**Education and Age-related Decline in Cognitive Performance: Systematic Review and
Meta-analysis of Longitudinal Cohort Studies**

Seblova, D.^{1,2,3}, Berggren, R¹., & Lövdén, M.¹

¹Aging Research Center, Karolinska Institutet and Stockholm University, Stockholm, Sweden

²Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden ³Taub Institute
for Research in Alzheimer's Disease and the Aging Brain, The Gertrude H. Sergievsky Center,
Department of Neurology, Columbia University, New York, NY, USA

Correspondence to:

Dominika Seblova

Karolinska Institutet, NVS/ARC

Tomtebodavägen 18 A

171 65 Stockholm

Tel +46 072 0376168

Primary email: dominika.seblova@ki.se

Secondary email: dseblova@gmail.com

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25 **Highlights**

- 26 • Association of education and change in cognitive performance is negligible.
- 27 • Articles included in meta-analysis displayed high unexplained heterogeneity.
- 28 • Theories of cognitive aging need to be updated with regards to this association.

29 **Abstract**

30 Central theories of cognitive aging propose that education is an important protective factor for
31 decline in cognitive performance in older age. We conducted a systematic review and meta-
32 analysis of reported estimates of an association between educational attainment and change in
33 performance in six cognitive domains (episodic memory, processing speed, verbal fluency,
34 crystallized intelligence, fluid intelligence, and global ability) in the general population of older
35 individuals. The systematic search (28th of September, 2018) identified 83 eligible articles. The
36 episodic memory domain had the highest number of estimates (37 estimates from 17 articles,
37 n=109,281) included in the meta-analysis. The fewest estimates (5 estimates from 5 articles,
38 n=5,263) were included for fluid intelligence. Pooled mean estimates from an inverse-variance
39 weighted random effects analysis were not statistically significant and indicated that any
40 association between education and change in cognitive performance is likely to be of a negligible
41 magnitude. Sensitivity analyses did not substantially alter these results. However, heterogeneity
42 was substantial, and remained largely unexplained by mean age, mean educational attainment,
43 maximum follow-up period, and publication year. Overall education is an important factor in
44 aging due to its robust association with level of performance. However, we conclude that the
45 current base of empirical evidence is not revealing a consistent and substantial association

46 between educational attainment and changes in cognitive performance in the general population.

47 Theories of cognitive aging must be updated to incorporate this pattern of findings.

48 **Keywords:** cognitive aging, education, cognitive decline, cognitive reserve, longitudinal

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1. Introduction

Maintaining high cognitive function in older age is important for a sustainable future of our aging societies. For older adults, decline of cognitive performance may limit independent living and the ability to execute basic activities, such as managing finances or taking medication (Salthouse, 2012). With aging populations worldwide, it is crucial to prevent crossing of such low threshold of cognitive performance. It is therefore important to map the factors that influence cognitive aging.

Educational attainment has been proposed as a protective factor that promotes healthy aging and may buffer against cognitive decline (Stern, 2012, 2002). Multiple mechanisms may be at play. For example, education may act by directly increasing cognitive performance in younger age (Brinch and Galloway, 2012; Ceci, 1991; Cliffordson and Gustafsson, 2008; Ritchie and Tucker-Drob, 2018). If sustained into older age, raising early-life cognitive performance would result in later surpassing of impairment thresholds. Furthermore, education could also shape changes of cognitive performance in aging. For example, researchers have proposed that education may alter how people process cognitive tasks. This, in turn, may reduce the negative effects of aging-related brain changes on cognitive performance (Stern, 2012, 2002). Education may also influence lifestyle and access to healthcare, for example by shaping adult socioeconomic conditions, which could result in slower brain aging (Nyberg et al., 2012).

Many empirical articles have examined the association between educational attainment and cognitive performance. Thus far, summaries of the evidence indicate that longer education is associated with a higher *level* of cognitive ability (Opdebeeck et al., 2016; Strenze, 2007) and a lower occurrence of dementia (Caamaño-Isorna et al., 2006; Meng and D'Arcy, 2012; Xu et al.,

2016). Attempts to synthesize the evidence on aging-related *changes* in cognitive performance have also been undertaken. In 2006, a non-parametric meta-analysis summarizing 13 articles that examined educational attainment in relation to cognitive decline was reported (Valenzuela and Sachdev, 2006). The conclusion was that education is positively associated with cognitive change, meaning that people with higher educational attainment decline at a slower rate. A narrative review of articles conducted prior to 1999 arrived at the same conclusion (Anstey and Christensen, 2000). On the other hand, a later narrative review of articles published after 1999 found a lack of consistent evidence for such an association (Lenehan et al., 2015). Recent larger-scale efforts to analyze longitudinal data harmonized over cohorts and countries are also reporting quite negligible associations of educational attainment with age-related change in cognitive performance (Dorina Cadar et al., 2017; Lipnicki et al., 2017).

