

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Developmental Review

journal homepage: www.elsevier.com/locate/dr

Review

Midlife risk factors for late-life cognitive decline

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ARTICLE INFO

Keywords:

Cognitive decline
Alzheimer's
Midlife risk

ABSTRACT

Cognitive aging is a distinct process of gradual change in cognitive function throughout the lifespan, with the most pronounced decline occurring in memory and reaction time during old age (Blazer, Yaffe, & Karlawish, 2015). A multitude of factors in midlife predict subsequent cognitive decline. This paper reviews research from five areas of midlife functioning that are associated with late-life cognitive impairment, ranging from mild decline to clinical manifestations of dementia. Within each area, risk and protective factors are discussed, and particular emphasis is placed on the ways in which these factors interact with the APOE genotype, a well-validated risk factor for cognitive decline (Poirier et al., 1993).

Introduction

Cognitive aging occurs as a series of gradual changes in cognitive functioning, beginning during early adulthood with declines in problem-solving and cognitive speed (Anstey & Low, 2004). Decline is most apparent in fluid abilities, while performance on measures of crystallized intelligence, such as vocabulary tests, continues to improve until age 60 or older (Salthouse, 2009). Although the slow rate of decline in fluid intelligence typically delays the appearance of cognitive impairment and diagnosis of dementia until late life, recent years have yielded an abundance of research on their midlife antecedents.

The focus of this review is on midlife risk factors that predict cognitive decline decades later. Because cognitive decline is best characterized as part of the normal aging process (Blazer et al., 2015), we primarily review longitudinal studies of cognitive aging in samples of healthy adults, though we also discuss research in which mild cognitive impairment (MCI) and late-onset Alzheimer's disease (AD) are included as outcomes. There is a line of research studying the progression of cognitive decline to dementia, but this topic is not a focus of this paper. Neither is early-onset AD, a hereditary disease caused by mutations in one of several genes (Chartier-Harlin & Crawford, 1991). We define midlife broadly, with the samples in the studies discussed here predominantly falling between the ages of 40 and 60. Neither childhood nor late-life risk factors are emphasized.

Spanning multiple domains, risk and protective factors in midlife differentially predict the presence and rate of subsequent cognitive decline. This review summarizes research related to cognitive reserve, personality, mental and physical wellbeing, and social support, all of which are associated with late-life cognitive functioning. Within the domain of cognitive reserve, we discuss the relationship of educational attainment and occupational status to later cognitive impairment. The section on personality focuses on several stable traits, particularly neuroticism, that have been identified as risk factors, while the section on mental health discusses the sequelae of disorders associated with high levels of neuroticism, including anxiety, depression, and bipolar disorder. The discussion of physical wellbeing addresses nicotine and alcohol use, body mass index (BMI), physical activity, and vascular risk factors, including hypertension, diabetes, and elevated cholesterol. Lastly, the section on social support discusses quantity and quality of social connections as predictors of decline.

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Genetic variants also contribute to cognitive decline. The best-validated finding is of the APOE4 allele, located on chromosome 19 within a region associated with AD (Poirier et al., 1993). There are three APOE alleles; the presence of the APOE4 variant increases risk of dementia additively, with the highest risk occurring in individuals with two copies of APOE4. Compared to homozygotes without the allele, those who are homozygous for APOE4 are more than eight times as likely to develop the disease (Corder et al., 1993). At a mechanistic level, carriers of APOE4 accumulate higher levels of amyloid β plaque in the cortex than non-carriers do, a change that precedes symptoms of AD (Selkoe, 2002). We will not review the literature on APOE4 as an independent risk factor, but we will discuss the ways in which the genotype interacts with other midlife risk and protective factors to affect cognitive performance in late life.

Methodological considerations

Because it is usually impossible to randomly assign human research participants to risk conditions, it is often difficult to infer causal mechanisms from mere statistical associations (Rutter, Pickles, Murray, & Eaves, 2001). Several threats to causal inference are particularly relevant to studies of midlife risk for late life cognitive decline. In the most limited study design that we will consider, individuals already in late life provide retrospective data about risk factors experienced many years before. Retrospective data of this kind are by their nature unreliable, and may be influenced by cognitive status at the time they are provided.

Prospective associations between risk factors and outcomes require longitudinal designs, in most cases with long intervals between assessment of risks at midlife and outcomes in late life. Even prospective longitudinal studies are still prone to bias, however, particularly selection bias (D'onofrio, Lahey, Turkheimer, & Lichtenstein, 2013). Research participants are not selected at random for exposure to risk conditions, and the selective factors that predispose some participants to risk can also be associated with later cognitive decline. Persistent poverty, for example, might be associated with both midlife risk factors and later decline, inducing statistical associations between the risks and the outcomes that are not in fact causal.

