Physical activity in the prevention of Alzheimer's disease

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Abstract:

Alzheimer's disease is a chronic illness characterized by clinical cognitive impairment. A behavioral strategy that is being explored in the prevention of Alzheimer's disease is physical activity. Evidence from randomized controlled trials (RCTs) testing the effects of physical activity for cognitively normal older adults supports that physical activity benefits cognitive performance. Evidence from prospective studies supports a protective effect of physical activity with reductions in the risk of cognitive decline ranging from 28% to 45%. RCTs with cognitively impaired older adults also generally support positive effects with greater benefits evident for aerobic interventions. Research examining the potential moderating role of apolipoprotein E (*APOE*) has yielded mixed results, but the majority of the studies support that physical activity most benefits those who are at greatest genetic risk of Alzheimer's disease. Future directions for research are considered with an emphasis on the need for additional funding to support this promising area of research.

Keywords: dementia | Alzheimer's disease | cognitive performance | physical activity | aging | cognitive decline

Article:

Alzheimer's disease is a chronic illness that is characterized by clinical cognitive impairment and a relatively slow progression (4–20 years) that ultimately results in death (Alzheimer's Association, 2014). Given the growing older population, the prevalence of Alzheimer's disease is expected to increase dramatically in the next several decades. Because there is no known treatment for Alzheimer's disease, researchers are interested in identifying strategies that might reduce the risk of or delay the onset of Alzheimer's disease. One behavioral strategy that holds promise in this regard is physical activity. After providing a description of cognitive decline as it relates to advancing age, evidence will be presented relative to the potential of physical activity as a preventative strategy for Alzheimer's disease. This evidence is presented from research on cognitively normal older adults, on cognitively impaired older adults, and relative to a genetic predictor of Alzheimer's disease that may moderate the effects of physical activity on cognitive performance.

Cognitive Decline With Advancing Age

Age-related cognitive decline describes the normal change in the ability to perform cognitive tasks and is associated with advancing age beyond adulthood. Cross-sectional evidence supports that across a variety of cognitive domains including reasoning, memory, and speed of processing, declines in performance are evident with advancing age, with some types of cognitive performance beginning to show decline as soon as early adulthood (i.e., in a person's 20s) (Salthouse, 1998; Schroeder & Salthouse, 2004). These changes in performance capabilities with advancing age are normal. However, when cognitive performance is worse than would be expected based upon a person's chronological age and education level, this may then be considered a clinical form of cognitive impairment. When a person's cognitive capabilities are worse than expected, but these decrements do not affect the person's ability to function in daily life, this is considered to be a mild neurocognitive disorder (American Psychiatric Association, 2013) and is referred to as mild cognitive impairment (MCI). When cognitive decrements are evident in several cognitive domains and these decrements affect daily functioning, this is considered to be a major neurocognitive disorder (American Psychiatric Association, 2013) and is referred to as dementia. The most common form of dementia, accounting for 70% of cases, is Alzheimer's disease, which is characterized by impairments that become progressively worse over time and that are associated with the accumulation of plaques (beta-amyloid proteins) and tangles (tau proteins) that eventually lead to neuronal death.

Alzheimer's disease currently affects 5.2 million people in the United States, with projections that 7.1 million will be affected by 2025 and 13.8 million by 2050 (Alzheimer's Association, 2014). In addition to the large numbers of people suffering from Alzheimer's disease, it is important to point out that Alzheimer's is a particularly burdensome disease because of the slow progression of the illness and because of the high costs in terms of skilled care (estimated at $214 billion) and high value in terms of unpaid caregivers (estimated value of $220 billion) (Alzheimer's Association, 2014). Given the lack of a treatment for Alzheimer's disease, the identification of methods to prevent Alzheimer's disease is an important priority for research. Recent trials have focused on the use of beta-amyloid antibodies, the use of a "heart-healthy" diet, cognitive training, and physical activity interventions. The focus of this review is on the potential of physical activity in reducing the risk of Alzheimer's disease.

Physical Activity and Cognitive Performance

Cognitively Normal Older Adults

Numerous studies have been conducted to help us understand the potential for physical activity to benefit cognitive performance by older adults. Etnier et al. (1997) conducted the first meta-analytic review of the literature on physical activity and cognitive performance. At this time, the research in this area was relatively large and consisted of empirical studies across a broad range with regard to design and quality. This meta-analysis provided an inclusive review that included the entire body of literature at that time. However, in addition to presenting data relative to overall effects, the authors also provided information regarding the average effect size for randomized controlled trials (RCTs) (across ages, $g = 0.18$) and for chronic exercise studies with adults (45‐60 years, Hedge's *g* = 1.02) and older adults (60‐90 years, *g* = 0.19). Since the conductance of this meta-analysis, the number of empirical studies exploring the potentially beneficial effect of physical activity has grown dramatically. Given the relatively large literature in this area, it is prudent at this time to focus our attention on the results of the strongest evidentiary studies, which are the RCTs and the epidemiological studies.

Three meta-analytic reviews of RCTs with cognitively normal adults have been conducted, with two focused exclusively on older adults (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Colcombe & Kramer, 2003) and one including all adult ages (Smith et al., 2010). Colcombe and Kramer (2003) analyzed the results of 18 RCTs with older (55‐80 years) adults. Their results indicated that exercise consistently benefited cognitive performance with an average overall *g* = 0.48. They additionally reported that the magnitude of the benefits differed across cognitive domains (controlled tasks: *g* = 0.46; spatial tasks: *g* = 0.43; speeded tasks: *g* = 0.27), with the largest benefits evident for studies testing executive function (*g* = 0.68). Angevaren et al. (2008) reviewed the results of 11 RCTs with older (> 55 years) adults and reported significant positive effects for exercise that ranged from 0.26 to 0.52 and were dependent upon the cognitive domain and the particular comparison group that was used. Smith et al. (2010) included RCTs conducted with adults ≥ 18 years, so results may not be directly comparable to the other two reviews. However, of the 29 studies included, only seven reported on findings for samples that included younger adults. Their findings indicated that aerobic exercise resulted in significant benefits in three cognitive domains with no evidence of preferential benefits for executive function tasks (attention and processing speed: *g* = 0.16; executive function: *g* = 0.12; memory: *g* = 0.13). Most recently, Carvalho, Rea, Parimon, and Cusack (2014) conducted a systematic review of the literature for older adults (> 60 years). Inclusion criteria were such that RCTs had to have tested at least 30 participants and had to have lasted at least six months. Given these inclusion criteria, the authors reported that 9 of the 10 RCTs yielded significant positive findings for the effects of physical activity on cognitive performance. In sum, empirical studies using RCT designs provide consistent support for a causal relationship between physical activity and the cognitive performance of cognitively normal older adults with effect sizes in the range of small-to-moderate.

