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Late-life cognitive activity and dementia: a systematic review and bias analysis

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Abstract

Background—Engaging in late-life cognitive activity is often proposed as a strategy to delay or prevent Alzheimer's disease (AD) and other dementias. However, it is unclear to what extent the available evidence supports a causal effect of cognitive activity in dementia prevention.

Methods—We systematically searched PubMed and EMBASE through June 2014 to identify peer-reviewed epidemiologic studies of cognitive activity and incidence of AD or all-cause dementia. Eligible articles analyzed data from cohort or nested case-control studies, explicitly defined cognitive activity, evaluated participants for AD or all-cause dementia using clearly defined criteria, and provided effect estimates adjusted for at least age and sex. We describe methodologic issues and biases relevant to interpretation of these studies, and quantify the degree of bias due to confounding and reverse causation required to nullify typically observed associations.

Results—We reviewed 12 studies involving 13,939 participants and 1,663 dementia cases, of which 565 were specifically evaluated as AD. Most studies found associations between late-life cognitive activity and lower AD and/or all-cause dementia incidence. Differences in cognitive activity operationalization across studies precluded meta-analysis of effect estimates. Our bias

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Author Contributions

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Potential Conflicts of Interest

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analysis indicated that the observed inverse associations are probably robust to unmeasured confounding, and likely only partially explained by reverse causation.

Conclusion—Our systematic review and bias analyses provide support for the hypothesis that late-life cognitive activity offers some reduction in AD and all-cause dementia risk. However, more data are needed to confirm this relationship and on the optimal type, duration, intensity, and timing of that activity.

Introduction

An estimated 47 million people worldwide have dementia in 2015, and this number is projected to triple by 2050.¹ Thus, the search for modifiable preventive factors is becoming increasingly urgent. One such potentially modifiable factor is cognitive activity, which is thought to contribute to building and maintaining brain structure and function,^{2,3} sometimes viewed as analogous to the contribution of physical exercise to cardiopulmonary and neuromuscular structure and function.

A variety of websites and publications encourage older adults to be mentally active (“use it or lose it”) to protect brain health. Although epidemiologic studies often show reduced risk of dementia with late-life cognitive activity, concerns about residual confounding and reverse causation cast doubt on these findings. Several characteristics and behaviors linked with greater late-life cognitive activity, such as greater formal education, higher socioeconomic status (SES), and better general health, also appear to be associated with reduced dementia risk, suggesting that residual or unmeasured confounding may influence study findings.⁴ Furthermore, falloff in cognitive activity in late life may be a *consequence* of cognitive losses prior to dementia onset, raising the possibility that reverse causation also contributes to the observed inverse associations.

To investigate these issues, we conducted a systematic review of epidemiologic studies of cognitive activity and incidence of Alzheimer’s disease dementia (AD) and other dementias, characterized and quantified the potential bias from confounding and reverse causation, and identified additional methodologic issues relevant to the interpretation of these studies.

Methods

Systematic search strategy

We conducted a systematic search of PubMed and EMBASE through June 2014 to identify relevant studies. To build our search strategy, we first obtained lists of index terms relevant to cognitive activity, AD, and dementia, and nested case-control and cohort studies using the PubMed Medical Subject Headings (MeSH) database and the EMBASE Emtree thesaurus. We also identified common synonyms for cognitive activity from primary and review articles and incorporated these terms into our search strategy (eTables 1 and 2).

Selection of studies

To be eligible for inclusion, studies had to be published in a peer-reviewed journal, be cohort or nested case-control studies in well-defined cohorts, have a clearly described

operationalization of cognitive activity, evaluate cognitive activity prospectively in relation to dementia, evaluate all participants (or a systematically drawn sample) for AD or dementia using established diagnostic criteria, provide effect estimates with confidence intervals or standard errors for the association between cognitive activity and AD or dementia, and adjust for at least age and sex. This review was conducted in part for the database of AD epidemiology findings AlzRisk (www.alzrisk.org), which uses these pre-specified criteria and complies with current standards for systematic review and meta-analyses of observational studies.^{5,6}

Data extraction

For each eligible study, we extracted the following: publication year; study cohort; study design; number of participants; baseline age distribution; follow-up time; method of ascertainment and operationalization of cognitive activity; number of AD and dementia cases; effect estimates, with confidence intervals or standard errors; and model covariates. Due to the heterogeneity of the exposure definitions used, we did not compute meta-analysis summary estimates.