Another variety of selection bias is genetic. Most “environmental” risk factors are partially heritable (Plomin & Bergeman, 1991), and the same genetic factors that predispose individuals to risky behavior or environmental exposure in midlife may also be associated with cognitive decline later, once again inducing a statistical association that does not represent a causal process. In the case of either environmentally or genetically mediated selection, statistical control using measured covariates can only provide a partial solution, because it is difficult to specify a complete set of measured covariates to control for. The most powerful research designs use familial controls such as siblings or twins (Turkheimer & Harden, 2014). If a pair of identical twins is discordant for a midlife exposure, within-pair associations between midlife exposure and later cognitive ability control for both measured and unmeasured genetic and environmental factors shared by the twins. Whereas the majority of the studies reviewed in this paper are not genetically controlled due to the rarity of such designs in this area of research, we focus on longitudinal measures of within-individual change, allowing for evidence of sequence in outcomes. We also note the covariates included in each model.

Midlife risk factors for cognitive decline

Cognitive reserve

The cognitive reserve hypothesis seeks to explain individual variation in cognitive aging and incidence of dementia by proposing that factors such as intelligence and educational attainment affect resistance to brain damage during the aging process (Tucker-Drob, Johnson, & Jones, 2009). The theory rests on the finding that individuals vary considerably in the correlation between their neurological changes and cognitive impairment (Sattler, Toro, Schönknecht, & Schröder, 2012). High IQ, higher education, and occupational and recreational demands on intellect can serve as buffers against cognitive decline. Due to the scarcity of research linking measured midlife intelligence to subsequent cognitive decline, we focus on studies that use education and/or occupation as proxies for intellect. Although some of the studies we discuss are of elderly, not middle-aged, adults, education is completed early enough in life to qualify as a midlife risk factor, and occupational status is based on primary occupation, which is typically held during midlife.

Education

Two studies from the Kungsholmen Project, a longitudinal Swedish study of aging in people aged 75 years and older, provided evidence of cognitive reserve using a dichotomous classification of educational attainment in which participants with eight or more years of formal education were deemed highly educated. Qiu, Bäckman, Winblad, Agüero-Torres, and Fratiglioni (2001) found that participants in the low-education group had a relative risk of 2.6 of developing AD and 1.7 of developing any type of dementia, when controlling for age, sex, occupation-based socioeconomic status (SES), performance on the Mini-Mental State Examination (MMSE), and presence of vascular disease. Karp et al. (2004) also identified low educational attainment as a risk factor for AD; participants in the low-education group had a relative risk of 3.3 of developing AD and 2.4 of developing any type of dementia. Both studies examined education as a risk factor independent of occupation-based SES, suggesting a direct link between education and dementia.

Other studies used nonclinical samples. Rather than dichotomize educational attainment, Anttila et al. (2002) analyzed it as a continuous variable in a longitudinal, representative sample of the Finnish population ranging in age from 25 to 64 at the start of the study. In a follow-up assessment roughly 21 years later of a subset of these participants aged 65–79, fewer years of education predicted onset of dementia. The odds ratio (OR) was 0.817. Participants diagnosed with dementia had a mean of 6.9 years of education, while those who had not been diagnosed had a mean of 8.7 years.

Sattler et al. (2012) investigated cognitive decline in a 12-year, longitudinal study of participants grouped by their degree of

cognitive impairment. The sample, which had a mean age of 74 at the last wave of data collection, was comprised of a healthy control group, a group with mild cognitive impairment (MCI), and a group that was in an early stage of AD but not yet severely impaired. Upon finding that the average level of cognitive activity, defined by results on a five-item measure of participation in cognitive leisure activities, did not differ between the mildly impaired group and the group with Alzheimer's, the authors merged the two groups for analyses. Control participants had a mean of 13.7 years of education, while those with MCI and AD had means of 12.3 and 11.7 years, respectively.

Participants were divided into three groups based on level of education. High educational attainment, defined as greater than 15 years of formal education, served as a protective factor against cognitive impairment, measured by the Mini Mental State Examination. When comparing the moderate and high educational groups, the OR for MCI/AD was 0.25, while it was 0.15 when comparing the low and high educational groups. By contrast, low educational attainment (< 10 years of education) did not emerge as a risk factor when compared to moderate educational attainment. The studies discussed earlier did identify low educational attainment as a risk factor. The discrepancy may be due to their differing definitions of low versus high attainment. Two of the studies classified participants with greater than eight years of formal education as highly educated, while a similar classification in this study required 15 years of education. None of the other studies reviewed here divided educational attainment into three categories.

Occupation

Studies of midlife occupation focus on type of work, level of prestige, and income, all of which correlate with educational attainment. Therefore, the studies that are most useful in establishing a direct link between occupation and cognitive reserve control for level of education. The majority of studies define occupational status based on primary occupation, or the job that was held the longest. There is considerable variation in the classification assigned to housewives, with some studies excluding them from analyses and others considering them to have held no occupation. In analyses of SES based on income, housewives are typically classified according to their husband's income.