Epidemiological studies conducted in this area have used retrospective, case control, and prospective cohort designs. As an example of a retrospective study, Middleton, Barnes, Lui, and Yaffe (2010) asked 9,344 older women (*M* = 71.6 years) to recall their physical activity levels as teenagers, when they were 30 years of age, 50 years of age, and late in life. After controlling for a variety of potential confounds, results showed that women who reported being active at any of those time points had lower odds ratios for clinical impairment (*OR* = 0.65‐0.80) than did women who reported being inactive at those same time points. Andel et al. (2008) conducted a case control study in which 3,134 older adult twin pairs were asked during middle age (*M* = 48.1 years) how physically active they had been from the ages of 25‐50 and then were followed for 30 years. Results indicated that after controlling for covariates, those who had been physically active during young adulthood had lower risk (*OR* = 0.34‐0.70) of being diagnosed with dementia 30 years later as compared with those who reported "hardly any" activity. Importantly, when twin pairs were compared (which allowed for the control of genetic and familial factors), more physically active twins had a lower risk (*OR* = 0.66) of dementia than their less active twin. Etgen et al. (2010) used a prospective cohort design to assess the influence of current physical activity levels on cognitive impairment two years later. Results showed that for 3,930 older adults (> 55 years), the risk of impairment was less (*OR* = 0.54‑0.57) for those who were active compared with those who were sedentary. In the aforementioned systematic review by Carvalho et al. (2014), the authors also reviewed prospective studies which met their inclusion criteria by including at least 100 participants and lasting at least one year. The authors observed that 16 of 16 prospective studies reported protective effects for physical activity on subsequent cognitive performance. In addition, evidence from five prospective studies supported a dose-response relationship such that greater physical activity at baseline was predictive of lesser cognitive decline over the years of the study. Several meta-analyses have been conducted to statistically summarize the results of the prospective studies (see Figure 1). All of these reviews indicate that physical activity reduces the risk of cognitive impairment whether defined as cognitive decline over time (Sofi et al., 2011), Alzheimer's disease (Daviglus et al., 2011; Hamer & Chida, 2009), or dementia (Hamer & Chida, 2009), with odds ratios for the more active groups ranging from 0.55‑0.72 in comparison with the lowest physical activity group (referent, *OR* = 1.0). When the question of dose-response was addressed in the Sofi et al. (2011) review, results indicated that the benefits of moderate (*OR* = 0.65) and high (*OR* = 0.62) physical activity were indistinguishable. In sum, the epidemiological evidence is robust and supports the role of physical activity in protecting against cognitive decline and clinical cognitive impairments in advancing age.

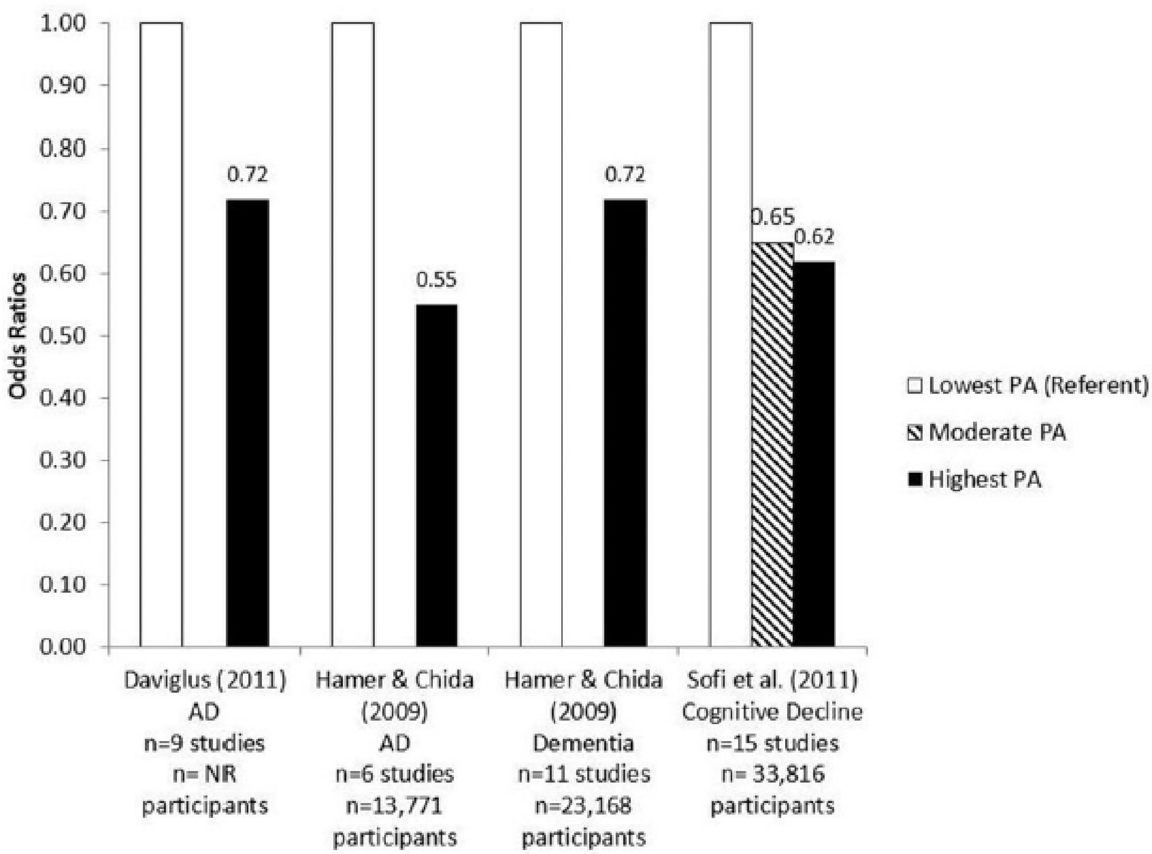

Figure 1. Odds ratios for cognitive impairment as reported in meta-analytic reviews of prospective studies. PA = physical activity; AD = Alzheimer's disease; NR = not reported number of.