Bias analysis method

Unmeasured confounding is likely present in all observational studies; more important is the *degree* to which such confounding biases estimated effects. We conducted a bias analysis⁷ to evaluate how reported hazard ratios (HR) for the effect on AD of ‘high’ versus ‘low’ levels of cognitive activity—obtained from one representative study⁸—would change under different assumptions about the magnitude of unmeasured confounding. As incipient dementia may be a shared cause of reduced cognitive activity and clinical dementia, we used this same approach to quantify how the observed association between cognitive activity and AD would be influenced by reverse causation.

We used a formal quantitative approach applicable to the case of a binary exposure, a hypothetical unmeasured binary confounder U, and a rare time-to-event outcome.⁷ It can be shown that the degree of confounding by U is a function of (1) the HR reflecting the association of U with AD, HR_{U-AD} , conditional on exposure and measured covariates; (2) the prevalence of U in the high-activity group, p_1 , conditional on measured covariates; and (3) the prevalence of U in the low-activity group, p_0 , conditional on measured covariates. To quantify how confounding by U would change an observed estimate reflecting the effect of cognitive activity on AD (HR_{CA-AD}), we calculated a bias-corrected estimate ($HR_{CA-AD|U}$), the estimated effect of cognitive activity on AD that would have been obtained with adjustment for the hypothetical confounder U (in addition to the measured covariates). This bias-corrected estimate is a function of the observed estimate of the effect of cognitive activity on AD, and the three parameters defining the degree of confounding and is given by $HR_{CA-AD|U} = HR_{CA-AD} / \{ [1 + (HR_{U-AD} - 1)p_1] / [1 + (HR_{U-AD} - 1)p_0] \}$. This approach entails an additional simplifying assumption of no interaction between the effects of U and cognitive activity on the hazard ratio scale. The impact of unmeasured confounding by U can be assessed in two ways. The first approach compares the observed estimate with the bias-corrected estimate under different specifications of U, and asks “given HR_{CA-AD} , and specifying HR_{U-AD} , p_0 and p_1 , what would $HR_{CA-AD|U}$ be?” The second approach calculates

how much confounding would be required for the observed association to be eliminated entirely, and asks “given HR_{CA-AD} , what values of HR_{U-AD} , p_0 and p_1 would make $HR_{CA-AD/U}$ become 1?”

To use this approach, we needed an effect estimate from a study that reported cognitive activity as a categorical exposure in relation to the time-to-event outcome of AD, and in which AD occurred relatively rarely (in general, this approach provides correct HR estimates when the disease occurs in up to 10% of both exposure groups in the study population). Among the cohort studies in our review, these conditions were most adequately met in Akbaraly et al.⁸, in which approximately 2% of the study population developed AD over a 4-year follow-up period. (AD incidence was in the range of 10–15% over the follow-up periods of the other studies, which would lead to only minor violations of the rare disease assumption.) Notably, Akbaraly et al. was similar to the other studies with respect to the types of cognitive activities assessed (eTable 3), the operationalization of cognitive activity as an exposure and the estimated magnitude of the association between cognitive activity and dementia (Table 1).

Akbaraly et al. compared AD risks corresponding to what the authors defined as “high” versus “low” (reference) engagement in both “stimulating” ($HR_{CA-AD} = 0.39$ [95% CI: 0.21, 0.71]) and “passive” ($HR_{CA-AD} = 0.68$ [0.41, 1.13]) activity. We estimated how much confounding would be needed to increase these point estimates to 1. To be more conservative in our bias assessment, we also performed similar calculations for the upper confidence limit of the HR for stimulating activity. We did not perform this calculation for the upper confidence limit for the passive activity HR as it already exceeded 1.

Application to unmeasured confounding—For our bias analysis, we posited the presence of a binary confounder U to represent an unmeasured risk factor with either a small ($HR_{U-AD} = 1.5$), moderate ($HR_{U-AD} = 2$) or large harmful effect on AD ($HR_{U-AD} = 3$). These three values encompass a range of effect estimates (risk, odds or hazard ratios) reported in studies of individual or multiple cardiovascular risk factors in relation to AD incidence.^{9,10} Depression,⁹ low education⁹ and lifecourse socioeconomic position^{11,12} are other potential confounders of the cognitive activity-AD association with effect estimates in this range. The studies we reviewed adjusted for confounding by these variables to varying degrees, so the specific unmeasured confounders represented by U, and the degree of residual confounding will differ across individual studies. We used these values of HR_{U-AD} , and allowed p_0 and p_1 to vary between 0 and 1 in the formula above, to calculate how the HR_{CA-AD} estimates from Akbaraly et al. would change under different amounts of confounding.