In summary, researchers have not been able to conclusively answer the question whether length of formal education is related to cognitive *change* in aging. The aim of this study is therefore to provide an up-to-date systematic review and meta-analysis of the current evidence on the association between educational attainment and change in cognitive performance from observational longitudinal cohort studies.

2. Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009) and the protocol was pre-registered in PROSPERO (CRD42017054606).

2.1. Systematic search

Articles were identified on the 16th of December 2016 by systematic searches in four databases (PubMed, PsycInfo, Web of Science, and Embase). In PubMed and Embase, a combination of indexed (MeSH) terms and keyword searches in titles and abstracts was used. In PsycInfo and Web of Science databases, only keywords were used. The search string had three blocks of keywords/indexed terms. Block one contained terms for cognitive performance. Block two had words related to change over time. The third block focused on education. The blocks were combined in the following manner: ((Block 1 AND Block 2) AND (Block 3)). In PubMed, PsycInfo, and Embase the results were further limited by age of the target population. The search strings used in all databases are provided in Supplementary Online Materials (SOM1). The searches were not limited by publication year, geographical region or language. One reviewer (D.S) screened the titles identified by the search. Subsequently, two reviewers (D.S and R.B) independently screened the remaining abstracts. Inter-rater agreement was high, with Cohen's kappa equal to 0.89. Finally, D.S assessed the full text articles for inclusion. In unclear cases, the article was discussed with M.L to arrive at a final decision.

In order to include more recent literature, the search was updated on 28th September 2018, using the same search strings but with time of publication starting after the end date of the first

search. In the second search only D.S. completed the screening, and problematic cases were discussed with a second reviewer (M.L).

2.2. *Inclusion and Exclusion Criteria*

The articles were included if they a) were peer-reviewed original research articles; b) had a prospective assessment of cognitive change in one of the six domains of interest assessed by a psychometric test; c) had a total follow-up of at least two years; d) reported an association between formal education and change in cognitive score between baseline and follow-up. Articles that reported quantitatively on the studied association were included in the meta-analysis. Those reporting incomplete quantitative or only qualitative results were kept for the systematic review. Articles were excluded if they a) primarily studied individuals diagnosed with neuropathological aging (i.e. dementia) b) did not have a suitable educational measure (i.e. short-term cognitive trainings, adult education, literacy only); c) were clearly not population based (i.e. hospital, clinical samples etc.) d) were not written in English or e) could not be found. The six cognitive domains were assigned by trained psychologists R.B. and M.L, based on the psychometric tests used, irrespective of the original categorization. Episodic memory tasks measured memory mainly by using delayed or immediate recall tasks. Processing speed was measured using psychomotor speed tests with small higher-order cognitive components (e.g. trail making test or symbol digit modalities). Verbal fluency measures assessed how many words could be generated based on initial letters, or given categories, within a given time period. Measures of crystallized intelligence included vocabulary and general knowledge assessments. Measures of fluid intelligence were various assessments of reasoning performance. Measures were classified as global cognition if they were composites of psychometric measures from multiple domains. We did not include screening measures, such as the Mini-Mental State Examination (Folstein et al.,

1975), as indicators of global cognition due to their common ceiling effect in the general population.

Articles based on the same or overlapping sample were further evaluated. If the articles assessed a certain cognitive domain using different test, both were included. If the exposure and outcome were the same, then the study where education was the main/independent predictor was included. If both articles in question examined education as main/independent predictor, then the one with a larger sample, longer follow-up, or statistical analysis that did not adjust for baseline cognitive performance was selected since they are less likely to be subject to regression to the mean (Glymour et al., 2005).

2.3. Data Extraction

From each article we extracted publication information (first author, journal, year of publication, country of sample), sample information (number of subjects, % males, average age, average educational level and/or number per group), data on study design (year of baseline, number of follow-ups, maximum follow up, % response rate, % drop out between follow ups), exposure and outcome data (measure of education & categorization procedures, psychometric test, cognitive domains assessed, measurement of cognitive change), data for meta-analytic effect calculation (mean and SE for the test for standardization, beta estimate for change and SE or CI or p-value), and analysis details (statistical method used, adjustment for baseline cognitive performance, methods for handling missing, inclusion of cognitive screening) and this information is reported in an online supplementary online Table S1 (meta-analytical articles) and S2 (systematic review articles). Several articles reported on multiple longitudinal and independent cohorts. In such a case, data for every individual cohort study were extracted.

