A Decade later on how to “Use It” so we don’t “Lose It”: An Update on the Unanswered Questions about the Influence of Activity Participation on Cognitive Performance in Older Age

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A Decade later on how to “Use It” so we don’t “Lose It”:

An Update on the Unanswered Questions about the Influence of Activity Participation on Cognitive Performance in Older Age

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Abstract

Activity engagement is a modifiable factor that has been widely-cited as being good for the aging brain and cognition, and represents a valuable target for reducing dementia risk. However, specific issues about activity engagement (mental, social and physical) and cognition in older adulthood remain, and Bielak (2010) reviewed seven major methodological and theoretical questions about this relation. We present an updated reflection on these key questions, focusing on work published in the last ten years. For some questions, a significant amount of work has been done and conclusions have become clearer; for others, there have been few additions to the literature and our knowledge remains much the same as it was a decade ago. We review the issues identified in the 2010 paper including the directionality and temporal nature of the relationship, whether specific activity domains offer different benefits to cognition and what domain(s) of cognition are affected, variation in the relation by age, gender, or education, potential mechanisms involved, and how activity engagement is assessed. For each, we present the most up to date research and discuss remaining challenges and possible future directions. This formal unifying of the information in the field is intended as a guide to support continued progress by spurring on studies addressing specific questions while reminding researchers of critical issues. We conclude with recommendations that future studies investigating the link between activity engagement and cognitive performance in adulthood should consider.
Delaying or reducing cognitive decline may be best characterized by framing environmental influences as marginal gains [1], where modifiable factors have small individual effects on a person’s cognitive performance, but collectively provide significant overall benefit. Activity engagement is one piece of this puzzle. Being mentally\(^1\), socially, and physically active is widely-cited as good for the aging brain [2, 3], earning the moniker “use it or lose it”, whereby activity participation is believed to maintain cognition into and throughout older adulthood. Older adults who participate in more activities score higher on cognitive tests [4-6], appear to show less cognitive decline with age [7-9], and are less likely to develop dementia [10-12]. However, Bielak [13] highlighted major unanswered methodological and theoretical questions about potential links between activity engagement and cognition in older adulthood. That in-depth review summarized what was known about each issue, and ended with a call to focus on addressing those.

With a further decade of research, we returned to those key questions, with the expectation that several issues would have become clearer. Despite a significant number of new publications on the activity-cognition relation in adulthood, our knowledge remains much the same (see Table 1). There remains inconsistency in measures, methods, and statistical techniques that make it challenging to provide clear answers to the unanswered questions in the field. However, there has been progress, including greater consideration of multiple activity domains within a single analysis, greater attention to early-life activity and cognition, and longitudinal work considering between- and within-person cognitive change. This updated review covers the past decade\(^2\), refocusing some questions and adding new considerations. The review is not

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\(^1\) The phrases intellectual, mental, and cognitive activities are interchangeably used in the literature. We refer to these as mental activities to avoid confusion with cognitive performance.

\(^2\) Published from 2010-2020 or early access 2021.
exhaustive; instead, we focus on work that helps address the critical questions, if not in terms of providing singular answers then at least in terms of clarifying the questions. We limit presenting cross-sectional research and studies that only include one cognitive domain, only doing so when the findings specifically progressed the understanding of an unanswered question. Additionally, unless noted otherwise, all referenced studies were observational.

We review the issues identified in the 2010 paper about the activity-cognition relation: directionality; temporality; whether one activity or cognitive domain offers/receives the most benefit; variation by age, gender, or education; mechanisms involved; and assessing activity engagement. Importantly, we discuss remaining challenges and possible directions to move each issue forward, concluding with recommendations for “best practices” for future studies investigating activity engagement and cognition. Answering these questions is critical as activity participation is a modifiable factor, representing one approach affording some possible control over how we age cognitively.

1. Does Activity Participation Impact Cognition, or Does Cognition Impact Activity Participation?

This question is often framed in the context of reverse causation, reflecting the possibility that activity-cognition associations at a given point reflect both being predicted by earlier ability [14]. The largest predictor of adult cognitive ability is earlier cognitive ability, and earlier ability also predicts other cognitively-beneficial factors, creating specific confounding [1]. Reverse causation also relates to shorter-term changes, for example withdrawing from activity as a consequence of declining cognition. Few studies consider life course reverse causation given limited long-term cognitive data, though commonly address lead-lag in shorter-term changes by re-analysing after selective exclusion (e.g., low baseline cognition, eventual cognitive
impairment/dementia). Given the long prodromal development of dementia, lead-lag issues are critical, as activity-cognition associations may be partly driven by decline-induced disengagement.

Relatedly, distinguishing between differential preservation and preserved differentiation is essential (Figure 1) (sometimes labelled neuroprotection versus neuroselection [15]). For either, reverse causation remains relevant as cognitive ability in the months/years preceding baseline assessment will predict cognitive and activity levels. More attention has been directed towards differential preservation (even if not explicitly mentioned), seeking to understand if and how activity engagement changes cognitive slope. However, there is increasing awareness that associations may instead reflect preserved differentiation; activity may still be beneficial if it predicts a higher functional level from which to decline.