In the study of education cited earlier, Anttila et al. (2002) divided midlife occupational status into three categories: sedentary occupation, physical occupation, and no occupation. Participants with a sedentary occupation were at lower risk of dementia compared to those in the other two categories, although the analyses did not control for intelligence or educational attainment. The OR of developing dementia was set at 1 for participants with a sedentary occupation. Those with no occupation had an OR of 1.802, and those with a physical occupation had an OR of 2.065. Low income in old age, not midlife, was a risk factor for dementia, suggesting that the association is the result of dementia decreasing one's ability to work. Housewives were classified as having no occupation.

Andel et al. (2005) obtained retrospective reports of midlife occupation from members of the Swedish Twin Registry, aged 65 and older. Occupational complexity was classified according to requisite work with data, people, and things, based on ratings from the *Dictionary of Occupational Titles*. In all dementia-discordant twin pairs, the OR associated with complexity of work with people was 0.47; in AD-discordant twin pairs, the OR was 0.05. In dementia-discordant monozygotic (MZ) twin pairs, the OR was 0.27. Complexity of work with data also predicted lower incidence of AD; in discordant MZ and dizygotic (DZ) twins, the OR was 0.17. The relationship was not significant in MZ twins alone, although the sample size of 17 pairs may have been too small to detect an effect. The study does not make reference to the classification of housewives.

Consistent with the results discussed above on occupational status, a study of World War II veteran male twins from the NAS-NRC registry found that occupational characteristics predicted incidence of dementia (Potter, Helms, Burke, Steffens, & Plassman, 2007). Born between 1917 and 1927, participants reported occupational history and were screened for dementia using the TICS-m, a modified version of the Telephone Interview for Cognitive Status, at several waves during the 1990s. Occupational status was based on primary occupation, which was classified according to the *Dictionary of Occupational Titles*. In twin pairs discordant for dementia onset by six or more years, jobs that required higher levels of language, reasoning, mathematics, and vocational training were associated with lower risk of dementia. The hazard ratios (HRs) ranged from 0.599 (language) to 0.631 (math). Of the 220 twin pairs, 112 were monozygotic. Although the authors reported larger effect sizes for MZ pairs than DZ pairs, zygosity was not significantly associated with the results, which were consistent with the notion that job complexity directly enhances cognitive reserve. Because the sample only included men, no participants were classified as housewives.

In the study of education cited previously, Karp et al. (2004) found that low SES at ages 20, 40, and 60, classified according to primary occupation, did not predict AD in participants aged 75 years and older when educational background was included in the model. Neither did socioeconomic mobility. Housewives were classified according to their second-longest-held occupation; those who had not held another job were excluded from analyses.

In a follow-up study of the same sample, however, Karp et al. (2009) evaluated primary occupation using the Nordic Occupational Classification system and found that complexity of work with data and/or people predicted lower incidence of AD, with relative risks of 0.85 and 0.88, respectively. The results were not significant after controlling for education, though less educated participants (< 8 years of formal education) whose work was coded as requiring the highest level of complex data analysis were at lower risk of AD compared to their counterparts whose work was less demanding; relative risk was 0.52. Housewives were classified as housekeepers, a job rated low in complexity, but results were unchanged when analyses excluding housewives were repeated in a subsample. Taken together, these two studies suggest a relationship between occupational status and cognitive performance in old age that is at least partially explained by education, although a highly complex job may mitigate some of the effects of low education.

Britton, Shipley, Singh-Manoux, and Marmot (2008) found that midlife SES, based on a combination of salary and work role in the civil service, predicted successful aging, defined as entering old age in the top third of cognitive and physical functioning and free of major diseases. Part of the Whitehall II study of SES and health outcomes in British civil servants, 5963 men and women ranging from

35 to 55 years old were followed for 17 years. At the end of this period, cognitive functioning was assessed using the Alice Heim 4-I cognitive test. Researchers also assessed walking speed and lung function and calculated a physical health score using the Short Form (36) Health Survey. Participants who scored in the top third of their respective gender distribution on at least three of the four measures were considered to be aging well. Adjusting for age and classifying SES as high, medium, or low, participants in the high SES group had an OR of 7.06 of aging successfully compared to those in the low SES group, although the analyses did not control for education. Because all participants worked in the civil service, none were classified as housewives.

Interaction of cognitive reserve with APOE genotype

Studies have reported mixed results regarding the interactions among APOE4 carrier status, cognitive reserve, and subsequent decline. Anttila et al. (2002) found no interaction between APOE status and several measures of cognitive reserve, including education, occupation, and income. Carrier status, educational attainment, and occupational status contributed to AD risk independently. Potter et al. (2007) also found no interaction of APOE genotype with occupation.