2.4. *Calculating effect sizes*

Estimates from individual studies were rescaled to correspond to an association of one more year of education with cognitive decline, where decline is expressed in standard deviations per decade. The baseline SD for a given cognitive test was used for the rescaling of the beta estimate and its standard error (SE). When only confidence intervals and p-values were provided, they were converted to SE according to procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011). If education was reported as a binary or ordinal variable, it was converted to years of education. We assigned an approximate value of years of education for every category based on studies from the same country or our knowledge. Using the number of individuals in every category the average length of education per category was calculated and the difference between the compared categories was used for rescaling of the estimate. When multiple estimates were reported for ordinal variables, we extracted the most extreme comparison. If a study provided multiple measures for a certain cognitive domain in the same sample, all estimates and their standard errors (variances) were extracted and pooled into one. The pooled estimate Y was simply the average of the observed estimates $Y1$ and $Y2$. When pooling variances $V1$ and $V2$ into a single variance V , we used the following equation

$$V = \frac{V1 + V2 + 2r\sqrt{V1}\sqrt{V2}}{4}$$

and assumed a conservative correlation between variables of $r = 0.5$. For

episodic memory, 11 estimates were pooled in this manner with 10 coming from a single multi-cohort article (Cadar et al., 2017). For processing speed 10 estimates were obtained by pooling. Here 9 of the pooled estimates came from single multi-cohort article (Lipnicki et al., 2017). For fluid intelligence one estimate was obtained by pooling (Karlsson et al., 2015). For the other three domains no pooling was needed. We judged that alternative ways of dealing with this clustering, such as performing a multi-level meta-analysis or robust variance estimation, would

add little beyond this pooling approach (but come with other drawbacks, such as lack of availability of some statistics for heterogeneity and publication bias).

2.5. Statistical Analysis

We performed an inverse-variance weighted random effects meta-analysis using REML estimation and the metafor package (Viechtbauer, 2015) in R (R Development Core Team, 2016). Throughout, we estimated the association of 1 additional year of education with the rate of 1 SD change per decade. First, we estimated the overall meta-analytic estimate, β , in a random effects model. Heterogeneity was assessed by Cochran's Q , H^2 , the estimated standard deviation of underlying true effects (τ), and I^2 (Higgins et al., 2003). Next, we ran a series of sensitivity analyses. We estimated the sensitivity of the results to single outliers (by estimate or SE) with a leave-one-out procedure. In addition, we classified studies as potential outliers if their confidence interval did not overlap with the confidence interval of the meta-analytic estimate or if their confidence intervals were more than 10 times as big as the confidence interval of the meta-analytic estimate. Sensitivity analyses were run with these potential outliers removed. Indications of publication bias was gauged by inspecting a funnel plot and using Kendall's τ and Egger's Z to test for funnel plot asymmetry. If asymmetry was present, we performed a trim-and-fill procedure. Finally, we performed four simple meta-regression analyses, assessing the influence of mean age, mean educational attainment, publication year, and maximum follow-up length on the estimate of education's association with cognitive change. The final multivariable meta-regression model included all four predictors at the same time. We used a threshold for statistical significance at $p < .05$.

3. Results

3.1. Search Results

The systematic database search identified 6,379 unique articles. The review of the titles reduced the number of articles to 655 abstracts. After subsequent review 73 full text articles were selected (Fig. 1). Additional 10 full text articles were identified through screening of references of articles included in the meta-analysis. The highest number of articles reported quantitatively or qualitatively on the association between education and change in episodic memory ($n=39$), followed by processing speed ($n=18$), global cognitive ability ($n=17$), verbal fluency ($n=10$) crystallized intelligence ($n=10$) and fluid intelligence ($n=9$). For some domains many of the articles were analyzing the same longitudinal cohorts (episodic memory $n_{\text{duplicate}}=20$, processing speed $n_{\text{duplicate}}=7$, global cognitive ability $n_{\text{duplicate}}=2$, verbal fluency $n_{\text{duplicate}}=2$, crystallized intelligence $n_{\text{duplicate}}=2$, fluid intelligence $n_{\text{duplicate}}=2$) and exclusion of overlapping data was the main reason for exclusion of articles from the meta-analysis. Some articles did not provide enough details to extract the desired estimate or commented on the studied association only in writing. Details regarding studies excluded from meta-analysis is presented in Supplementary online Table S2 and their results summarized qualitatively in section 3.2.