One study showed that associations between activity engagement and cognitive ability may be confounded by reverse causation depending on activity domain [14]. After accounting for childhood cognition, associations between mental/social activity and cognition were attenuated while associations with physical activity remained significant (see Box 1 for a consideration of effect sizes). Socially- and mentally-demanding activities are potentially outcomes (partly or wholly) rather than determinants of cognitive ability in later adulthood, while physical activity might be less prone to reverse causation and therefore a clearer lifestyle candidate promoting differential preservation [16]. This is, however, not always supported. Belsky et al. [15] found no link between midlife physical activity and later cognition after accounting for childhood cognition. Other work showed individual differences in physical activity were associated with baseline levels of cognition, not cognitive change [17], suggesting physical activity-cognition associations indicate preserved differentiation (consistent with [18]).
The directionality of the activity-cognition relation remains contested. For example, level-level associations were attenuated after controlling for earlier ability suggesting reverse causation, however, differential preservation was supported as physical activity (but not leisure activity) predicted reduced 20-year decline [16]. Analysis of four waves of data (6 years) showed changes in executive function predicted changes in physical activity, suggesting the results were due to reverse causation [19]. Further, in coordinated analyses of four longitudinal studies [20], level-level associations were rarely supported (27% of possible associations), and physical activity level was associated with cognitive change for only 13% of possible associations, suggesting preserved differentiation. Changes in physical activity did predict changes in cognition, however, change-change associations are difficult to interpret in terms of differential preservation versus preserved differentiation. Similarly, research reporting changes in physical activity coupled with changes in cognition was unable to specify a lead indicator [21].

For mentally engaging activities, cross-sectional activity-cognition associations are regularly reported, but less so with cognitive change [22]. Coordinated analyses showed neither mental nor social activities were predictive of subsequent cognitive changes [23, 24], supporting preserved differentiation. However, findings are varied with 12-year memory change being the lead indicator for changes in social activity, but changes in mental activity being the lead indicator for cognitive changes; differential preservation was thus observed for mental, but not social, activities [21]. Additionally, individuals with greater “analogue games” (e.g., cards, chess) engagement had higher cognitive ability at age 70, even controlling for earlier cognitive ability, and experienced less 9-year decline [25]. Further studies have been inconsistent, some supporting differential preservation [26], and others supporting preserved differentiation for mental and social activity [27, 28]. If differential preservation is apparent, it may be the
exception rather than the rule and moderated by other factors. For example, Ihle et al. [29] suggested mental activity supported differential preservation, albeit limited to young-old individuals, and those with high vocabulary or lower work demands. Studies therefore need to consider not just if differential preservation occurs, but in what context [26, 27].

While cross-sectional studies continue to report positive associations between activity engagement and cognitive ability, they are of limited utility. Longitudinal data can better determine whether those associations reflect differential preservation, preserved differentiation, or indeed reverse causation. Follow-ups of at least 10 years are required to distinguish those alternatives [30, 31], and markers of early cognition are needed to address the extent of reverse causation. This is critical in evaluating dementia risk [11]; a review focused on physical activity noted the majority of studies did not have sufficient follow-up to discount reverse causation [32]. Though many studies cannot address these issues, failure to acknowledge them remains common with real-world implications. Evidence derived from observational studies informs public health messaging, so if findings are at best overestimates (or at worst spurious) [1], the resultant messages will be affected. Similarly, when researchers use observational findings to identify intervention targets, those must represent genuine causative factors. Finally, even when differential preservation is not supported, activities are still relevant as raising the level of cognition across the life course can be as important as slowing decline [2, 28].

2. How Long does Past Activity Impact Current Cognition?

Bielak [13] noted that though few in number, studies considering activity in childhood and throughout adulthood reported associations with later cognitive performance. While short follow-ups remain common, an increasing number of studies have explored associations over
longer periods, considered between- and within-person effects (see Box 2), and micro-timeframes (see Box 3).

a) Activity throughout the life course

Studies beginning in later adulthood have employed retrospective activity assessments to account for the life course. Mental activity before age 13 was associated with executive function and processing speed in a small sample at mean age 67 [33]. Larger studies have also reported positive associations with lifetime mental activity, although assessed age periods varied [34-37]: Both retrospective midlife (age 45) and current late-life activity were associated with processing speed and verbal ability [35]; retrospective mid- (50-65 years) and late-life (mean 79 years) activity were associated with lower likelihood of cognitive impairment [6]; mental activity in mid- and late-life decreased 5-year risk of mild cognitive impairment (MCI; though relevant activities varied by life stage) [38]; and mental activity in childhood and midlife, but not young adulthood, predicted reduced later life cognitive decline [36].

Consideration of lifetime participation in social activities remains rare. The association between retrospectively-assessed midlife activity (age 45) and cognitive function was mediated by participant’s family network size and support [39], and higher midlife contact (though different from social activity) was associated with less 14-year cognitive decline [40].

Studies of lifetime physical activity are more plentiful. Less physical activity and more television viewing (proxy for sedentary behavior) assessed between 18 and 30 years were associated with poorer cognition over the subsequent 25 years, particularly processing speed [41]. Retrospective estimates of physical activity as a teenager, ages 30, 50, and current (late-life) all predicted the odds of later cognitive impairment assessed by the MMSE, but only teenage activity was uniquely significant [42]. In a large sample, midlife physical activity was
associated with less decline over 14 years, with stronger associations when physical activity was maintained across midlife [43] (see also [44]). Moderate or higher levels of midlife (50-65 years) non-exercise physical activity were associated with less 6-year cognitive change (baseline age 79) [45]. However, a study reported no level or slope relations between physical activity during midlife and 12-year cognitive change in women [46].

Specific activity domains may be relevant during certain stages. Gow et al. [34] retrospectively assessed mental/social and physical activity for early, mid- and later life. After accounting for childhood cognition, midlife mental/social activity was associated with higher cognitive ability in old age, whereas later life physical activity was associated with less cognitive decline throughout old age. More mentally demanding activities may enable reaching older age at a higher ability level, while later physical activity may be more critical to maintain optimal functioning and lower related (e.g., cardiovascular) risks [34, 36].