Using a between-siblings, quasi-experimental design, Cook and Fletcher (2015) found the opposite; in comparison to high school graduates, college graduates with one or two copies of the APOE4 allele did not show the decline in cognitive ability often seen in carriers. Cognitive decline was defined as change in performance between the ages of 64 and 72 on three cognitive tests measuring letter fluency, similarities, and word recall. After controlling for IQ, income, and personality traits, they proposed that the interaction was due to an enhancement of cognitive processes through formal education. The discrepant results may relate to their methodologies. Anttila et al. (2002) and Potter et al. (2007) examined dementia status, not cognitive decline. It is possible that the moderating role of cognitive reserve is more apparent when the outcome is not measured dichotomously.

Summary

Two measures of midlife cognitive reserve— educational attainment and occupational complexity— have been consistently linked to dementia and AD. Although the four studies of education discussed above use different definitions of high and low attainment, all link years of education to cognitive impairment in old age (Qiu et al., 2001; Karp et al., 2004; Anttila et al., 2002; Sattler et al., 2012). None of the studies, however, are in twin samples, so they do not control for preexisting differences that could be correlated with both education and late-life cognitive performance. Occupational characteristics and income predict incidence of dementia and AD (Anttila et al., 2002; Karp et al., 2009), as well as cognitive performance in a nonclinical sample of older adults (Britton et al., 2008). Two twin studies provide evidence of a causal relationship between occupational complexity and incidence of dementia and AD (Andel et al., 2005; Potter et al., 2007). Education may mitigate some of the effects of the APOE4 allele on cognitive performance in old age (Cook & Fletcher, 2015), although results are mixed (Anttila et al., 2002). There is little evidence to suggest an interaction between occupational complexity and APOE genotype (Potter et al., 2007). See Table 1 for a summary of studies on cognitive reserve.

Personality

The five-factor model is the most widely used empirical model of personality, reducing an innumerable quantity of traits to five core dimensions: openness, conscientiousness, extraversion, agreeableness, and neuroticism (Goldberg, 1990). Researchers have found that four of the five domains show associations between midlife personality and late-life cognitive performance.

Neuroticism & extraversion

The most robust link between midlife personality and cognitive decline involves neuroticism, or tendency to experience negative emotions (Costa, Mitter, & McCrae, 1994). A relatively stable trait, neuroticism is hypothesized to serve as an indicator of cumulative distress experienced in one's lifespan (Duberstein et al., 2011). Extraversion, or sociability, is often assessed in conjunction with neuroticism in studies of cognitive aging. In a sample from the Swedish Twin Registry, Crowe, Andel, Pedersen, Fratiglioni, and Gatz (2006) found that midlife neuroticism, assessed by a modified form of the Eysenck Personality Inventory (EPI) in participants in their 40s, predicted cognitive impairment 25 years later. Participants were classified as either impaired or unimpaired based on performance on the TELE cognitive screening instrument and the Blessed Dementia Rating Scale (BDRS). Analyses controlled for age, gender, and education. Results were significant in the case-control analyses (OR = 1.09) but not the co-twin control analyses (OR = 1.06), indicating that genetic and/or shared environmental factors may contribute to the association, although the similar odds ratios render it unlikely that the association is entirely due to these factors.

In the same study, the combination of high neuroticism and low extraversion, a personality type indicative of anxiety, was associated with significantly greater risk of cognitive impairment in the co-twin control analyses (OR = 2.81), while moderate extraversion served a protective function (OR = 0.48). Both of these trends were identified in the case-control analyses but were not statistically significant when controlling for smoking status, alcohol-use, and self-reported health. High neuroticism combined with high extraversion, indicative of impulsivity, carried the greatest risk of impairment in the case-control analyses (OR = 2.09) but did not significantly predict impairment in the co-twin control analyses (OR = 1.61), suggesting genetic and/or familial mediation rather than direct causality. Participants low in neuroticism and high in extraversion formed the reference group. Neuroticism and extraversion were dichotomized based on median scores. Co-twin analyses were based on results from 113 twin pairs discordant for cognitive impairment; the paper does not specify the number of pairs that were monozygotic.

Johansson et al. (2014) followed a sample of 800 middle-aged women for 38 years. Participants who reported high levels of neuroticism on the EPI were at greater risk of AD (OR = 1.04); the relationship was mediated by level of long-standing distress, assessed by self-report at each follow-up session. Extraversion by itself did not predict AD status but, consistent with the results from

Table 1
Summary of studies reviewed on cognitive reserve.

