analysis—Education—Longitudinal—Mental Status Exam—Meta-analysis—Mixed Model.

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 (IALSA) network (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 (Hofer & Piccinin, 2009, 2010; Piccinin & Hofer, 2008). 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 this article 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 Examination (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 article.

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 et al., 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 the coordination will occur at the construct level, which will be demonstrated in a subsequent article.

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Given recent interest in cognitive reserve (Stern, 2002, 2009), more often found that change in MMSE is not correlated with the predictors of interest, the meanings of this change with covariates such as education. For example, Van Dijk and colleagues (2008) found a nonsignificant linear rate of change in MMSE over 6 years in a linear mixed-model analysis of three waves of data with a time in

**Analysis of Change in the MMSE**

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 et al., 2007; Tucker-Drob, Johnson & Jones, 2009; Zahodne et al., 2011).

In their review addressing the effect 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, and 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, Wu, Berkman, Kawachi, & Robins, 2005). More recent publications, employing growth models based on 3–5 occasions of measurement have, with some exceptions (Muniz-Terrera, Brayne, & Matthews, 2010; Wilson et al., 2009), more often found that change in MMSE is not related to education (Muniz-Terrera et al., 2009; Laukka, MacDonald, & Bäckman, 2006; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008).

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 provided 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 (BP) 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 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 this article is, therefore, to explicitly evaluate the similarity of initial BP age differences and subsequent WP age changes (Sliwinski, Hoffman, & Hofer, 2010).

Another feature complicating research is the inclusion of different predictors in the various reports in the literature. 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 nonsignificant linear rate of change in MMSE over 6 years in a linear mixed-model analysis of three waves of data with a time in
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<td>5</td>
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<td>Laukka et al. (2006)</td>
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<td>1,475</td>
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<td>9</td>
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<td>TICS</td>
<td>Age-based growth model with age²</td>
<td>Aged-positive and significant; less acceleration in people with more education</td>
<td>6651</td>
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<td>Van Dijk et al. (2008)</td>
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<td>Wilson et al. (2009)</td>
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<td>$M = 72$</td>
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<td>3</td>
<td>Chicago Health and Aging Project</td>
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<td>Muniz-Terrera et al. (2009)</td>
<td>N</td>
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<td>75+</td>
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<td>Muniz-Terrera et al. (2010)</td>
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<td>2043</td>
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<td>9</td>
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<td>≤85 vs. &gt;85</td>
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Note. SPMSQ: Short Portable Mental Status Questionnaire (Pfeiffer, 1975); EPESE: Established Populations for Epidemiologic Studies of the Elderly; NIMH: National Institute of Mental Health; ECA: Epidemiologic Catchment Area; PAQUID: Personnes Âgées QuïD; TICS: Telephone Interview for Cognitive Status; AHEAD: Asset and Health Dynamics Among the Oldest Old; Groups: Age was treated as a grouping variable, rather than as a continuous covariate.
study metric and age, sex, education, and indices of mental and physical health as covariates. They also reported a nonsignificant 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 (nonsignificant) 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 nonimpaired 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 (Hofer & Piccinin, 2009) network, this article 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 Origins of Variance in the Oldest-Old (OCTO-Twin) study, 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 2. Sample size and percent of sample retained at each wave are listed in Table 3. 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 MMSE measurement.