Activity throughout life has been supported as cognitively beneficial, but findings vary. Further exploration is required as earlier periods of engagement might be differentially associated with later cognition [36], and mechanisms may differ. For example, although earlier physical activity was positively associated with midlife cognitive ability, physical activity benefits for cognition were already present by childhood and continued into adulthood through selecting healthier lifestyles [15].

b) Activity in later life and subsequent change

Studies commonly associate activity at a given point in old age with subsequent cognitive change. For example, greater mental engagement predicted less memory and general ability decline from age 70 to 79 [25], greater variety of mental activity predicted lower risk of cognitive impairment 9.5 years later [47], and social activity at age 80 was associated with less
5-year cognitive decline [8]. However, other studies reported no association between mental activity and subsequent cognitive change over 10-15 years [22, 48], though changes in mental activity were associated with changes in perceptual speed over 15 years [48].

There is accumulating support [49] for physical activity predicting less cognitive decline across 5 [50], 10 [4], and 26 years, and reducing dementia risk [32, 51]. However, between-person physical activity associations with cognitive level but not change over 8 [17] and 15 years [18] remain consistent with Bielak’s [13] conclusion that associations with level were common. Only within-person changes in physical activity were associated with cognitive changes [18] (and only for younger adults [17]), suggesting cognitive benefits were greater with sustained physical activity, and dissipated with reduced physical activity [18]. Similar findings existed for mental and social activity: between-person level predicted cognitive level, but not 8-year cognitive change [28].

Studies evaluating multiple activity domains in later life have reported mixed findings. After controlling for cognitive ability at age 50, neither mental nor physical activity at ages 50 to 70 were associated with cognition at age 60, but physical activity was associated with less 20-year decline [16]. Activity variety, rather than frequency, reported at mean age 71 was associated with cognitive change over the preceding 14 years, but only for those classified with MCI [52]. However, assessment of activity followed that of cognitive change, so could be confounded by reverse causation [52].

Several studies found higher activity engagement was associated with lower dementia and MCI risk only a few years later [53-59]. However, shorter timeframes produced more liberal odds ratios coupled with a greater likelihood the assessed activities were affected by prodromal behavior changes (Question 1) [60]. Studies focusing on dementia over longer timeframes have:
not found a relation with midlife physical activity (e.g., 27 [30] and 30 years [31]), or found only late-life exercise related to late-life cognitive performance and short-term (3-year) dementia risk [31]. Although total and social activity were related to dementia risk 15 years later, this was only significant 1-5 years after baseline [11]. While there is evidence of midlife activity predicting dementia as much as 44 years later [43, 51, 61-63], current or late-life activity levels were not accounted for; the association with midlife activity may represent a somewhat constant characteristic of the person’s habits, or preserved differentiation (Question 1).

Studies considering the lifespan would ideally have measures of activity at multiple timepoints to determine whether there is cumulative or specific beneficial periods for activity; without them, it is impossible to determine if a particular timeframe is a proxy for consistent activity habits. However, relatively long-term associations do not preclude benefits from late-life activity for cognition (e.g., foreign language acquisition in late-life was associated with better cognitive ability [64]). Though activity-cognition associations considered over years remain the predominant focus, recent work has considered day-to-day, where daily activities may be associated with cognitive performance hours or a day later (summarised in Box 3). As Bielak et al. [65] noted, short-term activity-cognition relations likely operate through different mechanisms than those underlying long-term relations, but the timeframes are related as daily activity contributes to long-term participation habits, and vice versa.

3. Does one activity or cognitive domain have the strongest relationship?

Although the 2010 review separately considered which activity domain might provide the most benefit to cognition, and which cognitive domain receives the most benefit, there is still no single answer from studies simultaneously analyzing different activity and cognitive domains. The questions of which activity domain is best/cognitive domain benefits most also needs
reframing; rather, we might better focus on the relative contributions and combined effects across activity domains. Further, varying timeframes, cognitive outcomes, quality of activity domain assessment, and grouping of activities into domains complicates any comparisons. Moreover, we reiterate the previous review [13]: where studies focus on one cognitive domain or a limited subset, it is difficult to conclude what domain(s) might derive the greatest benefit.

There is evidence that singling out activity domains may not be wise. First, no activity is a pure representation of one type of engagement. The degree to which an activity involves certain types of stimulation varies by person (e.g., talking or not during group exercise), and likely differs from one instance of that activity to the next. Cheng [66] argued that comparing benefits by activity type is only of academic value and that each likely works differently to benefit cognition. Indeed, Corley et al.’s [1] framing of marginal gains suggests asking “what type of activity is best?” is disadvantageous if it directs attention towards doing more of one thing, rather than small (perhaps more manageable) changes across a range of activities. Hence all activity domains (and lifestyle behaviors more broadly) are needed in concert. Positive findings from studies focused exclusively on single activities (e.g., crosswords [67], museum attendance [68]) are slightly misleading as no single activity is the driver of cognitive performance and change. Moreover, the activity domains associated with specific cognitive domains might vary by other factors such as gender [4, 7], activity variety [69, 70], or whether cognitive performance or intraindividual variability [71] are considered. To briefly review this work, general trends from studies that assessed a wide range of cognitive and activity domains are summarized.

a) Cognitive domains
Social activity has been shown to have benefits across domains including executive function and memory [72]. A combined measure of social and mental activities predicted higher baseline episodic and working memory, perceptual speed, and vocabulary [28], and greater social activity was associated with less 5-year decline in episodic, semantic, and working memory, perceptual speed, and visuospatial ability [8]. Other work [73] reported that social activity was associated with fluency, episodic memory, reasoning and vocabulary, although partly mediated via mental or physical activity. A review supported social activity’s associations with global function, processing speed, working memory, visuospatial ability, and executive function; however, associations with reasoning, attention, episodic memory and fluency were not [5].