Study authors	Sample size	Cognitive reserve measure	Sample age at cognitive reserve measure	Outcome measure	Sample age at outcome measure (or number of years later)	Outcome
Qiu, Bäckman, Winblad, Agüero-Torres, and Fratiglioni (2001)	983	Education (low < 8 years, high ≥ 8 years)	75 years and older	AD and dementia diagnoses	80 years and older (roughly 5 years later)	Low education predicts diagnoses
Karp et al. (2004)	931	Education (low < 8 years, high ≥ 8 years); SES based on primary occupation	75 years and older	AD and dementia diagnoses	80 years and older (roughly 5 years later)	Low education predicts AD; low SES does not
Anttila et al. (2002)	1449	Years of education; occupational status; income; APOE genotype, defined by presence of absence of APOE4 allele	25–64	Dementia diagnosis	65–79	Fewer years of education predicted dementia. Sedentary occupation was associated with lower risk. Midlife income did not predict outcome. No interaction between APOE and any measure of cognitive reserve
Sattler et al. (2012)	381	High (> 15 years), medium (10–15 years), and low (< 10 years) educational attainment	62 (mean age)	MMSE	74 (mean age)	High education is a protective factor
Andel et al. (2005)	10,079 (2622 twin pairs)	Occupational history coded by complexity of work with data, people, and things	N/A	Dementia, AD	65+	Complexity of work with people was associated with lower incidence of dementia within twin pairs. Complexity of work with people and data was associated with lower incidence of AD within twin pairs
Potter et al. (2007)	220 twin pairs	Occupational history coded by work characteristics of primary occupation	70–80	TICS-m	70–80	Job characteristics were associated with dementia incidence in dementia-discordant twin pairs. There was no interaction with APOE genotype
Karp et al. (2009)	931	Primary occupation; education (low < 8 years, high ≥ 8 years)	75 years and older	AD diagnosis	75 years and older	Less educated participants with complex work were at lower risk of AD
Britton et al. (2008)	5963	High, medium, and low SES based on salary and work role in the civil service	35–55	Alice Heim 4-I test; walking speed; lung function; Short Form (36) Health Survey	52–72	High SES predicted successful aging
Cook and Fletcher (2015)	467 sibling pairs	APOE genotype, defined by number of copies of APOE4; education (high school versus college graduates)	64	Cognition score based on 3 measures: letter fluency, similarities, word recall	72	The expected cognitive decline was not seen in APOE4 carriers who had graduated from college

Crowe et al. (2006), the combination of high neuroticism and low extraversion conferred the greatest risk of AD (OR = 1.98). Participants low in neuroticism and high in extraversion formed the reference group. High and low were defined as scoring in the highest or the lowest quartile of the trait. Because women consistently report higher levels of neuroticism than men (Lynn & Martin, 1997), generalization from an all-female sample should be interpreted with caution.

In a midlife sample that included men and women from the Baltimore Epidemiologic Catchment Area study, Hock et al. (2014) found that participants (mean age = 45.2) who scored higher on the neuroticism subscale of the Revised NEO Personality Inventory (NEO PI-R) exhibited greater decline in scores on the MMSE at a follow-up session roughly 11 years later. Neuroticism also predicted decline in performance on an immediate word recall task, but the relationship was no longer significant after adjusting for demographic and health-related covariates. Personality scores were standardized to a mean of 50 with a standard deviation of 10. Scores on the MMSE ranged from 0 to 30, and scores on the immediate word recall task ranged from 0 to 20. Each 10-point increase in neuroticism at baseline predicted a 0.15-point decline on the MMSE at follow-up. In a sample from the Baltimore Longitudinal Study of Aging (mean age = 56.5), participants scoring in the highest quartile of neuroticism using the NEO PI-R had an HR of 3.1 compared to those in the lowest quartile when assessed for AD, on average, 12 years later (Terracciano et al., 2014).

All of the studies of neuroticism discussed above controlled for years of education. There does not appear to be a significant relationship between neuroticism and intelligence (Crowe et al., 2006; Eysenck, 1971; Lynn & Gordon, 1961). The link between neuroticism and cognitive decline is often attributed to a compromising effect of chronic distress on brain structures, particularly in the limbic system, which regulates memory and response to stress (Wilson et al., 2007). In addition, psychological distress predicts an increase in production of interleukin-6, a cytokine that promotes inflammation and is associated with symptoms of AD (Crowe et al., 2006).

Conscientiousness

Few studies assess the long-term correlates of midlife conscientiousness, the tendency to be organized and goal-directed. In the Baltimore Epidemiologic Catchment Area study, participants who scored higher in conscientiousness on the NEO PI-R performed better on the MMSE and on an immediate word recall task at a follow-up assessment roughly 11 years later (Hock et al., 2014). Each 10-point increase in conscientiousness at baseline predicted a 0.18-point improvement on the MMSE and a 0.21-point improvement on the immediate word recall task at follow-up. No interaction was found between conscientiousness and any other personality domain. Analyses adjusted for baseline cognitive performance.

In the Baltimore Longitudinal Study of Aging, participants in the lowest quartile of conscientiousness had an HR of 3.26 for AD compared to those in the highest quartile (Terracciano et al., 2014). No interaction was found between conscientiousness and neuroticism in predicting AD. Analyses controlled for education but not cognitive ability. Taken together, these studies provide preliminary evidence of a protective role of conscientiousness in maintaining or improving cognitive performance late in life, potentially mediated by the tendency among conscientious individuals to engage in healthy behaviors (Hock et al., 2014; Terracciano et al., 2014).