Adults With Cognitive Impairment

Research with older adults who are already experiencing cognitive impairment is also somewhat promising. Four meta-analytic or systematic reviews have been conducted in this area with two focusing on MCI (Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013; Wang et al., 2014), one focusing on dementia (Forbes, Thiessen, Blake, Forbes, & Forbes, 2013), and one reporting separately on studies on participants with MCI and on studies with participants with dementia (Ohman, Savikko, Strandberg, & Pitkala, 2014).

Mild Cognitive Impairment. Gates et al. (2013) reviewed studies with adults over 65 years who had been diagnosed with MCI or who had scores on the Mini-Mental State Exam (MMSE) that were between 24‑28. From 14 RCTs, they reported that only 8% of cognitive outcomes that were assessed yielded statistically significant differences between treatment groups. They further reported that the overall effect size was negligible for measures of executive function, memory, and information processing, and was small (ES = 0.17) for verbal fluency. Based upon their findings, Gates et al. (2013) concluded that there was not strong evidence supporting the benefits of exercise for persons with MCI.

Wang et al. (2014) meta-analytically reviewed the findings of seven RCTs with participants with MCI. Their results indicated that significant benefits of exercise were evident for measures of global cognition ($SMD = 0.25$), but were not observed in any specific cognitive domains (executive function, memory). Important direction might be provided by the results of moderator analyses, which indicated that for global cognition, studies using shorter interventions (< 12 months) resulted in larger effects ($SMD = 0.43$) than those using longer interventions ($\geq$12 months), and that studies using aerobic exercise yielded larger effects ($SMD = 0.35$) than studies using nonaerobic exercise ($SMD = 0.16$). Importantly, effects were larger for higher quality studies ($SMD = 0.27$) than for lower quality studies ($SMD = -0.01$), suggesting that more rigorous studies yield stronger results. In summarizing their findings, Wang et al. (2014) concluded that exercise shows some potential for benefiting global cognition in MCI patients and urged future research to focus on identifying the best mode of exercise and the optimal intensity of exercise to produce cognitive benefits.

Ohman et al. (2014) identified RCTs exploring the effects of exercise on MCI ($n = 8$) and performed a box count of significant findings based upon whether the outcome was global cognition or performance in a specific cognitive domain. Results showed that findings for global cognition and attention were most promising with positive effects observed in three of five studies and four of four studies, respectively. Results were also somewhat promising for executive function, with significant differences reported in three of six studies. Based upon the evidence presented in their review, Ohman et al. (2014) concluded that for MCI, there was evidence of good quality supporting positive effects for cognition.

One limitation with regard to drawing a consensus from these reviews is that the conclusions drawn and the levels of enthusiasm for these conclusions are quite different. Based upon their observed results, Gates et al. (2013) were relatively pessimistic about the value of physical activity for cognitive benefits in persons with MCI whereas by contrast Ohman et al. (2014) and

Wang et al. (2014) were more enthusiastic. One reason for the different conclusions may relate to the studies included (see Figure 2a). Ohman et al. and Wang et al. had seven studies in common. By contrast, the Gates et al. review only shared six studies with the other two reviews and there were an additional seven studies that were unique to the Gates et al. review. It is important to point out that a limitation consistently identified by the reviewers is the heterogeneity with regard to the exercise interventions, control groups, cognitive outcomes, and specific cognitive abilities of the samples. Heterogeneity in these first three aspects is a common limitation of research in the area of exercise and cognitive performance, but in the case of the literature on MCI, our ability to synthesize the literature is further exacerbated by the lack of consistency in the definition of MCI. Thus, despite the efforts of the reviewers to include studies on MCI, the individual studies included may in fact be focused on participants who differ in terms of the subtypes of MCI. Given that MCI represents a transitional state between cognitive normality and dementia, this clearly presents a challenge in synthesizing the evidence, and research in this area will benefit from adopting a standard clinical definition of MCI so that more homogeneous samples can be observed.