Swedish Adoption/Twin Study of Aging.—This sample, drawn from the population-based Swedish Twin Registry (Pedersen, Lichtenstein, & Svedberg, 2002), started in 1984 with a survey completed by individuals aged 26–93 years of age (N = 2019; Finkel & Pedersen, 2004; Pedersen et al., 1991). 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 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 3-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.—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 1990, spaced at 4-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.—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.—The sample was drawn from the oldest cohort of the Swedish Twin Registry (Cederlöf & Lorich, 1978; Pedersen et al., 2002), which was comprised of all intact twin pairs, born 1913 and earlier, who were, or became, 80 years of age during the 3-year period of data collection that started in 1991 (737 pairs in 1,474 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 5 times at 2-year intervals providing up to 8 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 years (both community residing and institutionalized, born July 1, 1901 through June 30, 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, Nilsson, Palmertz, Andreasson, & Svanborg, 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 subset of the two, is also likely to affect scores. Co-calibration across studies (Crane et al., 2008) was not attempted, however, as this was not the purpose of this article. 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; Muthén & Muthén, 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 (BP age differences) and time (WP 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

\[ Y_{ii} = (\alpha_{00} + \beta_{00} \text{age}_i + \beta_{01} \text{sex}_i + \beta_{02} \text{educ}_i + u_{0i}) \]

\[ + (\alpha_{11} + \beta_{10} \text{age}_i + \beta_{11} \text{sex}_i + \beta_{12} \text{educ}_i + u_{1i}) \text{Time}_i + \varepsilon_{ii}. \]

**Coding of education variable.**—There were marked country and birth cohort differences in educational attainment. In the HOPE sample, 9 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 6 years of “folkskola.” LASA study participants also had a median of 6 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 (primary, primary, and lower secondary education), 3 (upper secondary education), and 4–6 (postsecondary education). However, this classification standard was developed for comparing current educational attainment and does not map directly onto 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 vs. >6 years) and SATSA (with four categories, rescored to match H-70). Mean education is reported in Table 2, 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, more than 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 (see Table 5). 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 aged 85 years at the first MMSE measurement and for education in H-70 and SATSA, as noted earlier. 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 7 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 less susceptible to publication bias. We used fixed-effects meta-analysis in STATA 11 to combine our independently obtained estimates and F 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 information criterion (AIC) or Bayesian information criterion (BIC) values, results presented here are based on the covariate main effect models.
On average, at age 80 years with 7 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 (0.1–0.2 points per year) and decline at a faster rate (0.01–0.08 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, and women in H-70 and SATSA 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 (0.2–0.4 points per additional year of education). Change in MMSE, on the other hand, was associated with education only in the full OCTO-Twin sample ($b = 0.08, p = .03$). Meta-analysis supports such a conclusion, suggesting that while educational attainment was associated with intercepts (Figure 2A: standardized effect size (ZES) = 0.27; 95% confidence interval [CI] = 0.25, 0.30), educational attainment was not related to WP changes in MMSE score (Figure 2B: ZES = 0.01, n.s.). Nonsignificant $I^2$ estimates suggest that these associations, or lack thereof, are stable.

**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 in all studies except 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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>SATSA</td>
<td></td>
<td>-0.00 (-0.08, 0.08)</td>
<td>9.52</td>
</tr>
<tr>
<td>LASA</td>
<td></td>
<td>0.01 (-0.03, 0.04)</td>
<td>50.00</td>
</tr>
<tr>
<td>HOPE</td>
<td></td>
<td>-0.07 (-0.15, 0.01)</td>
<td>9.73</td>
</tr>
<tr>
<td>CLS</td>
<td></td>
<td>0.03 (-0.03, 0.10)</td>
<td>14.31</td>
</tr>
<tr>
<td>OCTO-Twin</td>
<td></td>
<td>0.06 (-0.02, 0.14)</td>
<td>10.03</td>
</tr>
<tr>
<td>H70</td>
<td></td>
<td>0.06 (-0.04, 0.16)</td>
<td>6.41</td>
</tr>
<tr>
<td>Overall (I-squared = 26.3%, p = 0.238)</td>
<td></td>
<td>0.01 (-0.01, 0.04)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 2. Meta-analysis using estimated age-distributed between-person (BP) differences (education) and within-person (WP) change (education \times time) results for six studies. (**Top panel**) Educational attainment intercepts. (**Bottom panel**) Education \times Time. Note. Estimates have been standardized to account for sample size heterogeneity. Panel 2 uses nondemented estimates for change in educational attainment in the OCTO-Twin study. CLS = Canberra Longitudinal Study; HOPE = Healthy Older Person Edinburgh; H-70 = Gerontological and Geriatric Population Studies in Gothenburg, Sweden; LASA = Longitudinal Aging Study Amsterdam; OCTO-Twin = Origins of Variance in the Oldest-Old; SATSA = Swedish Adoption/Twin Study of Aging.
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, although 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.