Application to reverse causation—The magnitude of bias due to reverse causation will depend on the degree to which individuals with mild cognitive impairment (or potential incipient dementia more broadly, including subjective cognitive concerns¹³, engage in less cognitive activity ($p_1 - p_0$), and on the magnitude of their increased risk of developing clinical dementia (HR_{U-AD}). Such individuals are not excluded at baseline in most studies of the effect of cognitive activity on AD, and may account for a substantial portion of the study population; in three cohorts reviewed here, individuals with mild cognitive impairment made

up 19%, 26%, and 39% of all non-demented individuals.^{8,14,15} Indications of incipient dementia in cognitively normal individuals are strongly associated with eventual AD or dementia diagnosis, with hazard or odds ratio estimates ranging from 2.8 to 6.7.^{13,14,16–18} On the basis of these reports, we used an HR of 4.5 for the effect of incipient dementia on AD ($HR_{U-AD} = 4.5$), and again calculated how reverse causation would change the HR_{CA-AD} estimates from Akbaraly et al.

Results

Literature search results

Using our search strategy, we identified 926 citations. After removing 238 duplicate citations, and reviewing article titles and abstracts against our inclusion criteria, we identified 56 citations for full-text review. Of these, we excluded articles not in English. Twelve of the remaining English-language article met criteria for inclusion in our review (Figure).

Study design details

The 12 studies we reviewed included a total of 13,939 participants from 11 cohorts^{8,15,19–28} (Table 1; eTable 4). Two studies analyzed the same participants from the Kungsholmen cohort; we included both, as they examined different aspects of cognitive activity.^{23,26} Of these 12 studies, 10 were prospective cohort studies including a total of 13,431 participants^{8,15,21–28} and two were nested case-control studies^{19,20}. The prospective studies assessed cognitive activity at a baseline visit late in life. Almost all studies inquired only about current or habitual participation in leisure activities; one additionally inquired about activity at ages 6, 12, 18 and 40.¹⁵ The two nested case-control studies assessed cognitive activity earlier in life; one inquired about current mid-life activity (at mean age 45)¹⁹, while the other asked at age 57 about activity before age 40²⁰.

In the 10 prospective cohort studies, follow-up for dementia began immediately after the baseline visit. Six studies reported mean follow-up time (range, 2.5–6.1 years). In the two nested case-control studies with mid-life measures of cognitive activity, dementia follow-up began approximately 20 years after assessment of cognitive activity. All but one of our reviewed studies adjusted for education. Four studies additionally adjusted for SES, or a marker of SES such as occupation or income.

Dementia assessment

Most studies used multi-stage assessments for dementia, consisting of initial cognitive screening followed by more detailed clinical examinations under a standard protocol. Two studies conducted full annual examinations on all participants^{15,28}. Dementia and AD were diagnosed by standard clinical and research criteria^{29–32}. Diagnoses were available for AD alone in 3 studies^{15,27,28}, for both AD and all-cause dementia in three studies^{8,20,25}, and for all-cause dementia alone in six studies.^{19,21–24,26}

Definition, dimensions, and operationalization of cognitive activity

In all studies, popular leisure activities considered to require information seeking and processing were characterized as “cognitive.” Most studies assessed participation in a relatively narrow range of leisure activities, such as reading books, newspapers, or magazines; doing crosswords or playing cards; and watching television and listening to the radio. However, a few studies also inquired about activities such as participation in group discussions and attending cultural and social events (eTable 3).

The ways that studies operationalized cognitive activity varied widely. One study categorized activity based on frequency of participation across all cognitive activities, and did not distinguish different frequencies of participation in the specific activities assessed.²⁶ Most commonly, investigators started with reported frequency of participation in *each* activity, assigned a score corresponding to each frequency, and then combined scores across all activities into a composite score.^{8,15,21,25,27,28} Three studies used the total number of reported cognitive activities^{19,22,24}; one study used time devoted to cognitive activities²²; and one used a cognitive factor index score derived from an exploratory factor analysis of a mixture of leisure items²⁰. A few studies also assessed the intensity of cognitive activity and further sub-classified activities as stimulating or passive (e.g., reading versus watching television), but these terms were not used consistently across studies.^{8,19,23}

Summary of review findings

The 12 reviewed studies included a total of 1,663 dementia cases of which 565 were specifically AD. Most studies found inverse associations of late-life cognitive activity with AD and/or all-cause dementia (Table 1). In the six studies that operationalized cognitive activity using composite measures of participation frequency, greater participation was generally associated with lower incidence of AD and all-cause dementia.^{8,15,21,25,27,28} Similarly, in three studies that examined the *number* of cognitive activities, higher activity count corresponded to lower dementia incidence^{19,22,24}. In one study, time spent on cognitively engaging hobbies was also related to a lower dementia rate²². Among investigations of the intensity of cognitive activity, two found lower dementia incidence with engagement in stimulating but not passive activity^{8,23}, whereas another found the opposite¹⁹.