Figure 1. Flow chart of the systematic literature search and the screening process of published articles to be summarized in the systematic review and meta-analysis of longitudinal cohort studies examining the association of education with change in cognitive performance in six domains.

3.2. *Qualitative synthesis*

For most domains the majority of the estimates included in the systematic review indicated that there is no association between education and change in cognitive performance. The number of articles and estimates varied across cognitive domains. For episodic memory we included 24 articles with 30 individual estimates in the systematic review (online Supplementary Table S2) (Amieva et al., 2005; Bishop et al., 2016; Bosma et al., 2003; Christensen et al., 2009, 1997; Colsher and Wallace, 1991; Evans et al., 1993; Gerstorf et al., 2006; Gross et al., 2015; Hult et al., 2015; Karlamangla et al., 2009; Lipnicki et al., 2013; Manly et al., 2005; Masel and Peek, 2009; Proust-Lima et al., 2008; Reas et al., 2017; Schneider et al., 2012; Seeman et al., 2005; Singh-Manoux et al., 2011; Stephan et al., 2018; Van Dijk et al., 2008; Van Gerven et al., 2012; Wolinsky et al., 2011; Zaninotto et al., 2018). The majority of the estimates (21 out of 30 estimates, ~70%) reported no association between education and change in episodic memory. Five estimates (~17%) reported a faster decline in those with lower levels of education and three estimates (~10%) reported an opposite association. With regards to processing speed 10 articles with 22 estimates were included in the systematic review (Bosma et al., 2003; Christensen et al., 2009, 1997; Proust-Lima et al., 2008; Reas et al., 2017; Schneider et al., 2012; Stephan et al., 2018; Van Dijk et al., 2008; Van Gerven et al., 2012; Zaninotto et al., 2018). The majority (~86%) of the estimates reported no association between education and change in this domain. For global cognition 7 articles (Albert et al., 1995; Gross et al., 2015; Lipnicki et al., 2013; Proust-Lima et al., 2008; Seeman et al., 2005; Singh-Manoux et al., 2011; Zaninotto et al., 2018) reported 11 estimates and 8 of them (~73%) reported no association. For verbal ability 8 out of 9 estimates (~89%) coming from 6 articles also reported no association (Proust-Lima et al., 2008; Reas et al., 2017; Schneider et al., 2012; Singh-Manoux et al., 2011; Van Dijk et al., 2008;

Zaninotto et al., 2018). With regards to crystallized intelligence (Christensen et al., 2009, 1997; Gerstorf et al., 2006; Seeman et al., 2005; Singh-Manoux et al., 2011; Van Dijk et al., 2008; Van Gerven et al., 2012) and fluid intelligence (Christensen et al., 1997; Ronnlund et al., 2017; Seeman et al., 2005; Singh-Manoux et al., 2011) fewer estimates were included in the systematic review and the results were more mixed. For crystallized intelligence 60% of the estimates (6 out of 10) indicated no association between education and decline in this cognitive domain. However, 30% of estimates (n=3) reported a slower decline for those with higher education and 1 estimate (~10% indicated an improvement in crystallized intelligence in old age for those with higher education. There were only 5 estimates for fluid intelligence and 2 reported no association between education and cognitive decline in this domain, 2 reported that those with higher education decline at a slower rate and one study the opposite.

3.3. *Meta-analysis*

Below we first report the overall results from the main analyses. Next, we report the sensitivity analyses for each domain of cognitive performance. Forest plots are reported in the main article. Funnel plots, scatterplots, and additional details related to sensitivity analyses (e.g., tables for the cross-validation using leave-one-out) can be found in Supplementary Online Materials (SOM).

3.3.1. *Main analyses*

We found no evidence that years of education are substantially associated with the rate of change for any of the six domains of cognitive performance (crystallized intelligence, episodic memory, fluid intelligence, global cognition, processing speed, or verbal fluency). In other words, none of

the meta-analytic estimates reached statistical significance and the point estimates, which had quite high precision for most of the domains, suggested that the associations are likely to be of negligible magnitudes (Table 1; see Figures 2-7). All domains (except for crystallized intelligence) exhibited substantial heterogeneity (Table 2).

Table 1. Results from the random-effects meta-analysis estimating the association between formal education (in years) and change in cognitive abilities (in SD per decade) in six domains.