A review of physical activity suggested benefits in terms of reducing global cognitive decline and incidence of dementia [10], perhaps due to physical activity’s “widespread” effects on the brain [74] (Question 5). Not all cognitive domains display positive associations, with one review suggesting physical activity benefits global and executive functions, and semantic, verbal and auditory memory, but not working memory or attention [49]. This corresponds with substantially stronger within-person relations for physical activity and episodic memory compared to verbal fluency and visuospatial ability over 15 years [18], though is inconsistent with reported 5-year associations for processing speed and episodic memory, but not executive function or semantic memory [50]. Daly et al. [19] emphasized the bidirectional nature of the associations, and others highlighted physical activity associations with domains of perceptual speed, and short-term, working, and episodic memory at baseline, but not over time [17]. Unfortunately, studies considering only one or two cognitive domains remain common [10, 19], limiting understanding of physical activity effects across domains.
Studies that simultaneously consider mental, social, and physical activity can examine differences in the associations across cognitive domains, as well as the cumulative benefits broader activity engagement might provide. Over 2.4 years, higher social activity predicted reduced decline in global cognition; physical activity predicted less decline in language and episodic memory; and mental activity predicted less decline in global cognition, executive function, and language [9]. In other words, “different types of activities protected against cognitive decline on different cognitive domains” [9], underscoring the unsuitability of asking what cognitive domain benefits most from activity. Variations by activity domain on the same cognitive outcome exist, including: interactive effects of mental and physical activity on 5-year changes in working and semantic memory (but not with global cognition and 3 further domains) [75]; fifteen-year changes in mental activity associated with changes in perceptual speed, while changes in social activity associated with changes in episodic memory [48]; in a study with twin pairs, discordance in mental activities associated with discordance in speed and verbal abilities, discordance in social activities associated with discordance in memory, and no significant relations for physical activity [76]; and while changes in mental and social activities were associated with changes in episodic and semantic memory, and verbal speed, physical activity was only associated with two of the three domains [21].

Considering a specific activity domain simultaneously across diverse studies has also provided valuable insights. Using four distinct datasets with different measures of mental, social, and physical activity and cognitive ability, the same statistical procedures were followed to explore activity-cognition associations [20, 23, 24]. Pooling results across activity domains, there was support for cross-sectional associations with memory (8/12 possible associations), and to a lesser degree fluency (5/9), semantic knowledge (6/12) and reasoning (5/12). There was minimal
support for activity predicting change in any cognitive domain, however changes in activity were associated with changes in reasoning (10/12 associations) and memory (9/12), but less so fluency (6/9) and semantic knowledge (6/12) [20, 23, 24]. Therefore, the cognitive domain with the most consistent activity relation varied depending on whether level or change was the key focus.

b) Activity domains

There is evidence of specific activity domains being associated with cognition even when controlling for other activity domains: social activity predicting cognition accounting for physical and mental engagement [8, 69]; mental activity predicting cognition over social and physical activity [69, 77, 78]; and physical activity predicting dementia and MCI risk accounting for mental activity [54, 79]. In some cases, multiple activity domains were unique predictors of cognition and had similar sized effects (e.g., social and physical [72], social and mental [53], physical and mental [61]), while others produced remarkably different effect sizes (e.g., mental activity was at least double physical activity [17, 80], however, mental activity-cognition associations may be reduced after accounting for prior ability (Question 1; Box 1)). That multiple activity domains are uniquely associated with cognition underscores the importance of each domain and their, albeit potentially small [1], contributions to cognition [17]. Complicating this however is the potential mediation of benefits via other domains (e.g., physical activity benefits mediated by mental and social activity [81, 82]).

The combination of different activity domains may be relevant. High mental activity combined with any level of physical activity predicted the lowest 3-year risk of MCI, but high mental activity without physical activity provided no benefit compared to inactivity across domains [79]. However, few interactions between objectively measured exercise and self-reported mental activity were reported in predicting 4-year cognitive change [75]. A review
suggested the cognitive benefit of physical activity was greater when the activity was multicomponent or included mental engagement. Structured forms of exercise (e.g., sport, dance) may enable additional skill development such as strategic thinking or socialization, resulting in benefits more commonly associated with mental engagement or social interaction [83]. One study showed differentiation in 2.5-year cognitive change depending on combined engagement across mental, social, and physical domains: adults with low activity in all domains experienced decline; those with high activity in one domain maintained; and those with high activity in two or three domains improved [9]. Greater participation regardless of activity type has also been associated with lower MCI risk [38], and higher total activity predicted more variance in cognition than individual domains [78], but findings vary [69].

The most relevant activity domain may vary by time period, such that social activity was associated with decreased 15-year dementia risk, though further analyses showed this was only significant 5 years after baseline [11]. Similarly, while cognitive level relations were significant for mental and artistic activity, only physical and cultural activities were related to 7-year cognitive changes [71]. Relatedly, results for between-person associations and within-person changes have varied by activity domain. One study found no physical activity effects at the between-person level, but significant within-person effects [82]; this pattern was reversed for mental activity, while there were similar numbers of significant effects at both levels for social contact. Data from four independent longitudinal studies investigated the consistency of activity effects on cognition up to 21 years later [20, 23, 24]. At the between-person level, nearly all baseline activity-cognition relationships were significant for mental engagement, just over half for social activity, and only one-fifth for physical activity. For each activity domain, there were few associations for baseline activity predicting cognitive change. Finally, nearly all within-
person activity effects predicting cognitive change were significant for mental activity, while about half were for social and physical activity.