Bias analysis results

Bias due to confounding—Table 2 shows how an observed HR_{CA-AD} of 0.39 would change under our bias model if adjustment were also made for a strong unmeasured confounder, U ($HR_{U-AD} = 3$), calculated under different scenarios for the prevalence of U among the active and inactive groups. If U were more prevalent among the cognitively active, the observed HR_{CA-AD} of 0.39 would actually underestimate the true protective effect ($HR_{CA-AD/U} < 0.39$). Under the more likely scenario that a harmful U is more prevalent among the cognitively inactive, the observed HR_{CA-AD} of 0.39 would overestimate the protective effect ($HR_{CA-AD/U} > 0.39$). In these instances, the estimated protective effect would diminish with adjustment for U, but it would be eliminated entirely or reversed only if there were extreme imbalances in the prevalence of U between activity groups. One such scenario would require the prevalence of U to be 81% in the low-activity group when its prevalence was 1% in the high-activity group. Prevalences of U in the low-activity group

greater than 81% would make HR_{CA-AD} exceed 1 in U-adjusted analyses, reversing the observed inverse association. Increasing the observed upper 95% confidence limit for this estimate from 0.71 to 1 would require smaller but still quite substantial prevalence differences; for U prevalences in the high-activity group of 1%, 10%, 25% and 50%, the corresponding prevalences required in the low-activity group would be 22%, 35%, 56% and 91% respectively (eTable 5). If U were only moderately ($HR_{U-AD} = 2$) or weakly ($HR_{U-AD} = 1.5$) associated with AD, an observed HR_{CA-AD} of 0.39 would be weakened under U-adjustment but would not be nullified or reversed under any combination of U prevalences in the high- and low-activity groups.

Similarly, eTable 6 shows how an observed HR_{CA-AD} of 0.68 would change under this bias model if adjustment were made for a strong confounder U ($HR_{U-AD} = 3$). When the prevalence of U in the high-activity group is 1%, a prevalence of U in the low-activity group of 25% would be required to eliminate an observed association of this magnitude. For U prevalences in the high-activity group of 10%, 25% and 50%, the corresponding prevalences required in the low-activity group to eliminate the observed association would be 39%, 61%, and 98% respectively. If U were more weakly associated with AD (e.g., $HR_{U-AD} = 2$ or $HR_{U-AD} = 1.5$), larger prevalence differences than these would be required to eliminate an observed HR_{CA-AD} of 0.68 entirely.

Bias due to reverse causation—Table 2 and eTable 6 also show how estimated HR_{CA-AD} of 0.39 and 0.68 could reflect the presence of incipient dementia as specified ($HR_{U-AD} = 4.5$), under a range of incipient dementia prevalences in the active and inactive groups specified in our bias model. If the incipient dementia prevalence was only 1% in the active group, then a prevalence of 48% in the inactive group would be required for an observed HR_{CA-AD} of 0.39 to increase to 1 upon adjustment for incipient dementia. An incipient dementia prevalence of 10% in the high-activity group would require an incipient dementia prevalence of 71% in the low-activity group for an HR_{CA-AD} of 0.39 to increase to 1 (Table 2).

Under our bias model, smaller prevalence differences are required to increase an HR_{CA-AD} of 0.68 to 1 (eTable 6). Calculating similarly, for incipient dementia prevalences in the high-activity group of 1%, 10%, 25% or 50%, the corresponding prevalences required in the low-activity group to eliminate the observed association, upon adjustment, would be 15%, 28%, 50% and 87% respectively. Similar prevalence differences would be required to nullify a HR of 0.71, the upper 95% confidence bound of the HR_{CA-AD} point estimate of 0.39 (eTable 5).

Discussion

These epidemiologic studies generally reported associations of greater participation in late-life cognitive activities with lower risk of both AD and all-cause dementia. We consider the implications of our bias analysis on the extent to which these findings might result from confounding or reverse causation, and issues relevant to the definition, ascertainment and operationalization of cognitive activity that might also have led to biased results.