Domain	# estimates	n	β	SE	(95% CI)	Z	p
Episodic memory	37	109,281	0.0019	0.0035	(-0.0049; 0.0088)	0.5477	0.5839
Processing speed	20	48,339	0.0012	0.0030	(-0.0047; 0.0070)	0.3941	0.6935
Global cognition	17	69,729	0.0215	0.0154	(-0.0087; 0.0518)	1.3950	0.1630
Verbal fluency	15	55,719	-0.0185	0.0160	(-0.0498; 0.0128)	-1.1583	0.2467
Crystallized intelligence	6	6,730	0.0001	0.0018	(-0.0049; 0.0051)	-0.2821	0.7778
Fluid intelligence	5	5,263	-0.0022	0.0064	(-0.0147; 0.0102)	-0.3513	0.7254

Note: β is estimated effect size in standard deviations per decade for 1 additional year of education. SE=standard error. CI=confidence interval.

Table 2. Heterogeneity measures for the random-effects meta-analysis models estimating the association between formal education (in years) and change in cognitive abilities in six domains.

Domain	# estimates	n	τ	I ²	H ²	Q	Q _{df}	Q _p
Episodic memory	37	109,281	0.0171	89.50%	9.52	154.7270	36	< .0001
Processing speed	20	48,339	0.0105	89.25%	9.30	136.7729	19	< .0001
Global cognition	17	69,729	0.0605	99.90%	983.01	158.2777	16	< .0001
Verbal fluency	15	55,719	0.0579	99.69%	324.42	393.8094	14	< .0001
Crystallized intelligence	6	6,730	0.0021	4.83%	1.05	6.9413	5	0.225
Fluid intelligence	5	5,263	0.0115	68.41%	3.17	13.3928	4	0.0095

Note: τ is the estimated standard deviation of underlying true effects. I² is the percentage of variability due to heterogeneity. H² is the proportion of total variability to sampling variability. Q is Cochran's Q on k-1 degrees of freedom (reported as Q_{df}) with p-value for heterogeneity measured by the Q signified as Q_p.

3.3.2. Sensitivity analyses

For episodic memory 17 articles, reporting in total 37 independent estimates, were included in the meta-analysis (Alley et al., 2007; Anstey et al., 2014; Berggren et al., 2018; Bishop et al., 2016; Cadar et al., 2017; Christensen et al., 2001; Ericsson et al., 2017; Glymour et al., 2012;

285 Gottesman et al., 2014; Hulur et al., 2015; Lee et al., 2006, 2004; Li et al., 2017; Lipnicki et al.,
286 2017; Marden et al., 2017; Mungas et al., 2018; Schneider et al., 2012; Zahodne et al., 2011).
287 Cross-validation using leave-one-out did not reveal any overly influential study (SOM3A).
288 However, we classified 8 estimates as potential outliers (Alley et al., 2007; Cadar et al., 2017:
289 Spanish sample; Christensen et al., 2001; Ericsson et al., 2017; Lee et al., 2006; Li et al., 2017;
290 Lipnicki et al., 2017: Greek sample; Weng et al., 2018). There was substantial heterogeneity even
291 after removing outliers (SOM2A) and the meta-analytic estimate remained non-significant ($\beta =$
292 0.003, $p = .24$; SOM2A; Figure 2B). Funnel plots (SOM4A) and Egger's rank test (SOM5A)
293 indicated no statistically significant evidence of publication bias. Based on the meta-regressions
294 the estimates were not related to age, education, follow-up period, or publication year (SOM6 &
295 7A) in a statistically significant way.

Episodic Memory

Fig 2. Forest plots summarizing individual and meta-analytical pooled estimates from A) all studies and B) non-outlier studies for association of education (1 more year) with change in episodic memory (in SD per decade). Point estimates and 95% confidence intervals are represented. Size of points corresponds to weight in meta-analysis.

For processing speed 11 articles, providing 20 independent estimates, were included in the meta-analysis (Alley et al., 2007; Anstey et al., 2014; Christensen et al., 2001; Ericsson et al., 2017; Gottesman et al., 2014; Lee et al., 2006; Darren M. Lipnicki et al., 2017; Nishita et al., 2013; Tucker-Drob et al., 2009; Weng et al., 2018; Zahodne et al., 2011). Cross-validation using leave-one-out did not reveal any overly influential study (SOM3B). Six studies were classified as outliers (Christensen et al., 2001; Ericsson et al., 2017; Gottesman et al., 2014; D M Lipnicki et al., 2017; Singaporean sample; Weng et al., 2018). There was substantial heterogeneity even after removing outliers (SOM2B) and the meta-analytic estimate remained non-significant ($\beta = 0.002$, $p = .47$; SOM2B; Figure 3B). There was no evidence of publication bias (SOM4B & 5B). Meta regression analyses suggested that articles with longer follow-up period tended to find a stronger negative relationship between educational attainment and rate of change ($\beta = -0.001$, $p = .01$; SOM6B & 7B).