**BP Age Differences Versus WP Age Changes**

Where median values for age and education in each study were used for centering of covariates, the BP age differences and WP 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**

*Nonlinear 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 (2009), education squared was a statistically significant predictor of change in MMSE scores ($b = −0.06, p = .04$) 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 Diagnostic and Statistical Manual, 3rd ed., Revised [DSM-III-R] and National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et L’Enseignement en Neurosciences [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 \( n = 477 \)) 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 nonsignificant (0.033 \( SE = .021 \)).

**DISCUSSION**

This article is a demonstration of the coordinated analysis approach advocated by Piccinin and Hofer (2008) and Hofer and 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. Although this consistency is visible in the raw estimates, in the conclusions based on significance levels, and in 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 in the same way 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 multioccasion 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 effect at lower as compared with higher levels of education. A positive time \(*_x_\) 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

### 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

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>SATSA</th>
<th>LASA</th>
<th>HOPE</th>
<th>CLS</th>
<th>OCTO-Twin</th>
<th>H-70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>28.195 (1.33)</td>
<td>27.437 (1.074)</td>
<td>27.844 (1.27)</td>
<td>27.075 (1.37)</td>
<td>25.897 (1.366)</td>
<td>25.207 (1.539)</td>
</tr>
<tr>
<td>Time</td>
<td>-0.117 (0.021)</td>
<td>-0.190 (0.013)</td>
<td>-0.159 (0.040)</td>
<td>-0.221 (0.033)</td>
<td>-1.272 (0.125)</td>
<td>-1.119 (0.202)</td>
</tr>
<tr>
<td>Baseline age</td>
<td>-0.072 (0.011)</td>
<td>-0.125 (0.007)</td>
<td>-0.129 (0.022)</td>
<td>-0.132 (0.024)</td>
<td>-0.297 (0.062)</td>
<td>na</td>
</tr>
<tr>
<td>Female</td>
<td>0.022 (0.151)</td>
<td>0.396 (0.113)</td>
<td>0.311 (0.163)</td>
<td>0.467 (0.182)</td>
<td>0.258 (0.436)</td>
<td>-0.260 (0.625)</td>
</tr>
<tr>
<td>Education</td>
<td>0.817 (1.400)</td>
<td>0.283 (0.018)</td>
<td>0.274 (0.035)</td>
<td>0.226 (0.034)</td>
<td>0.490 (0.076)</td>
<td>3.244 (0.622)</td>
</tr>
<tr>
<td>Time (*<em>x</em>) age</td>
<td>-0.008 (0.002)</td>
<td>-0.015 (0.001)</td>
<td>-0.022 (0.008)</td>
<td>-0.027 (0.005)</td>
<td>-0.084 (0.023)</td>
<td>na</td>
</tr>
<tr>
<td>Time (*<em>x</em>) female</td>
<td>-0.077 (0.025)</td>
<td>0.004 (0.015)</td>
<td>0.027 (0.051)</td>
<td>0.025 (0.036)</td>
<td>0.144 (0.139)</td>
<td>-0.413 (0.182)</td>
</tr>
<tr>
<td>Time (*<em>x</em>) education</td>
<td>-0.001 (0.027)</td>
<td>0.001 (0.002)</td>
<td>-0.018 (0.011)</td>
<td>0.008 (0.008)</td>
<td>0.077 (0.027)</td>
<td>0.209 (0.177)</td>
</tr>
</tbody>
</table>