We encourage researchers to focus less on finding the singular best activity or cognitive domain, and instead focus on the holistic benefit of activity engagement. Studies should use a broad range of cognitive domains, each assessed by multiple markers, and incorporate multiple activity domains (Table 2). We also suggest bi-factor models to allow the simultaneous assessment of associations between activity and cognition at both general and specific levels. These evaluate how different cognitive domains benefit once the common variance across cognitive functions is accounted for.

4. Does the Relationship Differ According to Age, Education, or Gender?

The activity-cognition relation may be modified by key demographics. Greater activity-related cognitive effort may be required with age, providing more benefit from participation in older adulthood [48], or conversely putting an age limit on cognitive compensation [29]. High activity engagement may not independently contribute to cognition over high educational attainment, suggesting those with lower education might benefit more from participation [35]. Further, gender differences in activity patterns [7] and sex differences in biological mechanisms (see [84]) may influence the relevance of an activity to cognition.

Few studies have investigated age differences in activity-cognition relations. Two studies using a multi-cohort sample (ages 20-24, 40-44, 60-64) found few age differences over 8 years [17, 28]. Effect sizes for between-person differences in mental and social activity on cognitive domains were uniformly small across adulthood [28]; only the 20s showed stronger physical activity associations [17]. Age groups were also similar in what was not significant: between-person activity did not predict cognitive change, and within-person changes did not covary with
cognitive change (except the 20s for physical activity). There is, however, evidence of differential effects within older adulthood. Adults over 75 had stronger concurrent and change relations over 15 years for mental activity and perceptual speed than adults 65-75 [48], but no differences existed for other activity and cognitive domains. Findings are mixed for dementia, where the activities associated with reduced risk 3.5 years later differed for those aged 65-74 versus 75 and older [55] (though reverse causation is a concern, Question 1), but adults who engaged in exercise at least once/week were less likely to develop AD over 17 years regardless of being younger or older than 75 [62].

Explicit studies of educational influences are scarce. Cross-sectional analyses have shown stronger activity-cognition relations for those with lower education, suggesting activity compensation [35, 85, 86]. However, many studies involve highly educated samples where the mean split into high/low education is not substantially different (e.g., high school versus university). Rather, having no education may adversely affect the benefit of activity engagement. Older adults with at least one year of education had a reduced risk of cognitive impairment (per the MMSE) from high activity participation 5 years earlier compared to those with no formal education [57]. Further, only those with some formal education benefited from mental activities. Educational experiences may develop skills to productively engage in activities, influencing motivation, enjoyment [57], and establishing lifetime habits of mentally challenging activities [87]. Television, therefore, may offer cognitive stimulation for those with little/no education as it was associated with lower risk of cognitive impairment [57]. Few studies have investigated educational differences on the impact of physical activity, with one finding greater benefit for the highly educated [18], and another finding no educational differences [62].
Most recent work on gender differences has considered physical activity. Older women, but not men, who walked more and maintained that over 10 years had higher baseline processing speed and less decline [4]. Barha et al. [84] argued that the male advantage in how biological systems respond to physical activity may lead to greater cognitive benefits for females. However, studies have found no gender differences in AD risk reduction by physical activity [62], and a meta-analysis showed little gender difference in reducing the risk of all-cause dementia and AD, although women experienced more protection against cognitive decline [60]. Age may also influence the gender moderation of physical activity effects. Compared to those who exercised twice/week or more in midlife, exercising 2-3 times/month or less was associated with higher risk of dementia 28 years later, but only for men [63]. Maintaining or increasing physical activity after midlife was associated with lower dementia risk for both genders. Similarly, men who retrospectively estimated participating in non-exercise physical activity (e.g., vacuuming) at least 1-2 times/week in midlife showed less cognitive decline on 80% of possible associations compared to non-active men [45]. Active women in midlife showed less cognitive decline on only 25% of associations. The pattern reversed for late-life associations, with most effects significant for active women, and only a quarter for active men.

Even when higher engagement benefits cognition to the same extent [9], men and women might benefit from different activities [55]. Social activity [9], engaging with more social groups, and hobby and volunteer groups [88] were associated with less short-term cognitive decline for women; however, socialization with neighborhood associations and local event groups was protective for men [88]. As noted in 2010 [13], gender differences may be partially explained by traditional roles [7]. Completing ‘non-traditional’ activities may add variety, positively affecting cognition (men completing more domestic activities in midlife [7]), whereas activities that
confirm gender roles may have the opposite effect (more domestic activities predicted steeper 8-year spatial ability and memory decline for women [7]). However, this hypothesis is not always supported: women participating in more midlife mental-cultural activities had steeper 8-year memory decline [7].

Consideration of age, education, and gender differences in the activity-cognition relation has grown in the past decade. In addition to directly studying these characteristics, researchers are encouraged to consider these factors as sub-analyses in their studies.

5. How does Activity Engagement Impact Cognition?

Identifying mechanisms through which activity engagement might reduce age-associated cognitive declines remains a priority. The 2010 review [13] highlighted that mechanisms ‘explaining’ activity-cognition associations may be used descriptively, such as mentioning cognitive or brain reserve (environmental factors that permit adaptive neurological processing or enhanced brain structures) [89]. For a mechanistic understanding, reserve must be clearly characterised, addressing how activity affects brain physiology, function, and structure (notwithstanding indirect mechanisms via health or behaviour [13]). This latter type of research continues to be limited.