Fig 3. Forest plots summarizing individual and meta-analytical pooled estimates from A) all studies and B) non-outlier studies for association of education (1 more year) with change in processing speed (in SD per decade). Point estimates and 95% confidence intervals are represented. Size of points corresponds to weight in meta-analysis.

For global cognition 13 articles, together reporting 17 independent estimates, were included (Anstey et al., 2014; Brewster et al., 2014; Ericsson et al., 2017; Gale et al., 2012; Glymour et al., 2005; Gonzalez et al., 2013; Gottesman et al., 2014; Lee et al., 2006; Li et al., 2017; Sha et al., 2018; Weng et al., 2018; Wilson et al., 2009; Zahodne et al., 2015). Cross-validation using leave-one-out did not reveal any overly influential study (SOM3C), but we classified 2 studies as outliers (Lee et al., 2006; Li et al., 2017). There was substantial heterogeneity even after removing outliers (SOM2C) and the meta-analytic estimate remained non-significant ($\beta = 0.0004$, $p = .73$; SOM2C; Figure 4B). Funnel plots (SOM4C) and Egger's rank test suggested evidence of publication bias (Egger's $Z = 2.80$, $p < .01$; SOM5C). However, performing trim-and-fill did not change the estimate substantially ($\beta = -0.0008$, $p = .86$; SOM2C). Simple meta regression analyses suggested that age was weakly but significantly associated with the pooled estimates and the multiple meta-regression analysis showed that all predictors moderated the association (SOM6C & 7C). According to this final multivariate model, the relationship between educational attainment and rate of change is more positive in cohort studies of older people ($\beta_{\text{age}} = 0.0008$, $p < .001$), in samples with higher mean education ($\beta_{\text{ed.}} = 0.0042$, $p < .001$), and later published papers ($\beta_{\text{year}} = 0.0032$, $p < .001$). In addition, we found that studies with longer follow-up reported more negative association ($\beta = -0.0011$, $p < .001$). Nevertheless, given the absence of major associations in simple models and, in particular, the suggestions of publication bias for this domain, we should interpret these association carefully.

Fig 4. Forest plots summarizing individual and meta-analytical pooled estimates from A) all studies and B) non-outlier studies for association of education (1 more year) with change in global cognition (in SD per decade). Point estimates 95% confidence intervals are represented. Size of points corresponds to weight in meta-analysis.

For verbal fluency, 5 articles, reporting in total 15 independent estimates, were included in meta-analysis (Glymour et al., 2012; Gottesman et al., 2014; Lee et al., 2006; D M Lipnicki et al., 2017; Weng et al., 2018). Cross-validation using leave-one-out did not reveal any overly influential study (SOM3D). Two studies were classified as outliers (Lee et al., 2006; Lipnicki et al., 2017: Greek sample). There was still a substantial heterogeneity after removing outliers ($I^2 = 71.3\%$; SOM2D). Interestingly, the meta-analytic estimate reached statistical significance after outliers were removed, but contrary to theoretical predictions the estimate was negative ($\beta = -0.006$, $p < .001$; SOM2D; Figure 5B). There was no significant evidence of publication bias (SOM4D & 5D). The estimates did not significantly relate to age, education, follow-up period or publication year (SOM6D & 7D).

Fig 5. Forest plots summarizing individual and meta-analytical pooled estimates from A) all studies and B) non-outlier studies for association of education (1 more year) with change in verbal fluency (in SD per decade). Point estimates and 95% confidence intervals are represented. Size of points corresponds to weight in meta-analysis.

For crystallized intelligence 6 articles were included in the meta-analysis (Anstey et al., 2014; Berggren et al., 2018; Christensen et al., 2001; Deary et al., 1998; Nishita et al., 2013; Zahodne et al., 2011). Cross-validation using leave-one-out did not reveal any overly influential study (SOM3E). Crystallized intelligence was the only domain that did not exhibit substantial heterogeneity with or without outliers included (SOM2E). Two studies were classified as outliers (Christensen et al., 2001; Deary et al., 1998). The meta meta-analytic effect size remained non-significant after excluding outliers ($\beta = -0.0003$, $p = .86$, SOM2E). There was no evidence of publication bias (SOM4E & 5E). The findings did not seem to depend on any simple combination of age, education, follow-up period or publication year (SOM6E & 7E). The more complex multivariate meta-regression model could not be estimated due to the number of parameters being larger than the number of observations.