Bias due to confounding and reverse causation

Confounding by shared causes of cognitive activity and dementia—

Characteristics associated with higher cognitive activity such as formal education and higher SES have also been consistently associated with reduced dementia risk.^{33,34} Almost all studies adjusted their estimates for formal education, and a few additionally adjusted for occupational history⁸, or income and indicators of early-life SES¹⁵, with generally unchanged results. However, some concern about residual confounding remains warranted, given the strong associations between different dimensions of SES and dementia risk^{34,35}, and because education and SES are often measured and modeled inadequately.⁴ Given the correlation between higher SES and lower cardiovascular risk, adjustment for cardiovascular risk factors may also help reduce residual confounding by SES. Another potential source of confounding is longstanding intellectual ability, which is likely correlated with cognitive activity,³⁶ education, and a variety of dementia risk factors; in one study, adjustment for intelligence quotient at age 11 mostly eliminated the positive associations between late-life cognitive activity and late-life cognitive performance.³⁶ Additionally, as some of the cognitive activities frequently assessed in these studies also involve social engagement or the ability to travel (e.g., attending group activities, visiting the cinema/theatre), failure to adjust for general health status (or a proxy such as physical or social activity), which is also related to dementia³⁷, may lead to an overestimated influence of cognitive activity on dementia risk.

However, under the bias model used in our analyses, the bias from residual confounding by these variables is unlikely to be large enough to completely explain inverse associations of the magnitude observed in the reviewed studies. Our calculations indicate that to eliminate protective HRs of 0.68 and 0.39, a strong harmful confounder, U, would need to be at minimum 24 and 80 percentage points more prevalent, respectively, among inactive individuals. Such large prevalence differences are indicative of very strong associations between U and cognitive activity; a 24-percentage point greater prevalence of U among inactive individuals would correspond to, at minimum, a U-cognitive activity OR of 2.66 (when $p_1 = 0.38$ and $p_0 = 0.62$). Imbalances between activity groups of this size are also larger than those reported for important confounders in other studies. In Akbaraly et al., the largest imbalance across activity groups reported for any measured confounder was 17 percentage points for low education, and imbalances of just 2, 5, and 6 percentage points were reported for diabetes, hypertension, and vascular disease, respectively.⁸ In a different study of cognitive function in which the size of similar confounder-cognitive activity relationships was reported, the prevalence imbalances were similarly modest.³⁸ Additionally, our bias analysis suggests that even the bias-corrected upper confidence limit for this estimate would remain under 1. Arguably, correcting the upper confidence interval from a single study may be overly conservative; a hypothetical pooled estimate based on several studies would have a smaller upper confidence limit than the one used in this calculation.

Given the interrelationships between SES markers such as income and occupational attainment, as well as the association of these variables with cardiovascular risk factors and health status, confounding by collective effects of multiple unadjusted or incompletely-adjusted SES-related variables may be of concern. While our simple analyses cannot quantify such complex biases we would expect that adjustment for education, which was

done in almost all studies, would capture much of the confounding attributable to SES or related variables. In addition, correlations among these imperfectly adjusted variables might further decrease the expected bias.

Reverse causation—Individuals in the prolonged preclinical stages of dementia might be more likely to eschew participation in cognitive activities than their healthy counterparts^{15,39}, resulting in an inverse association between activity and dementia risk. In most reviewed studies, analyses excluding individuals judged more likely to be in the prodromal stages of dementia (e.g., those with a mild cognitive impairment diagnosis, or poorer screening test performance, or dementia diagnosis early in the follow-up period) returned largely unchanged results. However, such exclusions may be insufficient, considering that average follow-up time in the late-life cognitive activity studies was between 2 and 7 years, whereas detectable cognitive decline begins as early as 5–8 years prior to dementia diagnosis^{40–42}, and even more subtle impairments, perhaps noticeable only to affected individuals themselves, occur still earlier.^{43,44} If some of those with incident dementia in these studies were impaired enough at baseline to affect their cognitive activity, it is likely that the observed relationship at least partially reflects reverse causation.

We also analyzed how robust the observed associations might be to such reverse causation observing that associations of incipient dementia with both late-life activity and AD diagnosis would need to be large to completely explain findings of the magnitude observed. The magnitude of the effect of incipient dementia will differ between studies based on their average duration. We used an HR (4.5) from the middle of the range of reported estimated effects of indications of incipient dementia on risk for clinical dementia.^{13,14,16–18} Smaller HRs for the effect of incipient dementia yield results similar to those described for confounding, and would be unlikely to entirely explain the observed associations. However, under our bias model, with larger HRs for the effect of incipient dementia, smaller prevalence differences would be sufficient to fully explain an HR_{CA-AD} of 0.68, attenuate an HR_{CA-AD} of 0.39 and increase its upper confidence bound from 0.71 to 1. Overall, contingent on the validity of our model, it is plausible that reverse causation could bias these findings; the degree of bias could be substantial if the disparity in incipient dementia prevalence between high- and low-activity groups is large.