Two caveats are necessary. First, potential mechanisms are often considered separately by activity domain, but as activities encompass varying degrees of mental, social, and physical engagement, any cognitive benefit may require multiple pathways [13]. Second, many mechanistic studies involve training or learning, rather than observation. Mechanisms driving short-term activity benefits may differ from mechanisms underlying longer-term participation [72, 90]. Though interventions support our understanding (examples are highlighted below), they cannot necessarily elucidate the benefits of lifetime engagement.
Mental challenge is often considered critical for protecting cognition, though the mechanisms remain relatively underexplored and “very nonspecific” [66]. Mentally-challenging activities may support later-life brain plasticity [91-93] (e.g., by ensuring diverse brain pathways and connections are continuously strengthened), and higher lifetime mental activity was associated with lower β-amyloid deposition [94], particularly in APOE e4 carriers [95]. However, not all studies support associations between mental engagement and MRI-derived parameters [96]. Volunteering programs encompassing both mental and social engagement have resulted in increased hippocampal and cortical volumes [97], but the specificity or generality of structural brain changes may depend on the nature of engagement (e.g., language learning in younger adults changed language-specific brain regions [92]). Functional plasticity was also evident from cognitive training [98], including better modulation of brain activity (i.e., decreased for simple tasks). Improvements in processing efficiency also occurred after mentally-challenging interventions [99], though embedding functional measures within longer-term observational studies remains rare.

The mechanistic pathway between physical activity and cognitive ability was [13] and remains better articulated than other activity domains [100]. Benefits via improved prefrontal cortex and hippocampus grey matter volumes, reduced age-associated atrophy in gray and white matter, and better white matter integrity have been supported [66, 96, 101-104]. Associations between physical activity and brain parameters also differ by sex: 10-year maintenance of physical activity was associated with higher prefrontal cortex volume in females, higher hippocampal volume for males, but lower hippocampal volume for females [4]. The impact of physical activity on the brain may be via numerous pathways, including reduced vascular risk. Bherer et al. [105] reported the cognitive benefits of a physical activity intervention were entirely
accounted for by cardiorespiratory changes amongst those 70 and older, but not those 65-70, suggesting mechanisms also vary by age. Interventions that promote cardiorespiratory fitness are more likely to be associated with cognitive benefits, with effects on angiogenesis, neurogenesis, and synaptogenesis [100, 106]. A conceptual review [74] suggested that while structural brain benefits were often general (e.g., reduced atrophy), specificity was observed with stronger effects for hippocampal or prefrontal regions; a systematic review confirmed the specificity of the physical activity benefit to regions associated with dementia [104]. It is also possible the benefit of physical activity operates through cognitive engagement when it involves skill development and learning [83].

Potential pathways at the molecular level are developing, with a specific focus on brain-derived neurotrophic factor (BDNF) due to the protein’s role in neuronal growth and maintenance. In a review of experimental studies, moderate intensity physical activity increased BDNF levels [107]. These changes may be moderate after a single exercise session, though potentially lower in women and over regular exercise [108]. Though promising [109], effects of physical activity on brain health are “modest” [110], and mechanistic work is required at finer-grained levels of analysis (e.g., changes in brain structure or functional connectivity) [109, 111].

The mechanistic understanding for social engagement remains limited, often exploring indirect pathways via social support, influence, and instrumental assistance [112]. Associations between support and cognition may be accounted for by structural brain parameters: people receiving more emotional support had better cognitive performance, partly mediated by larger hippocampal volumes [113]. In addition, lonelier individuals had higher amyloid burden [114], and social connectivity may reduce the negative impact of stress, or provide opportunities for mental stimulation [112]. Interventions incorporating social engagement have suggested
intergenerational volunteering slows or reverses age-related hippocampal volume loss, particularly for men [97], but the aspect of engagement (mental or social) driving the effect was difficult to discern. Work comparing high-mental challenge with low-mental challenge or purely social groups [99] suggested mental challenge remains more critical.

Interactivity between domains of engagement complicates identifying potential mechanisms. Both mental and social activity were significant mediators between physical activity and cognition [82], and mental activity [73] or physical activity and markers of mental health [115] partly mediated the association between social activity and cognition. Activity domains may provide differential dementia risk reduction through different mechanisms: Najar et al. [61] reported midlife mental activity was associated with reduced risk of all-cause dementia and AD, while midlife physical activity was associated with lower risk of mixed dementia, dementia with cerebrovascular disease, and total dementia risk. Mental activity may increase cognitive reserve (i.e., compensatory activation patterns) and thereby decrease AD risk, whereas physical activity might lower cardiovascular risk factors, specifically decreasing risk of mixed and CVD-related dementia [61].

The potential mechanisms for the cognitive benefits of mental, social, and physical engagement overlap and involve other factors (see Figure 2) [116]. Notwithstanding shared mechanisms, Cheng [66] suggested domains of activity likely build ‘reserve’ in different ways, for example physical activity supporting the ‘hardware’, while mental activity strengthens the ‘software’. For the field, this is perhaps a trickier aspect to progress as assessing mechanisms is often tied to higher resource demands. We encourage large longitudinal studies to evaluate existing variables as proxies of various mechanisms, and the creation of studies specifically designed to examine mechanisms.
6. What is the Optimal Way of Assessing Activity Engagement?

a) Which activities should be assessed?

The most common method of assessing activity participation continues to be self-report. There remains little consensus on the best scale to use, and questionnaires vary widely in which (e.g., crafts, playing instruments, hunting/fishing) and how many activities are included (e.g., five [53]; thirteen [9]; twenty-three [47]; fifty-seven [78]), and the timeframe considered (e.g., over a typical week [52], the past three months [11], or year [29]). Such variation in assessment contributes to inconsistency in results, and we cannot differentiate methodological limitations from a true null effect. We encourage researchers to consider measurement issues, including iterative scale assessment to determine which types of activities are relevant. One study focused on improving the psychometric properties of an activity questionnaire [117], using factor analysis to produce a scale with strong reliability and validity. Further validation work will improve the methodological rigor of activity scales [118].