Fig 6. Forest plots summarizing individual and meta-analytical pooled estimates from A) all studies and B) non-outlier studies for association of education (1 more year) with change in crystallized intelligence (in SD per decade). Point estimates and 95% confidence intervals are represented. Size of points corresponds to weight in meta-analysis.

For fluid intelligence there were 5 articles included (Berggren et al., 2018; Ericsson et al., 2017; Karlsson et al., 2015; Nishita et al., 2013; Tucker-Drob et al., 2009). There were no outliers according to our criteria and cross-validation using leave-one-out did not reveal any overly influential study (SOM3F). Egger's rank suggested evidence of publication bias (Egger's $Z = -2.25$, $p = .02$; SOM5F). Performing trim-and-fill did not change original conclusion, as the meta-analytic estimate (SOM2F) remained non-significant ($\beta = 0.004$, $p = .52$). The simple meta-regression analysis suggested that studies with longer follow-up period tended to find a more positive relationship between educational attainment and rate of change ($\beta = 0.0015$, $p < .01$; SOM6F & 7F).

Fig 7. Forest plots summarizing individual and meta-analytical pooled estimates from A) all studies and B) non-outlier studies for association of education (1 more year) with change in fluid

intelligence (in SD per decade). For individual studies point estimates and 95% CI are represented. Size of points corresponds to weight in meta-analysis.

1. Discussion

The positive association between educational attainment and level of cognitive function is well-established. Important theoretical frameworks (Stern, 2012, 2002) also predict that higher educational attainment affects cognitive decline, but the evidence for this prediction has been mixed. In this meta-analysis, we summarize a total of 100 estimates of the relationship between education and rate of change in cognitive performance in adulthood and older age across six cognitive domains. Neither our qualitative synthesis of articles that could not be included in the meta-analysis nor the results from the meta-analysis supported the hypothesis that educational attainment is consistently and positively associated with inter-individual differences in rate of cognitive change in any cognitive domain.

To put our point estimates into perspective, for example with regards to episodic memory, the estimate (0.002) indicates that a difference in decline for an individual with 12 vs 17 years of education (corresponding to high school diploma vs. a university degree) would be 0.01 SD per decade (0.002×5 years). In comparison, the average rate of episodic memory decline of at least 0.4 – 0.5 SD per decade in older age is 40 times larger (Berggren et al., 2018; Schaie, 2005). Further, this can be compared to the expected difference in level of episodic memory functioning related to a difference between 12 and 17 years of education, which has been estimated to be at the very least 0.25 SD (Berggren et al., 2018; Dorina Cadar et al., 2017). From this follows that the current body of evidence indicates that education-related differences in the rate of change in episodic memory (and the other studied domains) are likely to be of negligible magnitude. Such conclusion is further supported by the relatively high precision of the estimates for several of the

cognitive domains (and for essentially all of the domains when potential outlier estimates were removed).

Overall, our findings were in line with the more recent narrative reviews of the association between education and rate of cognitive decline. For example, Lenehan et al concluded that “there is little consistent evidence to support the assumption that education moderates age-related cognitive decline across any cognitive domain(s) in older healthy adults” (p. 160) (2015). However, they called for caution in interpreting the results due to methodological constraints, such as short follow-up periods, and range-restriction in educational attainment. Here, we included more recent studies using advanced statistical techniques and with longer follow-up periods (between 2 and 25 years) across a wide span of educational tiers, and arrived at the same conclusion. Recent analyses of harmonized data over countries and cohorts further corroborate this conclusion (Cadar et al., 2017; Darren M. Lipnicki et al., 2017). This more recent evidence contrasted with earlier summaries of findings (Anstey and Christensen, 2000; Valenzuela and Sachdev, 2006). The more widespread application of appropriate statistical tools for analyzing longitudinal data (e.g., latent growth curve models in the linear mixed or structural equation modeling frameworks) in recent years may partly explain why the bulk of recent studies arrived at different conclusions than earlier studies (Glymour et al., 2005).

Our results indicated a substantial heterogeneity across the studies. This heterogeneity remained even when outliers were excluded. The high estimates of heterogeneity are partly a consequence of the relatively high precision of many of the individual estimates. Further, the relatively small estimates of the standard deviation of the underlying true effects (τ), together with only few significant estimates from individual studies, suggest that the high estimates of heterogeneity in some of the measures should be carefully interpreted.