However, quantifying the degree to which incipient dementia is more prevalent among low- rather than high-activity individuals is difficult. In Akbaraly et al., cognitive impairment at baseline, defined as scoring less than 24 on the Mini-Mental State Examination, was more common among those with low (7.8%) rather than high (1.9%) levels of stimulating activity.⁸ Data on how late-life cognitive activity changes with declining cognition are sparse. In Wilson et al., baseline mild cognitive impairment was associated with lower cognitive activity at baseline, although not with decline in activity over a three-year follow-up.¹⁵ The same investigators also showed that whereas cognitive activity predicted global cognitive function over the following year, global cognitive function did not predict subsequent degree of cognitive activity. However, performance in two specific cognitive domains, working memory and perceptual speed, was associated with decline in cognitive activity over the following year.⁴⁵ To better understand the influence of reverse causation,

longitudinal data on the extent and timing of cognitive activity changes will have to be evaluated in parallel with changes in cognition in longer prospective follow-up studies.

While the calculations reported here provide some measure of the potential degree of bias for a typical effect estimate, analyses using study-specific parameters will be better able to assess the degree of bias in individual studies. Nonetheless, our bias analyses can be informative in interpreting other studies in which the conditions required for use of this approach are met. These conditions are unlikely to be severely violated in the cohort studies reviewed here, where AD incidence over the relatively short study follow-up periods remains quite low. Additionally, the formula we used to calculate a bias-corrected HR applies analogously to odds ratios when the assumptions specified are met.^{7,47} Overall, under the specifications of our bias analysis and conditional on the validity of its assumptions, we found that the observed inverse associations are likely robust to unmeasured confounding, and likely only partially explained by reverse causation.

Methodologic considerations in measurement of cognitive activity

Type and context—Although cognitive activity scales are being developed,⁴⁸ further investigation into valid measurement of the construct is warranted. In an effort to isolate the effect of purely cognitive activities,⁴⁸ most studies focussed on leisure activities that are primarily or exclusively cognitive. Some of the more frequently assessed leisure activities (e.g., reading, attending theatre) are more likely to be favored by individuals of higher SES or educational attainment. Failure to assess other leisure or non-leisure activities requiring cognitive processing (e.g. home repair, gambling) would result in underestimating overall late-life cognitive activity for many individuals, and could bias estimates of its effect on dementia risk depending on the assessed activities' associations with higher SES/education.

Self-reporting—Valid measurement of cognitive activity is particularly challenging in populations that may have cognitive deficits. All reviewed studies used self-reported data, but validation against other sources (e.g., diary records, electronic devices) was rare even though individuals with memory loss would be expected to self-report less accurately.^{49,50} If individuals with mild cognitive impairment or subjective cognitive concerns systematically under-report cognitive activity, lower participation would be spuriously linked with greater dementia risk. Alternatively, if participation frequency is overstated because of failure to accurately recognize or recall declines from lifetime activity levels, this would attenuate any protective association.

Timing and 'dose'—A critical question from a prevention perspective is whether the inverse association between late-life cognitive activity and dementia can be attributed *specifically* to greater *late-life* cognitive activity, which would suggest that even cognitively 'sedentary' individuals might benefit from increasing their cognitive activity late in life. Two studies in the same cohort concluded that the effect of cognitive activity depends on *late-life* activity because even after adjusting for activity earlier in life, late-life activity was strongly associated with lower AD incidence.^{15,46} Similarly, more detailed investigation of the 'dose' of cognitive activity associated with lower AD risk will be required to inform prevention guidelines. Questions about timing and dose of activity are germane to possible benefits of

intervening throughout the lifecourse, such as recommending engagement in specific types of activities in midlife and possibly even policies and practices that shape childhood intellectual development.

Cognitive training versus cognitive activity—These epidemiologic findings, coupled with the hypothesized neuroprotective effects of cognitive activity, have inspired interest in cognitive training as a means to enhance late-life cognitive function. The largest trial to date, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, compared three group-based behavioral interventions in 2,786 cognitively normal, independently living adults (mean age 74). The interventions individually targeted memory, reasoning, and processing speed, and were compared with a no-contact regime.⁵¹ Post-training improvements were maintained for at least 5 years in all three arms.^{52–54} Additionally, self-reported difficulty performing instrumental activities of daily living was lower in the training arms than among controls from year 2 onwards. However, the training interventions had no effects on performance-based measures of neurocognitive function at any of the follow-up points,⁵³ and a secondary analysis including 189 incident dementia cases found no difference between trained and untrained groups in the rate of dementia occurrence over 5 years of follow-up.⁵⁵ Expanding training to simultaneously target multiple cognitive domains, lengthening intervention time, and targeting an older-old population, have been suggested as modifications that may yield treatment effects on dementia incidence, but such strategies remain untested.