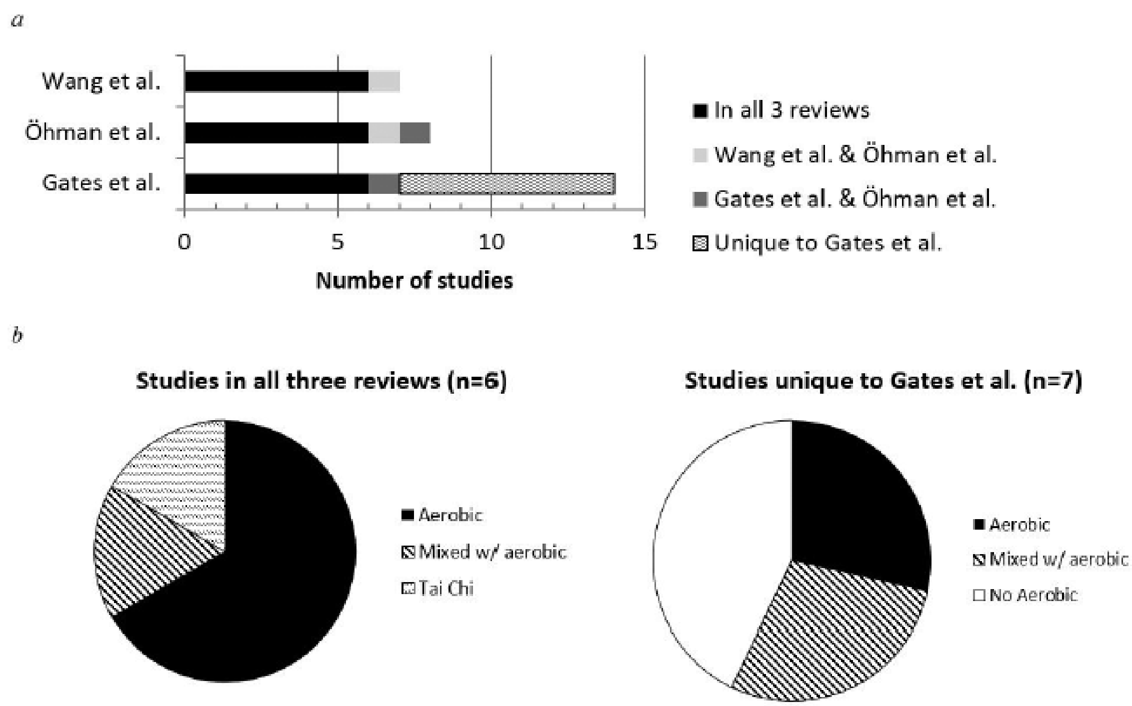

Figure 2. Comparison of studies included in the reviews on mild cognitive impairment. *(a)* Overlap among studies included in the reviews. *(b)* Mode of exercise used in the studies that were shared as compared with the studies unique to Gates et al. (2013).

Another variable that may have impacted the different conclusions drawn in these reviews is that there was heterogeneity in the mode of exercise used in the included studies (see Figure 2b). Of the six shared studies, four used aerobic interventions, one used a Tai Chi intervention, and one used a mixed intervention including an aerobic component. By contrast, in the seven studies that were only included in the Gates et al. (2013) review, two used aerobic interventions, two used mixed interventions including an aerobic component, and three used interventions without an aerobic component. Given the suggestion by Wang et al. (2014) that the effects of exercise on cognitive performance may depend on both the cognitive task and the modality of the exercise, it is possible that the inclusion of a more heterogeneous group of studies with regard to exercise modality explains the less positive results reported by Gates et al. (2013). That being said, this is only one possibility as there are numerous other variables (such as the aforementioned differences in MCI definitions) that may also explain the heterogeneous conclusions.

Dementia. In their review, Ohman et al. (2014) also included RCTs exploring the effects of exercise on dementia (*n* = 14). These studies were described as being of lower quality than the studies on MCI and results were not as promising. Results showed that in the two studies testing effects for global cognition there were no beneficial effects. By contrast, studies testing the effects on executive function did yield positive effects (3 of 4 studies), however these positive effects were only reported in studies described as being of low quality and were not evident in the study deemed to be of moderate quality. In studies testing the effects on measures of memory, three studies looking at delayed recall, six studies looking at working memory, and three studies examining declarative memory all yielded nonsignificant effects. Hence, the authors concluded that evidence supporting beneficial effects of exercise for persons with dementia are not promising, with positive effects only being reported in studies of poor methodological quality.

Forbes et al. (2013) also meta-analytically reviewed studies focused on persons with dementia. They included 14 RCTs focused on cognitive outcomes and reported that exercise had a significant positive effect on cognitive performance (*SMD* = 0.55). Given their findings, these authors concluded that exercise can improve cognitive performance by persons with dementia and recommended that health-care providers and caregivers should “feel confident in promoting exercise among this population” (p. 19) because of the prospect of slowing patients’ cognitive decline.

In considering the findings of the reviews on exercise in patients with dementia, it is not clear why the conclusions are so dramatically different. However, it is important to again point out that the two reviews did not include the exact same literature. There were eight studies that were included in both reviews, but there were an additional six unique studies to each review (see Figure 3). Again, it is likely that the different conclusions are thus reflective of the heterogeneity in experimental designs and cognitive measures of studies included in these reviews.

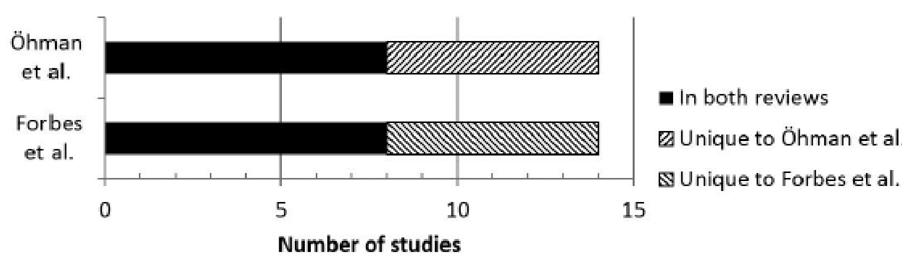

Figure 3. Comparison of studies included in the reviews on dementia.

Summary. In sum, results from studies exploring the potential cognitive benefits of physical activity for cognitively impaired older adults are mixed, but there is some evidence of beneficial effects with reported effect sizes ranging from small to moderate. It is critically important that additional research be conducted to improve our understanding of how to optimally design exercise programs to ensure that cognitive benefits result for persons suffering from clinical cognitive impairment.

Moderators

One interesting approach to understanding the role of physical activity in the prevention of dementia is to explore the moderating role of the apolipoprotein E (*APOE*) genotype on the relationship between physical activity and cognitive performance. *APOE* is a susceptibility gene for Alzheimer's disease with the e4 allele being predictive of increased risk. In particular, persons who carry one copy of the e4 allele (heterozygotes) are at 2–3 times greater risk and persons who carry two copies (homozygotes) are at 8–15 times greater risk of Alzheimer's disease in comparison with persons with no copies of the e4 allele (noncarriers) (Corder et al., 1993; Farrer et al., 1997). Studies exploring the role of *APOE* genotype as a moderator have used correlational and prospective designs.

Etnier et al. (2007) assessed aerobic fitness and cognitive performance in cognitively normal older (ages 51–77 years) women. Their results showed that the relationship between aerobic fitness and cognitive performance was nonsignificant for the noncarriers and heterozygotes, but was significant and explained 33% of the variance for the homozygotes. In particular, higher levels of fitness were predictive of better performance on three measures of memory and one measure of attention for the homozygotes. Deeny et al. (2008) measured physical activity and working memory performance in older (50–70 years) cognitively normal men and women. Similar to the findings from Etnier et al., results indicated that the relationship between physical activity and cognitive performance was significant only for the e4 carriers.