Notes. AIC = Akaike information criterion; BIC = Bayesian information criterion; CLS = Canberra Longitudinal Study (median age = 76 years, education = 11 years); HOPE = Healthy Older Person Edinburgh study (median age = 76 years, education = 10 years); H-70 = Gerontological and Geriatric Population Studies (age = 85 years, education dichotomized 6 vs. > 6 years); LASA = Longitudinal Aging Study Amsterdam (median age = 70 years, education = 9 years); na = not applicable; OCTO-Twin = Origins of Variance in the Oldest-Old (median age = 83 years, education = 6 years); SATSA = Swedish Adoption/Twin Study of Aging (median age = 64 years, education dichotomized 6 vs. > 6 years).

\(^{p < .05}\) \(^{**}< .001\)
Figure 4. Scatterplots of years of formal education by individual fitted linear slope for each study and for Octogenarian Twins including and excluding individuals diagnosed with dementia. CLS = Canberra Longitudinal Study; HOPE = Healthy Older Person Edinburgh; LASA = Longitudinal Aging Study Amsterdam; OCTO-Twin = Origins of Variance in the Oldest-Old; SATSA = Swedish Adoption/Twin Study of Aging.
time $\times$ education term, paired with a significant negative
time $\times$ education$^2$ term was observed in CLS (but not in
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 comple-
tion 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 educa-
tion in the future (Glymour, Kawachi, Jencks, & Berkman,
2008). Measures of education quality (e.g., Glymour &
Manly, 2008; Manly, Jacobs, Touradji, Small, & Stern,
2002; Richards & Hatch, 2011), unavailable for our analy-
zes, would further enhance research on the role of education
in cognitive aging.

Self-rating of literacy (e.g., Kave, 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 avail-
able for the current analyses, they may provide a reason-
ably 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 preclinical stages (or
absence) of dementia, but it 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, van Boxtel, Van Gerven,
van Hooren, & Jolles, 2009; Piccinin, Muniz, Sparks, &
Bontempo, 2011).

Impact of Ceiling Effect

Given that ceiling effects may bias results when demen-
tia screening measures are used as an index of cognitive
function, it was important to first evaluate the potential
effect on the conclusions of having used the MMSE. In this
case, based on the comparison of typical versus Tobit mod-
els, 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 sam-
pies studied here, between 4.1% and 19.9% of individuals
scored at ceiling at any one occasion, considerably fewer
than the maximum of 40% considered by Wang and col-
leagues (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 stand-
ard 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 effect 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 equiva-
 lent interpretations for the parameter estimates conditioned
upon them. Although 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 esti-
mates 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 pre-
dictors. In the analysis of these six studies, different cen-
tering of the covariates influenced the trajectory parameter
estimates but not their estimated associations with the covar-
iates themselves. In other words, interpretation of the aver-
age level and rate of change in performance was affected
(e.g., average decline was greater for older reference ages
and the estimates were more similar when the same refer-
ence age was used), but, again, not the conclusions regard-
ing the covariates such as the association between education
and cognitive decline, at least for the centering choices con-
sidered here. Attention to such differences, through either
pre- or postanalysis centering is recommended as a way of
appropriately comparing results across studies.

BP Age Differences Versus WP Age Changes

On average, in all the samples, MMSE scores were
lower in older individuals, they declined over time, and the
BP and WP effects were similar at the sample age medi-
ans. 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 par-
ticipant (Mendes de Leon, 2007) effects in studies of aging
with age heterogeneous initial samples, where initial per-
formance 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 over-
estimated 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 this 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 of more than 19 at baseline. OCTO-Twin, on the other hand, although 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 interindividual 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 nondementing 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 WP age declines and BP age differences until after 80 years of age.

Understanding the generalizability of the impact of birth cohort and national differences in education, socioeconomic 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 endeavors.

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REFERENCES