Although evidence from randomized trials so far does not support the efficacy of specific cognitive *training* interventions in preventing dementia, this does not rule out potential benefits of cognitively active *lifestyles*. The short-term influence of prescribed training interventions may differ from the cumulative stimulation attained via habitual performance of personally selected cognitive leisure activities. Interventions in line with a way of life that more fully incorporates cognitive activity as practiced in observational studies are difficult to define and operationalize in randomized trials. Evidence for any salutary effects of this broader notion of “engagement” (social, cognitive and otherwise) on late-life cognition may be better assessed by trials of more holistic interventions.⁵⁶

Conclusion

Our systematic review and bias analyses suggest that late-life cognitive activity may offer some reduction in risk of AD and all-cause dementia. Our bias analyses appraised these epidemiologic findings with respect to two critical potential sources of bias—confounding and reverse causation—by quantifying the potential degree of these biases for a typical effect estimate. Under the parameters specified in our bias analysis, the observed inverse associations are unlikely to be explained entirely by unmeasured confounding, but reverse causation remains a more plausible but still little understood source of bias. Although a number of limitations in the measurement of cognitive activity might have led to bias, they do not appear sufficient to account for the observed findings. It remains possible, however, that confounding, reverse causation and measurement limitations could combine to substantially bias estimates. As with any bias analysis, our conclusions are conditional on the validity of our bias model.

Over time, better characterization of the type, duration, intensity, and timing of activity^{57,58} associated with late-life cognitive benefit will be required to develop more specific recommendations applicable over the lifecourse. Observational studies like those reviewed here can shed light on benefits associated with the performance of habitual, self-selected cognitive activities. Interventions under development extend this work by targeting cognitive activity and other modifiable dementia risk factors simultaneously.^{56,59} This type of multi-modal approach was used in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability, in which the intervention group received diet, exercise and vascular risk monitoring regimens in addition to cognitive training.⁵⁹ Another interventional program, Experience Corps, aims to increase older adults' cognitive, physical and social activity by giving them meaningful volunteer roles in public elementary schools.⁵⁶ Evidence from these different types of approaches will be critical to help us better understand the relationship of cognitive activity with late-life cognition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure.
Flow chart showing how studies were selected for inclusion

Table 1

Summary of Results – Cognitive Activity and Incidence of Alzheimer's Disease (AD) and All-cause Dementia

First Author	N	Cognitive activity exposure	Exposure level/contrast	Effect estimate measure	AD cases	AD effect estimate (95% CI)	All-cause dementia cases	All-cause dementia effect estimate (95% CI)	Covariates / Restrictions
Cohort studies									
Akbaraly	5698	Stimulating activity	Mild vs. low (ref.)			0.45 (0.26, 0.77)		0.49 (0.32, 0.75)	Age, education, gender, marital status, occupation, APOE, depression, diabetes, high cholesterol, hypertension, vascular disease, ADL impairment, baseline MMSE score, study site
			High vs. low (ref.)	HR	97	0.39 (0.21, 0.71)	147	0.49 (0.31, 0.79)	
Akbaraly	5698	Passive activity	Mild vs. low (ref.)			1.02 (0.62, 1.69)		0.89 (0.59, 1.36)	Age, education, gender, marital status, occupation, APOE, depression, diabetes high cholesterol, hypertension, vascular disease, ADL impairment, baseline MMSE score, study site
			High vs. low (ref.)	HR	97	0.68 (0.41, 1.13)	147	0.75 (0.50, 1.12)	
Eriksson Sjöman	1475	Mental activity index	Per 1 unit increase	HR			357	0.95 (0.90, 1.01)	Age, education, gender, marital status, depression, alcohol, chronic disease, smoking, stress
Hughes	942	Hours/week on cognitive activities	4–6 hours vs. 0–3 hours (ref.)					0.72 (0.40, 1.29)	Age, education, gender, depression, functional impairment, health status, medications, physical activity, residential township
			> 6 hours vs. 0–3 hours (ref.)	HR			111	0.32 (0.25, 0.75)	
Hughes	942	# of cognitive activities	Per 1 activity increase	HR			111	0.86 (0.75, 0.99)	Age, education, gender, depression, functional impairment, health status, medications, physical activity, residential township
Karp	732	Cognitive intensity	High vs. low (ref.)	HR			123	0.71 (0.49, 1.03)	Age, education, gender, depression, functional impairment, baseline MMSE, comorbidities