Several prospective studies have been conducted to test the moderating effect of *APOE* on the effects of baseline physical activity on subsequent cognitive decline (see Figure 4 for results from each study). Interestingly, the results of these studies are not consistent. Schuit, Feskens, Launer, and Kromhout (2001) reported findings from the Zutphen Elderly Study, in which physical activity and cognitive performance were assessed in older (65–84 years) men at baseline and then cognitive performance was assessed again approximately three years later. Although they did not statistically test the interaction term for *APOE* 3 physical activity, they did present results separately for noncarriers and carriers. These results indicated that physical activity significantly reduced the risk of cognitive decline (operationalized as a $\geq$ 3 point decline on the MMSE) for the carriers (*OR* = 3.7), but had no benefit for the noncarriers. Niti, Yap, Kua, Tan, and Ng (2008) tested participants in the Singapore Longitudinal Aging Study at baseline and after a one-year follow-up. They reported that *APOE* genotype significantly moderated the effects of leisure activity on cognitive decline (operationalized as a $\geq$ 1 point decline on the MMSE) such that beneficial effects were greater for carriers than noncarriers, but were evident for both (carriers: *OR* = 0.36–0.37; noncarriers: *OR* = 0.65–0.68). Podewils et al. (2005) assessed physical activity in nondemented older adults (> 65 years) enrolled in the Cardiovascular Health Study at baseline and determined whether they met criteria for dementia approximately 5.4 years later. Results of this study supported a moderating effect of *APOE* genotype on the effects of physical activity on dementia risk, but in contrast to the previous studies, the effects showed that the benefits of physical activity were limited to the *APOE noncarriers*.

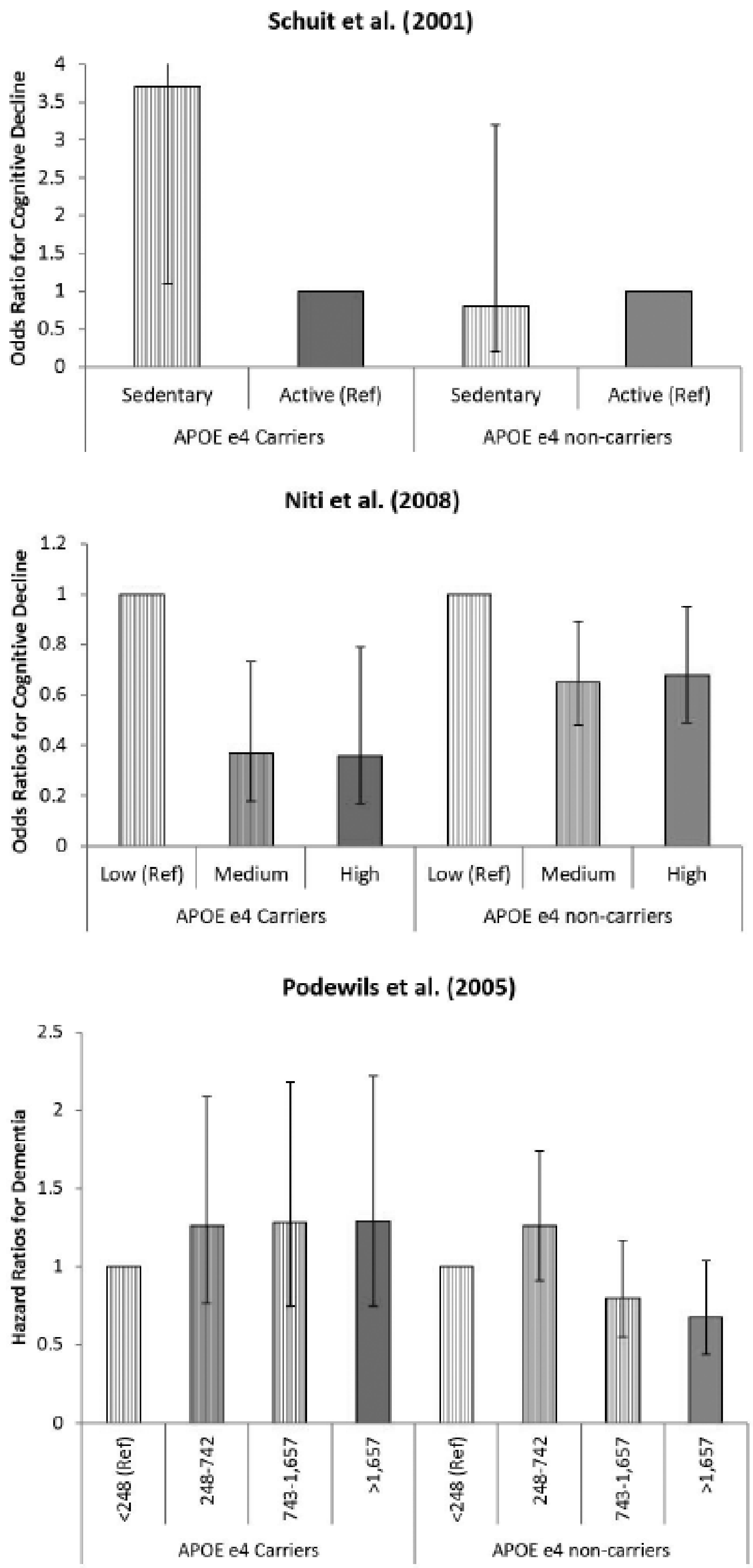

Figure 4. Results from prospective studies testing the moderating effects of *APOE* genotype on the effects of baseline physical activity on future risk of clinical impairment. Note. Confidence interval for Schuit et al. (2001) sedentary *APOE* e4 carriers = [1.1-12.9]; Ref = referent group.