Openness

Openness, defined as pursuing novel ideas and experiences (McCrae & Costa, 1999), appears to relate to cognitive performance at all ages. In a middle-aged and elderly sample from the Swedish Twin Registry, Sharp, Reynolds, Pedersen, and Gatz (2010) found that higher openness, measured using six items from the NEO Personality Inventory, predicted better performance on a battery of 13 cognitive tests measuring verbal and spatial skills, memory, and processing speed, administered to participants five times over 20 years. At each wave, twin pairs who had turned 50 were added to the sample. Correlations between openness and performance on each cognitive measure ranged from 0.13 (processing speed in women at Wave 6) to 0.47 (processing speed in men at Wave 5). Results were similar in men and women, and the relationship was consistent across the age range. Openness did not predict rate of decline. It appeared to have a protective function throughout the lifespan, which the authors speculated may be due to cognitive reserve, such that individuals scoring above average on a measure of openness may engage more frequently in cognitive leisure activities.

In the Baltimore Epidemiologic Catchment Area study, Hock et al. (2014) found that participants high in openness scored better on the MMSE and the immediate and delayed word recall tasks 11 years later, but the results were not significant in the fully adjusted model. Because the study assessed cognitive decline rather than baseline ability, these results are not inconsistent with those reported by Sharp et al. (2010). There is little evidence that openness predicts rate of cognitive decline in old age.

Agreeableness

Hock et al. (2014) found that agreeableness predicted performance on the delayed word recall task in the fully adjusted model. Using the same 50-point scale described earlier, each 10-point increase in agreeableness at baseline predicted a 0.20-point increase on the task at follow-up. The relationship between agreeableness and performance on the MMSE and immediate word recall task was not significant, and there is otherwise little evidence that midlife agreeableness predicts late-life cognitive performance.

Interaction of personality with APOE genotype

Little research has explored midlife personality in conjunction with APOE genotype. Two of the studies discussed above genotyped participants. Johansson et al. (2014) controlled for presence or absence of the APOE4 allele in a subsample of 306 participants and found the same association between elevated neuroticism and AD diagnosis that was identified in the unadjusted model. They did not appear to test for any interactions. Terracciano et al. (2014) also included APOE genotype as a covariate and found little change

in the results described above for neuroticism and conscientiousness. They did report an interaction of the genotype with openness and agreeableness; elevated openness served a protective role in APOE4 carriers, and elevated agreeableness served a protective role in non-carriers. HRs for the interaction terms were 0.58 and 1.87, respectively. No significant interactions with the other three personality factors were found. A line of research has identified interactions related to neuroticism, extraversion, and conscientiousness in other age groups (Dar-Nimrod et al., 2012; Kunz, Reuter, Axmacher, & Montag, 2017), but the findings have yet to be replicated in studies that assessed personality during midlife.

Summary

Several personality traits, measured in midlife, predict cognitive decline in late-life. The combination of high neuroticism and low extraversion appears to confer the greatest risk of cognitive impairment, a relationship that remained significant in a discordant twin sample (Crowe et al., 2006). High neuroticism, independently and in combination with high extraversion, also predicts cognitive decline, but these relationships may be the result of genetic and/or familial confounding (Crowe et al., 2006; Johansson et al., 2014; Hock et al., 2014). Two studies provide preliminary evidence that high conscientiousness predicts better cognitive performance and lower incidence of AD (Hock et al., 2014; Terracciano et al., 2014), although the studies were not genetically informed. Openness predicts cognitive performance at all ages but not rate of late-life decline (Sharp et al., 2010; Hock et al., 2014), while agreeableness has not been found to predict impairment. Only midlife openness and agreeableness have been found to interact with APOE genotype, such that high openness protects against AD in APOE4 carriers and high agreeableness has a similar protective role in non-carriers (Terracciano et al., 2014). See Table 2 for a summary of studies on personality.

Mental health

Consistent with the research identifying neuroticism as a risk factor, disorders associated with high levels of the trait, including anxiety and depression, predict cognitive decline. Because anxiety and depression are highly comorbid (Fava et al., 2000), we note whether studies of each disorder control for symptoms of the other. Research on the mental health-related antecedents of cognitive impairment has focused on depression as a risk factor more so than anxiety, so studies of anxiety often control for depressive symptoms, while the reverse is rarely true. The studies of depression we discuss control for a variety of demographic and health-related factors, but not anxiety. Studies of elderly samples include retrospective reports that assess mental health symptoms and diagnoses during midlife. We also review research on other forms of psychopathology, including bipolar disorder and schizophrenia, which have been linked to cognitive decline in psychiatric patients.