First Author	N	Cognitive activity exposure	Exposure level/contrast	Effect estimate measure	AD cases	AD effect estimate (95% CI)	All-cause dementia cases	All-cause dementia effect estimate (95% CI)	Covariates / Restrictions
Scarmeas	1772	# of cognitive activities (<i>previous month</i>)	Per 1 activity	HR			207	0.76 (0.61, 0.94)	Age, education, occupation, race/ethnicity
Verghese	469	# activity-days per week	Per 1 activity-day	HR	61	0.93 (0.88, 0.98)	124	0.93 (0.90, 0.97)	Age, education, gender, baseline cognition, chronic disease
Verghese	469	# activity-days per week	Middle third vs. bottom third (ref.)	HR			124	0.48 (0.29, 0.74)	Age, education, gender, baseline cognition, chronic disease
			Top third vs. bottom third (ref.)					0.37 (0.23, 0.61)	
Wang	732	Frequency of participation in mental activities	Less than daily vs. none (ref.)	OR			123	0.83 (0.54, 1.30)	Age, education, gender, depression, comorbidity index, physical activity, physical performance, social activity baseline MMSE
			Daily vs. none (ref.)					0.59 (0.37, 0.96)	
Wilson	733	Participation score	Per 1 unit increase	HR	111	0.67 (0.49, 0.92)			Age, education, gender
Wilson	835	Participation score	Per 1 unit increase	OR	139	0.39 (0.21, 0.73)			Age, education, gender, APOE, occupation, race/ethnicity, follow-up
Wilson	775	Participation score	Per 1 unit increase	HR	90	0.53 (0.32, 0.86)			Age, education, gender, APOE, income, past cognitive activity, physical activity, social activity, indicators of early-life household and community SES
Nested case-control studies									
Carlson	294	# of stimulating activities (<i>during midlife</i>)	Per 1 activity increase	OR			147	0.81 (0.57, 1.13)	Age, gender (male twin pairs)
Carlson	294	# of passive activities (<i>during midlife</i>)	Per 1 activity increase	OR			147	0.55 (0.33, 0.92)	Age, gender (male twin pairs)

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First Author	N	Cognitive activity exposure	Exposure level/contrast	Effect estimate measure	AD cases	AD effect estimate (95% CI)	All-cause dementia cases	All-cause dementia effect estimate (95% CI)	Covariates / Restrictions
Crowe	214	Intellectual/cultural activity (<i>before age 40</i>)	More active vs. less active (ref.)	OR	67	0.55 (0.28, 1.08)	107	0.80 (0.49, 1.31)	Age (twin study), gender, education

HR: hazard ratio. OR: odds ratio. TIA: transient ischemic attack. APOE: apolipoprotein E. MMSE: Mini-Mental State Examination. ADL: activities of daily living. SES: socioeconomic status.

Table 2

Bias-corrected Alzheimer's Disease (AD) HR (comparing high versus low participation in cognitive activity), adjusted for U, when $HR_{U-AD} = 3$ or $HR_{U-AD} = 4.5$, given that hazard ratio unadjusted for U = 0.39.

		Prevalence of U among low-activity participants, p_0^*							
	HR_{U-AD}	1%	10%	25%	50%	75%	90%	99%	
1%	3.0	0.39	0.46	0.57	0.76	0.96	1.07	1.14	
	4.5	0.39	0.51	0.71	1.04	1.37	1.56	1.68	
	3.0	0.33	0.39	0.49	0.65	0.81	0.91	0.97	
10%	4.5	0.3	0.39	0.54	0.79	1.05	1.20	1.29	
	3.0	0.27	0.31	0.39	0.52	0.65	0.73	0.77	
25%	4.5	0.22	0.28	0.39	0.57	0.75	0.86	0.93	
	3.0	0.20	0.23	0.29	0.39	0.49	0.55	0.58	
50%	4.5	0.15	0.19	0.27	0.39	0.51	0.59	0.63	
	3.0	0.16	0.19	0.23	0.31	0.39	0.44	0.46	
75%	4.5	0.11	0.15	0.20	0.30	0.39	0.45	0.48	
	3.0	0.14	0.17	0.21	0.28	0.35	0.39	0.42	
90%	4.5	0.10	0.13	0.18	0.26	0.34	0.39	0.42	
	3.0	0.13	0.16	0.20	0.26	0.33	0.37	0.39	
99%	4.5	0.09	0.12	0.16	0.24	0.32	0.36	0.39	

* conditional on other covariates.

Note: U is a hypothetical unmeasured binary confounder of the effect of cognitive activity on AD. HR_{U-AD} reflects the magnitude of the association between U and AD. When $HR_{U-AD} = 3$, the bias-corrected AD HR will be exactly 1 when $p_1 = 1\%$ and $p_0 = 81\%$. When $HR_{U-AD} = 4.5$, the bias-corrected AD HR will be exactly 1 when $p_1 = 1\%$ and $p_0 = 48\%$, and when $p_1 = 10\%$ and $p_0 = 71\%$.