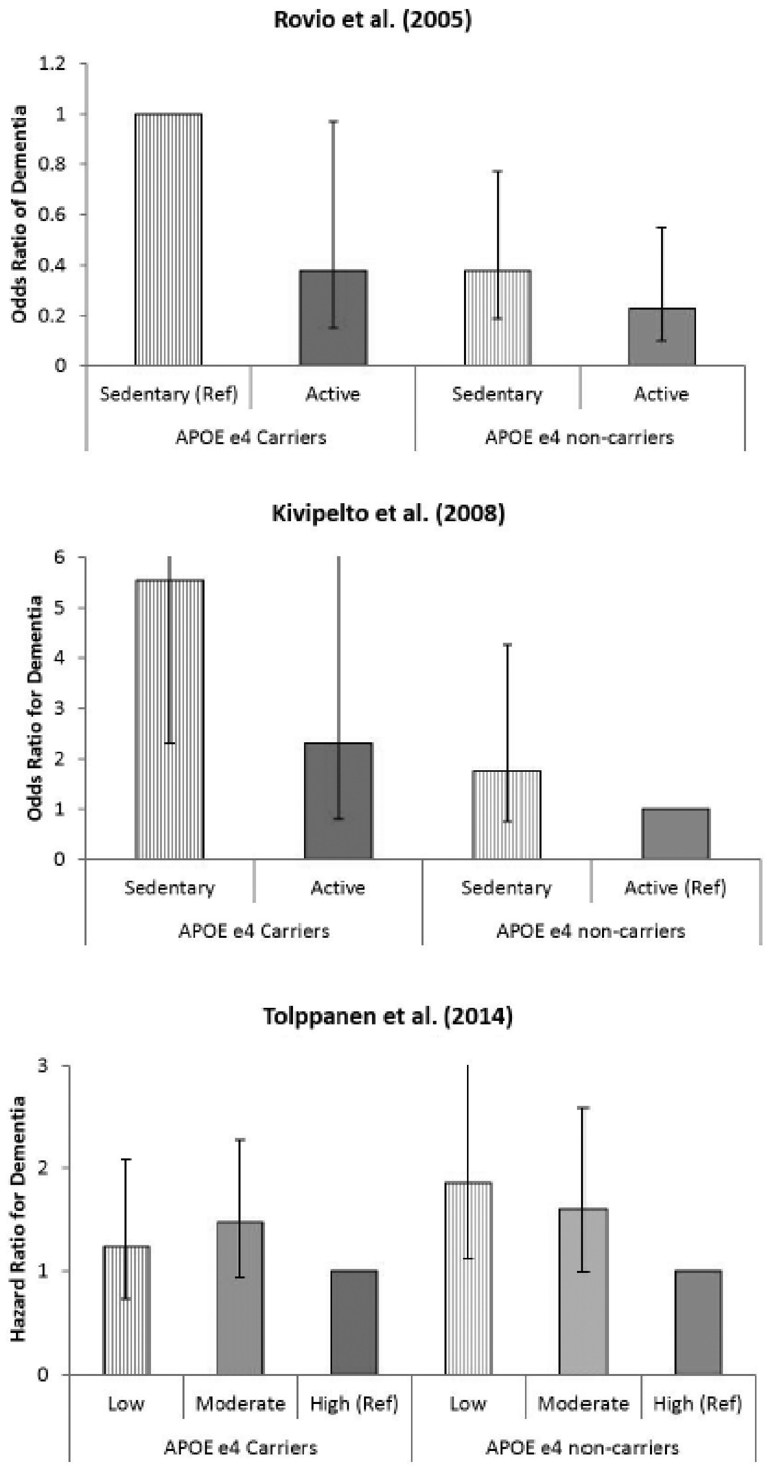

Figure 5. Results from prospective studies reporting on data from the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study. Note. Confidence interval for Kivipelto et al. (2008) sedentary *APOE* e4 carriers = [2.31-13.23] and for active *APOE* e4 carriers = [0.81-6.49]. Confidence interval for Tolppanen et al. (2014) low active *APOE* e4 non-carriers = [1.12-3.06]; Ref = referent group.

Three prospective studies reported on participants enrolled in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study in which leisure-time physical activity was assessed at baseline, and dementia and Alzheimer's disease were assessed at subsequent examinations (see Figure 5 for results from each publication). Rovio et al. (2005) and Kivipelto et al. (2008) reported on the findings from the first reexamination visit, which occurred approximately 21 years after baseline testing. Both Rovio et al. (2005) and Kivipelto et al. (2008) reported nonsignificant interaction terms for *APOE* on physical activity for the outcome of dementia, but then provided the stratified findings for the carriers and noncarriers. Both Rovio et al. (2005) and Kivipelto et al. (2008) reported that protective effects of physical activity for dementia are only evident for the *APOE* e4 carriers. Relative to the outcome of Alzheimer's disease, Rovio et al. (2005) reported a significant interaction term with results indicating that the risk of Alzheimer's disease is significantly reduced for active carriers but that there is no effect of physical activity for noncarriers. Kivipelto et al. (2008) also reported that associations for Alzheimer's disease were stronger, but they do not share those results in the publication. Tolppanen et al. (2014) collapsed together the data from the first and the second (approximately 7–10 additional years later) reexamination visits for CAIDE participants. Despite the larger sample size, the results of this study also indicated that the effects were not significantly moderated by *APOE* carrier status. However, the authors did report relationships between physical activity and dementia and reported that the risk of dementia was lowest for the high active group regardless of *APOE* carrier status.