Anxiety

A limited amount of research has explored midlife anxiety as a risk factor for cognitive impairment. In a study of men in late middle-age, Gallacher et al. (2009) found that anxiety, measured on the Spielberger State Trait Anxiety Inventory, predicted dementia 17 years later, with an OR of 2.37. Participants were screened using a battery of cognitive assessments and were diagnosed according to DSM-IV criteria. The study did not control for depressive symptoms.

In a genetically informed study of adults in late middle-age, participants from the Swedish Twin Registry who reported a high level of anxiety on the State-Trait Personality Inventory (STPI) were at greater risk of dementia over a 28-year follow-up (Petkus et al., 2016). Controlling for depressive symptoms, measured on the Older American Resources and Services depression subscale, and neuroticism, measured on the EPI, the HR was 1.04, a small effect that was significant in this sample of 1082 participants. The anxiety subscale of the STPI contains 10 items, each of which is scored on a Likert scale from 1 to 5. Higher scores indicate greater anxiety. In the 63 twin pairs discordant for dementia, the mean baseline score on the STPI for those without dementia was 17.11, and for those with dementia was 21.01. The relationship between anxiety and dementia was significant in dizygotic twins (HR = 1.11) but not in monozygotic twins, suggesting a role of genetic mediation rather than direct causality.

Both of these studies classified anxiety by either clinical diagnosis or performance on scales measuring general levels of the trait. They did not divide anxiety by subtype when assessing its association with cognitive decline. The subtypes may differentially predict cognitive performance in old age and operate through varying mechanisms. Subsequent research should explore the relationship of each anxiety subtype to cognitive decline, because each subtype has its own characteristic pattern of symptoms and correlates (Nitschke, 1998).

Depression

Late-onset depression has been implicated as a prodromal symptom of dementia (Herbert & Lucassen, 2016). Studies exploring the sequelae of depression beginning in midlife provide evidence of its role as an independent risk factor. Most studies focus on major depressive disorder (MDD), rather than other subtypes of depression. Discussion of a potential causal role of depression with respect to dementia centers around the glucocorticoid cascade hypothesis, which proposes that the prolonged stress associated with MDD results in an increased secretion of glucocorticoids, a class of anti-inflammatory steroids, causing neuronal death in the hippocampus (Sapolsky, Krey, & McEWEN, 1986). Future research, however, is needed to clarify causal mechanisms.

In a case-control study of individuals with AD and their affected relatives, Green et al. (2003) found a significant relationship between depression and AD, with an adjusted OR of 2.13. Participants were classified as having been depressed if they answered 'yes' to a question asking if they had ever experienced an episode of depression. Unaffected participants answered on behalf of their affected relatives. All participants were older than 50; the mean age was 70.2. While some participants' history of depression occurred during old age, a subset of 398 experienced symptoms more than 15 years before AD onset. These participants constitute our

Table 2
Summary of studies reviewed on personality.

Study authors	Sample size	Personality measure	Sample age at personality measure	Outcome measure	Sample age at outcome measure	Outcome
Crowe et al. (2006)	4039 (113 twin pairs)	EPI-Q	40–49	TELE cognitive screening instrument; Blessed Dementia Rating Scale AD diagnosis	65–74 (mean age of 69)	High neuroticism, by itself and in combination with low extraversion, predicts impairment. Moderate extraversion is protective High neuroticism, by itself and in combination with low extraversion, predicts AD
Johansson et al. (2014)	800	Eysenck Personality Inventory NEO PI-R	38–54	MMSE; Immediate and delayed word recall tasks	38 years later Roughly 11 years later	High neuroticism predicts decline on the MMSE. High conscientiousness predicts improvement on the MMSE and the immediate word recall task. High agreeableness predicts improvement on the delayed word recall task
Hock et al. (2014)	561	NEO PI-R	45.2 (mean age)	AD	1–22 years later (mean = 12 years later)	High neuroticism and low conscientiousness predict AD
Terracciano et al. (2014)	1671	NEO PI-R	56.5 (mean age)	Performance on cognitive test battery	54–95	Openness predicts cognitive performance during the second half of the lifespan
Sharp et al. (2010)	857	NEO-PI	50–88			

midlife sample. Analyses were stratified based on timing of depressive symptoms. Consistent with research identifying depression as a prodrome of dementia, a strong relationship existed when depressive symptoms occurred within one year prior to AD diagnosis (OR = 4.57). The relationship was smaller but persisted for the 234 participants whose depression occurred more than 25 years prior to AD diagnosis (OR = 1.71). For participants whose depression occurred more than 15 years before AD onset, the OR was 1.58, implicating depression prior to old age as a risk factor.