One criticism of typical questionnaires is that each activity is valued equally when participation is summed. Carlson et al. [47] incorporated the relative level of mental stimulation of each activity by multiplying the frequency of participation by its expert-rated demand (though see recommendations). Relatedly, studies have increasingly accounted for exercise intensity by multiplying time spent in each physical activity by respective metabolic equivalent values (METs) [17, 30, 43, 52, 56, 119], but there are limitations regarding broad intensity categories and age differences in METs [120]. Bielak [78] suggested an alternative where characteristics associated with engagement (e.g., organizing, planning), rather than specific activities, may be more relevant to cognition. This approach circumvents several methodological issues (e.g., which and how many activities are assessed; permits multiple components of stimulation per
activity; allows individualization in activity completion), and the resulting questionnaire predicted adults’ fluid cognitive performance.

Work has reconsidered relying on activity frequency as the primary metric, investigating whether engaging in a variety of activities might better support cognition [47] by exposing individuals to different situations requiring diverse behaviors [70]. Controlling for activity frequency, women with greater activity variety experienced less subsequent cognitive impairment [47]. However, activity frequency indices have also produced slightly higher [69], or similar [121], associations with cognition versus variety. The most active individuals also had the most diverse engagement, so high engagers would be identified by both metrics (r = .91-.94) [69]. Given the strong frequency-variety overlap, a variety index (i.e., yes/no participation in an activity) may provide a time-saving assessment [69]. In contrast, one study used an activity diversity index incorporating breadth and consistency of engagement. While associated, variety and frequency had distinct components; greater activity variety, and increases over 10 years, were positively associated with cognition, independent of total activity time which was also a significant predictor [70]. The independence of activity variety and frequency requires further investigation.

Bielak [13] discussed the challenges of creating an ideal activity questionnaire, and those issues remain (e.g., cultural, geographic, and seasonal differences in common activities). Another issue is the aging of activity questionnaires, with some activities becoming dated. Consider “writing letters” [122], “arithmetic calculations” [117], and “balance checkbook” [47], compared to technology-supported alternatives of emails, calculators, and online banking. “Computer activities” [38] is particularly vague given the range of tasks that encompasses. Even activities that remain relevant have changed in how they are carried out, questioning whether the same
stimulation is involved (e.g., yearly tax returns [117] using paper forms versus online). Questionnaires need to be updated and some changes might be as simple as providing more examples (e.g., include socialization via video calls [78]). Relatedly, given the importance of midlife to later cognition, items need to reflect the different activities completed across the life course.

b) How should this information be acquired?

Although self-report remains standard, multiple methods may be valuable. A comparison of a 2-year retrospective questionnaire, 7-day daily diary, and 7-day questionnaire showed that each had unique associations with cognition, though predicted more variance together than alone [78]. Hess et al. showed that although daily and retrospective activity assessments were positively correlated, each captured slightly different information [123]. Relatedly, there was evidence that older adults’ weekly activity estimates were lower than their reported daily activities [124], each with unique associations with cognition.

Studies are increasingly considering daily assessments of activity [70], using either end-of-day reporting, or ecological momentary assessment where participants report activities in real-time via a smartphone. Both methods are less likely to have recollection errors and reduce inaccuracies common in long-term retrospective reports due to seasonal or yearly shifts in engagement. However, care must be taken to schedule daily activity collection around unusual events (e.g., vacation, visitors). As different assessments provide different participation metrics, incorporating a short-term activity assessment in conjunction with longer-term activity is recommended.

Although objective measures of mental and social engagement remain limited, some studies have included objective physical measures (e.g., accelerometers [125]). Physical activity
determined by these measures predicts concurrent cognitive impairment [122] and dementia risk when controlling for self-reported physical activity [125]. It is unclear whether these objective indices are more informative than self-reported data. The average difference between accelerometer and self-reported moderate-to-vigorous physical activity was 4 minutes and not significant, though the difference ranged widely across participants [126]. Further comparison of objective and subjective reports of physical activity are needed.

**Conclusion**

The past decade has seen continued investigation of the relation between activity and cognition, highlighting the challenges of definitively answering these complicated issues. This unifying of information is intended as a reminder of critical issues and an encouragement for studies addressing specific questions. To assist this, we provide three additional resources.

First, although this review focused on research from the past 10 years, issues in the 2010 review [13] remain relevant. Table 1 presents general conclusions for each question based on the evidence in 2010 and now, with specific next steps to address each issue. In some cases, our knowledge about an issue has become more refined, while in others, the same limitations exist.

Second, we have compiled recommendations for future studies investigating the link between activity engagement and cognition (Table 2). When followed, these will support addressing key questions and minimizing inconsistencies in methodology. We recognize the challenges of adhering to these practices, and not addressing every item does not presuppose a study’s value. However, we encourage researchers to evaluate their own and other’s work in relation to these recommendations, highlighting limitations that exist.

Finally, to assist in taking activity-cognition research to the next level we have created Figure 3. This provides an idealized study design that could address significant questions in this
research area. We encourage researchers to incorporate aspects of this design into their current work and use it to set goals for future work. Such practices will enable the next decade to be one of progress in terms of understanding how we might “use it to not lose it”.
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References


Figure Legend

Figure 1. Differential preservation versus preserved differentiation

Note. Where an association is reported between activity engagement and cognitive ability, being more active may predict better outcomes over time, in terms of improved ability or protection against age-related decline (differential preservation); or both active and inactive groups may change in the same way over time, with the only difference being the level at which they start from (preserved differentiation). Panel a) Differential preservation: While on average, both activity engagement groups experience cognitive change over time, the people who are more active/engaged experience decline to a lesser degree (i.e., cognitive abilities are “differently preserved” depending on the level of activity engagement). Panel b) Preserved differentiation: Both groups experience the same rate of cognitive change over time, but the more active/engaged group starts at a higher cognitive level. In this model, while being more active/engaged would not appear to be beneficial in terms of slowing decline, activity engagement might still be advantageous if that is one of the factors that determines a higher cognitive starting point. In both scenarios, there may also be pre-existing differences in level of cognitive ability, illustrated by the double-headed arrows. Those pre-existing differences relate to considerations of reverse causation where those starting at a higher level in older age may always have been performing better cognitively, and their higher level of functioning is what predisposed them to their higher level of activity/engagement.