Clearly it is difficult to bring this body of literature to consensus due to the relatively small number of studies, the wide range of follow-up times, the unique samples, and the variety of measures used for physical activity and for cognitive outcomes. In considering the reasons for the mixed results reported in the prospective studies, it is also perhaps important to mention that the decision of how to categorize the e2/e4 genotypes may influence the findings. As previously mentioned, the e2 allele is protective against Alzheimer's disease, thus the e2/e4 genotype consists of one protective allele and one allele that is associated with an increased risk of Alzheimer's disease. The e2/e4 genotype makes up approximately 3% of the population (McKay et al., 2011), and although studies are limited there is evidence that this group is at the same relatively low risk of Alzheimer's disease as are persons with the e3/e3 genotype (Corder et al., 1994; Corder et al., 1993). Thus, it seems that persons who are e2/e4 should be categorized as noncarriers. However, the e2/e4 genotype was included with the carriers in the Podewils et al. (2005) study and in the Niti et al. (2008) study, and how persons of this genotype were categorized is not explicitly stated in the other prospective studies. Hence, this is an additional source of variation that may have contributed to the heterogeneity of the results. That being said, both of the cross-sectional studies and four of the six prospective studies provide results supportive of the benefits of physical activity being most evident for persons at greatest genetic risk for Alzheimer's disease. If future evidence supports this interpretation of the current findings (i.e., that physical activity is most beneficial for those at greatest genetic risk for Alzheimer's disease), this will be critically important because it will provide additional evidence that physical activity may be an effective behavioral intervention in the prevention of Alzheimer's disease.

Summary and Conclusions

Overall, the extant literature clearly shows that regular participation in physical activity benefits cognitive performance for cognitively normal older adults, and there is some evidence that these benefits can also be obtained by cognitively impaired older adults. The literature also consistently shows that the *APOE* genotype moderates the relationship between physical activity and cognitive performance, but positive relationships have been observed for both carriers and noncarriers so future research will be necessary to improve our understanding of this effect. One important direction for future research is to consider other genetic predictors of Alzheimer's disease, which may interact with the *APOE* genotype in influencing the relationship between physical activity and cognitive performance. In addition, future research focused on mechanisms of the effects will certainly contribute to our ability to understand how to best implement a physical activity intervention with a goal of benefiting cognitive performance and delaying the experience of Alzheimer's disease. This is a critical direction for research as Brookmeyer, Gray, and Kawas (1998) reported that a treatment that delays the incidence of Alzheimer's disease by five years would reduce the incidence by 50%. Further, Barnes and Yaffe (2011) reported that a reduction in physical inactivity levels by 10% would decrease the number of people in the United States with Alzheimer's disease by 90,000 and a reduction in physical inactivity levels by 25% would result in a decrease of those with Alzheimer's by 232,000. In fact, their data indicate that reductions in physical inactivity would have a greater impact on the incidence of Alzheimer's disease than would changes in other modifiable factors such as hypertension, obesity, and smoking. Hence, it is critical for future research to further our understanding of how to use physical activity interventions to slow age-related cognitive decline and lessen the risk of MCI and Alzheimer's disease.

As a final comment, I would like to make a plea for funding agencies to commit additional resources to advancing our understanding of the potential role of exercise in mitigating age-related cognitive decline and reducing the risk of clinical cognitive impairment. In conducting this review of the literature, I was struck by the frequency with which the authors of reviews concluded that the literature is limited by the poor quality of the research and by the lack of sufficiently powered clinical trials. Although this is certainly an accurate characterization of the literature, I believe it is important to emphasize that this is not a reflection of the quality of the researchers working in this area, but rather is an indication of the lack of financial support directed toward understanding the effects of exercise on cognition.

As an example of the lack of financial support in this area, it seems important to point out that the largest funding agency of health research in the United States (the National Institutes of Health [NIH]) has historically demonstrated a lack of interest in research on exercise and cognitive performance. This is evidenced by the historic lack of program announcements (PAs) and requests for applications (RFAs) targeting this topic and by the general failure to include persons with exercise expertise on scientific review groups. There have been encouraging recent signs that there is now interest in exploring the benefits of physical activity for cognitive performance based upon the occasional RFAs that have explicitly encouraged applications focused on the effects of exercise on cognitive outcomes (e.g., RFA-AG-09-009 and RFA-AG-14-016). However, these RFAs were only offered for one cycle of funding and a current search of active RFAs and PAs available from the NIH indicated that 0 records were returned when exercise was entered as a keyword (search conducted on 10/22/2014). When physical activity was used as a keyword, 14 records were retrieved, with six of these providing funding through smaller funding mechanisms (R21, R03, R33) in parallel to the same call using a larger funding mechanism (R01). Hence, there were eight unique RFAs or PAs relative to physical activity. Of these eight, the focus is largely on the prevention of overweight and obesity (RFA-13-153, PA-13-110, PA-13-100, PAR-12-257, PAR-12-228), with other calls focused on physical activity assessment (RFA-AG-15-015, PAR-12-198) and physical activity promotion (PAR-14-315). Although these are clearly important directions for physical activity research, it is inexplicable that there is not a single active funding opportunity through the NIH supporting research on exercise (or physical activity) and cognitive performance. Given the evidence supporting the potential benefits of exercise for cognition and the current and projected personal and public health impact of age-related cognitive decline and of Alzheimer's disease in particular, it is critical that funding agencies provide adequate resources for well-designed sufficiently powered RCTs to be conducted in this area of research and that they place persons with exercise expertise on scientific review panels to ensure that the exercise programs are well-designed and logical based upon the extant literature.

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References

Alzheimer's Association. (2014). 2014 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 10*(2), 15-23.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual* (5th ed.). Washington, DC: Author.

Andel, R., Crowe, M., Pedersen, N.L., Fratiglioni, L., Johansson, B., & Gatz, M. (2008). Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 63*(1), 62-66. doi:10.1093/gerona/63.1.62

Angevaren, M., Aufdemkampe, G., Verhaar, H.J., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews, 2*, CD005381.

Barnes, D.E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurology, 10*(9), 819-828. doi:10.1016/S1474-4422(11)70072-2

Brookmeyer, R., Gray, S., & Kawas, C. (1998). Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *American Journal of Public Health, 88*(9), 1337-1342. doi:10.2105/AJPH.88.9.1337

Carvalho, A., Rea, I.M., Parimon, T., & Cusack, B.J. (2014). Physical activity and cognitive function in individuals over 60 years of age: A systematic review. *Clinical Interventions in Aging, 9,* 661-682.