Nevertheless, some heterogeneity no doubt exists and could for example be the result of diverse biases playing different roles in different studies. One potential bias in longitudinal studies stems from drop-out during follow-up. There was a high variability in attrition in the included longitudinal cohort studies (range 11.7 to 76%), with an average 38% (SD 21.5). Thus, it is possible that attrition, which includes both selective mortality and selective dropout for other reasons, may modify the studied relationship. In particular selective mortality may under some conditions mask a positive association between education and change in cognitive performance (Mayeda et al., 2018, 2016). However, studies that have attempted to address this issue have not reported substantially altered estimates (Foverskov et al., 2018; Glymour et al., 2012; Gottesman et al., 2014). Unfortunately, drop-out was not consistently reported in the available articles and therefore could not be included as a factor in the meta-regression. Yet, length of follow up, which could be proxy for drop-out, was the only predictor that played a role in the meta-regressions for more than one domain. For processing speed shorter follow-up was associated with more positive estimates. For fluid intelligence the association was the opposite. The mixed evidence here may emanate from difference in length follow up periods for these two measures - fluid intelligence articles covered almost 30 years, meanwhile follow ups for processing speed were at most 15 years. Nevertheless, given the mixed evidence, we are hesitant to make strong interpretations of these results. We also note that mean age was not a statistically significant moderator (neither was the mean level of education). If mortality introduced significant biases then we would have expected an association with age, such that older samples would show a less positive association between education and rate of change due to selection forces. Notably, the only significant association found for global cognition was in the opposite direction of the expected one. Other studies, which focus on the adult life-span (35 years and above), also show no indication that

associations between education and rate of change are larger in younger adulthood (Berggren et al., 2018).

Heterogeneity may also be an important finding in itself, since it may reflect a true variation in the studied relationship. It has for example been speculated that education relates differently to level and change in cognitive performance in different societies, perhaps reflecting differences in whether privilege or ability determines educational attainment (Branigan et al., 2013; Johnson et al., 2010). The robust association between education and level of performance may also present problems for the assessment of the association between education and change. With individuals of different education levels operating in different portions of the measurement scale, groups of higher and lower education may be differentially affected by scaling issues, such as ceiling and floor effects. Subsequently, this may result in apparent protective associations in some studies and opposing associations in others. Some longitudinal studies may have included individuals with cognitive impairment and/or dementia, which may be another reason for high heterogeneity. However, articles (Berggren et al., 2018; Deary et al., 1998; Ericsson et al., 2017; Gale et al., 2012; Glymour et al., 2012; Gonzalez et al., 2013; Nishita et al., 2013; Tucker-Drob et al., 2009; Weng et al., 2018; Zahodne et al., 2015) that excluded those with cognitive impairment and/or dementia did not differ in their conclusions from articles without cognitive screening of their participants. Furthermore, articles presenting sensitivity analysis excluding those with cognitive impairment and/or dementia in the same data also arrived at the same overall conclusions (Proust-Lima et al., 2008; Tucker-Drob et al., 2009; Zahodne et al., 2015). It remains for future research to explain the importance of the observed heterogeneity.

Verbal fluency was the only domain where some of the sensitivity analyses (excluding potential outliers) indicated a possible association between education and change in cognitive

performance. Notably, this association was quite small (-0.006) and, contrary to the theoretical predictions, in the negative direction. In other words, it indicated that higher educational attainment tended to be associated with stronger decline in verbal fluency. Given the number of statistical tests that were run and the unexpected direction of the association, we are hesitant to make much out these results.

We however note that several research questions remain to be answered in this field. For example, some researchers have investigated whether education is associated with the shape and acceleration point of normal cognitive decline (Christensen et al., 2001; Clouston et al., 2015), but the evidence remains mixed here. The role of turning points (e.g., retirement) (Finkel et al., 2009), cohort effects and societal differences (Karlsson et al., 2015), education-differential retest effects (Christensen et al., 2001), and selective mortality (Glymour et al., 2012) is also not fully understood. However, we can conclude that the reported associations between education and change in cognitive performance in the general population are generally of negligible importance relative to the benefit associated with education-related impact on level of cognitive performance. Theories of cognitive aging (Nyberg et al., 2012; Stern, 2012, 2002) must be updated to incorporate this pattern of findings.

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506 Author contributions

507 ML conceived the study and secured funding. DS had prepared the PROSPERO protocol,
508 planned and completed all the searches, and did the screening and data extraction. RB and ML
509 assisted with planning of the searches and with parts of the screening. All authors have taken part
510 in planning and performing the statistical analysis, interpreting data, and drafting and revising of
511 the manuscript.

512 Declarations of interest: none.

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