Figure 2. Potential mechanisms promoting brain health
Figure 3. Aspirational research design to address significant questions about activity-cognition relationship.

Notes. The provided figure is aspirational in terms of addressing key unanswered questions within a single study. Inclusion of all aspects would require resources and an extended period of follow-up that is possible only in rare circumstances. However, we encourage our colleagues to consider how they can incorporate pieces of this design into their future research, and work towards addressing key aspects of these goals (e.g., objectively measuring the cognitive stimulation provided by activity).

1 Studies should consider a life course perspective to enable assessment of a lifetime of exposure. Different activity domains may present different associations with cognition during distinct periods of the life course, requiring decades of follow-up. As cognitive domains also develop and change in characteristic ways, a life course approach is needed to explore whether and when activity builds capacity or reduces decline. Sample sizes need to be in the thousands to account for attrition across decades of follow-up.

2 Where possible, baseline measures should be collected from early adulthood (i.e., required to consider issues of reverse causation).

3 Activity engagement assessments should consider multiple domains of activity, measured as frequency and variety. Subjective measures of activity engagement should be supplemented with objective measures, ideally including yet-to-be-developed measures of the cognitive stimulation.
derived from engagement. Cognitive assessments should consist of a standardized cognitive battery (multiple tests per domain and a broad coverage of domains).

4Repeat assessments should occur at regular intervals through midlife (e.g., every 5-10 years). Assessment batteries should be repeated from previous waves but may be supplemented with one-off assessments (e.g., lifetime occupational assessments).

5Each assessment wave should assess mediators, moderators, and potential mechanisms for the activity-cognition relation (e.g., physical and mental health, social support). Assessments should include broad coverage of other determinants of cognitive aging (e.g., diet, sleep) to assess the relative contribution of activity engagement. Where possible, brain imaging should be included to explain activity-cognition relations in terms of structural and functional brain changes.

6Repeat assessments might occur more frequently in later life when age-related cognitive changes are most observable (e.g., every 3-4 years).

7Within a large-scale, longitudinal study, subsamples could complete different sub-studies to address additional research questions. For example, a sub-study might consider daily assessments of activity and cognition to assess day-to-day relations. Other sub-studies might consider different follow-up periods (e.g., reassessments every 1-2 years versus 3-4). Sub-studies could also embed specific interventions between reassessments. Drawing intervention samples from large observational studies would enable a range of life course confounders/moderators to be considered.
Box 1: Activity-cognition associations are likely small

Assuming that activity benefits cognition, effects are likely small. Small effect sizes are to be expected as Corley et al. [1] noted that different lifestyle determinants of cognitive aging might each only account for 1-2% of the variance. Though statistically small, such effects remain important if acted upon at the population level [1].

The small effect sizes from activity-cognition associations highlight two issues that require careful consideration. Activity effects may be overestimated given shared variance with other lifestyle predictors (e.g., if activity accounted for ~2% of the variance in cognition, after controlling for other relevant factors such as education or sleep, the effect size attributable to activity is likely to be reduced. Further, if the stability of cognition across the life course is not accounted for, the effect sizes of activity-cognition associations may also be inflated (e.g., associations between mental-social activity and cognitive domains ranged from partial $\eta^2$ .03 to .06, but were reduced to .00-.01 after adjusting for prior cognition [127].

Whenever effect size estimates cannot be adjusted for other factors or prior cognition directly, researchers are urged to report those cautiously to avoid the interpretation of larger than likely effect sizes.

Box 2: Between-person differences and within-person change

The majority of work looks only at group-level relationships, where average activity level is evaluated in relation to cognitive performance. However, there is a growing number of studies that consider both between- and within-person associations. Between-person effects evaluate if there are differences between people in the relation to cognition based on each individual’s average score. Within-person associations evaluate if an individual’s change in activity is
related to their own change in cognition (i.e., whether the variables covary across time). These effects address different questions about the activity-cognition relation: between-person effects ask if average activity is associated with baseline cognitive ability (level) or change; and within-person effects ask if on occasions when someone is more or less active than usual, does their cognitive performance also change? Both types of effects are influenced by the number of assessments (i.e., greater reliability of between-person scores with more assessments), and the time between assessments (i.e., within-person changes evaluated every year for 5 years would be different than if evaluated every month for 6 months).

Box 3: Day-to-day variability in activity and cognitive change

Though most studies exploring the activity-cognition relationship do so over years or decades, some work has considered shorter timeframes, specifically how variability in activity over a period of days might be associated with changes in cognition over the same timeframe. For example, on physically active days, individuals reported fewer memory failures that day and the next [128], but another study did not find correspondence between physical activity and cognitive changes [129]. Other work showed that only engagement in mentally-stimulating activities over the previous 3 hours was associated with better semantic memory [130], and that daily activity fluctuations were associated with corresponding changes in speed, memory, and reasoning [65]. The effects were strongest for social-private activities (i.e., interactions with close contacts), where more engagement than usual was associated with better cognitive scores, but some associations were negative: on days with more-than-usual television viewing, reasoning performance was worse.
Though it is likely that day-to-day activity-cognition associations operate via different mechanisms than longer-term associations [65], that remains to be tested. To do so, researchers might consider daily data collection bursts for activity and cognition in the context of longer-term follow-ups.