Colcombe, S., & Kramer, A.F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science, 14*(2), 125‐130. doi:10.1111/1467-9280.t01-1-01430

Corder, E.H., Saunders, A.M., Risch, N.J., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Jr., . . .Pericak-Vance, M.A. (1994). Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nature Genetics, 7*(2), 180‐184. doi:10.1038/ng0694-180

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., . . . Pericak-Vance, M.A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science, 261*(5123), 921‐923. doi:10.1126/science.8346443

Daviglus, M.L., Plassman, B.L., Pirzada, A., Bell, C.C., Bowen, P.E., Burke, J.R., . . . Williams, J.W., Jr. (2011). Risk factors and preventive interventions for Alzheimer disease: state of the science. *Archives of Neurology, 68*(9), 1185‐1190. doi:10.1001/archneurol.2011.100

Deeny, S.P., Poeppel, D., Zimmerman, J.B., Roth, S.M., Brandauer, J., . . . Hatfield, B.D. (2008). Exercise, APOE, and working memory: MEG and behavioral evidence for benefit of exercise in epsilon4 carriers. *Biological Psychology, 78*(2), 179‐187. doi:10.1016/j.biopsycho.2008.02.007

Etgen, T., Sander, D., Huntgeburth, U., Poppert, H., Forstl, H., & Bickel, H. (2010). Physical activity and incident cognitive impairment in elderly persons: the INVADE study. *Archives of Internal Medicine, 170*(2), 186‐193. doi:10.1001/archinternmed.2009.498

Etnier, J.L., Caselli, R.J., Reiman, E.M., Alexander, G.E., Sibley, B.A., Tessier, D., & McLemore, E.C. (2007). Cognitive performance in older women relative to ApoE-epsilon4 genotype and aerobic fitness. *Medicine and Science in Sports and Exercise*, 39(1), 199‐207. doi:10.1249/01.mss.0000239399.85955.5e

Etnier, J.L., Salazar, W., Landers, D.M., Petruzzello, S.J., Han, M., & Nowell, P. (1997). The influence of physical fitness and exercise upon cognitive functioning: A meta-analysis. *Journal of Sport & Exercise Psychology, 19,* 249‐277.

Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R., . . . van Duijn, C.M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *Journal of the American Medical Association, 278*(16), 1349‐1356. doi:10.1001/jama.1997.03550160069041

Forbes, D., Thiessen, E.J., Blake, C.M., Forbes, S.C., & Forbes, S. (2013). Exercise programs for people with dementia. *Cochrane Database of Systematic Reviews, 12,* CD006489.

Gates, N., Fiatarone Singh, M.A., Sachdev, P.S., & Valenzuela, M. (2013). The effect of exercise training on cognitive function in older adults with mild cognitive impairment: A meta-analysis of randomized controlled trials. *The American Journal of Geriatric Psychiatry, 21*(11), 1086‑1097. doi:10.1016/j.jagp.2013.02.018

Hamer, M., & Chida, Y. (2009). Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence. *Psychological Medicine, 39*(1), 3‑11. doi:10.1017/S0033291708003681

Kivipelto, M., Rovio, S., Ngandu, T., Kareholt, I., Eskelinen, M., Winblad, B., . . . Nissinen, A. (2008). Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. *Journal of Cellular and Molecular Medicine, 12*(6b), 2762‑2771. doi:10.1111/j.1582-4934.2008.00296.x

McKay, G.J., Silvestri, G., Chakravarthy, U., Dasari, S., Fritsche, L.G., Weber, B.H., . . . Patterson, C.C. (2011). Variations in apolipoprotein E frequency with age in a pooled analysis of a large group of older people. *American Journal of Epidemiology, 173*(12), 1357‑1364. doi:10.1093/aje/kwr015

Middleton, L.E., Barnes, D.E., Lui, L.Y., & Yaffe, K. (2010). Physical activity over the life course and its association with cognitive performance and impairment in old age. *Journal of the American Geriatrics Society, 58*(7), 1322‑1326. doi:10.1111/j.1532-5415.2010.02903.x

Niti, M., Yap, K. B., Kua, E. H., Tan, C. H., & Ng, T. P. (2008). Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon 4 genotype in Chinese older adults. *International Psychogeriatrics, 20*(2), 237-251.

Ohman, H., Savikko, N., Strandberg, T.E., & Pitkala, K.H. (2014). Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review. *Dementia and Geriatric Cognitive Disorders, 38*(5-6), 347‑365. doi:10.1159/000365388

Podewils, L.J., Guallar, E., Kuller, L.H., Fried, L.P., Lopez, O.L., Carlson, M., & Lyketsos, C.G. (2005). Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology, 161*(7), 639‑651.

Rovio, S., Kareholt, I., Helkala, E.L., Viitanen, M., Winblad, B., Tuomilehto, J., . . . Kivipelto, M. (2005). Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *The Lancet Neurology, 4*(11), 705‑711.

Salthouse, T.A. (1998). Independence of age-related influences on cognitive abilities across the life span. *Developmental Psychology, 34*(5), 851‑864. doi:10.1037/0012-1649.34.5.851

Schroeder, D.H., & Salthouse, T.A. (2004). Age-related effects on cognition between 20 and 50 years of age. *Personality and Individual Differences, 36,* 393‑404. doi:10.1016/S0191-8869(03)00104-1

Schuit, A.J., Feskens, E.J., Launer, L.J., & Kromhout, D. (2001). Physical activity and cognitive decline, the role of apolipoprotein e4 allele. *Medicine and Science in Sports and Exercise, 33*(5), 772‑777.

Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., . . . Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosomatic Medicine, 72*(3), 239‑252. doi:10.1097/PSY.0b013e3181d14633

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G.F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *Journal of Internal Medicine, 269*(1), 107‑117. doi:10.1111/j.1365-2796.2010.02281.x

Tolppanen, A.M., Solomon, A., Kulmala, J., Kareholt, I., Ngandu, T., Rusanen, M., . . . Kivipelto, M. (2014). Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. *Alzheimer's & Dementia*. Epub ahead of print. doi:10.1016/j.alz.2014.01.008

Wang, C., Yu, J.T., Wang, H.F., Tan, C.C., Meng, X.F., & Tan, L. (2014). Non-pharmacological interventions for patients with mild cognitive impairment: A meta-analysis of randomized controlled trials of cognition-based and exercise interventions. *Journal of Alzheimer's Disease, 42*(4), 663‑678.