In a retrospective study of a non-demented, elderly sample, participants who had experienced early-onset depression, occurring at a mean age of 45, were at greater risk of developing AD when assessed at follow-up sessions up to eight years after baseline measures were taken (Geerlings, den Heijer, Koudstaal, Hofman, & Breteler, 2008). The HR was 3.76. History of depression was classified according to whether a participant had experienced an episode requiring counseling or medical treatment. The authors assessed structural changes in the hippocampus and amygdala using MRI but found that they did not mediate the association between depression and AD, though they note that their sample may have included an insufficient number of severe cases of depression to identify a relationship. Participants whose onset of depression occurred at age 60 or older were also at greater risk of AD (HR = 2.34). Early and late onset were defined dichotomously; the study did not explore the sequelae of chronic depression.

In a prospective study, Dotson, Beydoun, and Zonderman (2010) followed a sample of adults (mean baseline age = 55.5) for an average of 25 years to assess the relationship between number of depressive episodes and subsequent MCI and dementia. Depression was assessed every one to two years using the Center for Epidemiologic Studies Depression Scale. Each episode of depression conferred a greater risk of dementia, with an HR of 1.87 after one episode and an HR of 2.08 after two or more. Incidence of MCI was unrelated to depressive history. An average of 5.92 years elapsed between first depressive episode and diagnosis of dementia, which, coupled with the dose-dependent relationship identified in the study, points to a role of depression in conferring risk for dementia that exists apart from its status as a prodrome.

Other psychopathology

A small line of research has focused on other forms of psychopathology as possible predictors of cognitive decline. Bipolar disorder in midlife has been implicated as a risk factor for cognitive decline and dementia. In a study of psychiatric bipolar patients (mean baseline age = 52), the number of affective episodes was associated with subsequent dementia, diagnosed upon readmission to the hospital (Kessing & Andersen, 2004). Excluding participants whose last affective episode occurred within one year of dementia diagnosis, each episode was associated with an 8% greater risk of dementia. Likewise, a retrospective study of an elderly Taiwanese sample found that participants with a history of bipolar disorder were at greater risk of dementia (Wu et al., 2013). In an effort to control for the presence of prodromal bipolar disorder, they repeated the analyses in subgroups with differing latency periods. Participants with one year between bipolar and dementia diagnoses had an OR of 3.89, while participants with five years between diagnoses had an OR of 4.15. ORs for two and three-year latency periods were similar. These studies provide preliminary evidence supporting bipolar disorder as a risk factor for dementia, although future research is needed to assess dementia incidence after longer periods of latency.

Schizophrenia may also confer risk for cognitive impairment. In a case-control study of Australian dementia patients, those who had a history of schizophrenia, occurring between ages 30 and 65 and at least 10 years prior to dementia onset, were at greater risk of dementia in late life (Zilkens, G Bruce, Duke, Spilsbury, & B Semmens, 2014). The adjusted ORs for participants aged 65–69, 70–74, and 75–79 were 12.07, 6.67, and 3.69, respectively. In a large, population-based Danish study, participants with a history of schizophrenia were more than twice as likely as those without to develop dementia (Ribe et al., 2015). The mean age of schizophrenia onset was 44.6, and the mean age of dementia onset was 80.6. The increase in risk was particularly pronounced in individuals younger than 65, a finding that the authors suggest may be due to the accelerated aging of the brain identified in some schizophrenics.

Interaction of mental health with APOE genotype

Little research has explored interactions with the APOE genotype in anxious, bipolar, or schizophrenic patients. The genotype does not appear to moderate the relationship between midlife depression and late-life cognitive decline. Steffens et al. (1997) found no evidence of an interaction between prior diagnosis of MDD and APOE genotype in predicting AD in a sample of elderly twins. Likewise, Green et al. (2003) repeated their analyses controlling for the presence or absence of the APOE4 allele in a subset of 1918 participants and found no meaningful difference in results.

Burke, Maramaldi, Cadet, and Kukull (2016) found no interaction between lifetime depression, defined as self-reported depression occurring more than two years prior, and APOE genotype, when comparing heterozygotes, homozygotes, and non-carriers. The outcome of interest was AD.

Summary

Internalizing disorders at midlife predict late-life dementia and AD. Although preliminary research implicates anxiety as a risk factor (Gallacher et al., 2009), the association may be genetically mediated (Petkus et al., 2016). The association between depression and dementia does not appear to be merely prodromal, because depressive episodes prior to old age have been identified as having a dose-dependent relationship with dementia (Dotson et al., 2010). Limited research has explored midlife bipolar disorder and schizophrenia as predictors of dementia. Both have been identified as risk factors (Kessing & Andersen, 2004; Wu et al., 2013; Zilkens et al., 2014); schizophrenia in particular may predict early-onset dementia (Ribe et al., 2015). The studies of depression, bipolar disorder, and schizophrenia discussed in this paper do not control for genetic or familial confounding. There does not appear to be an interaction between depression and APOE genotype (Steffens et al., 1997; Green et al., 2003; Burke et al., 2016). Little research has

Table 3
Summary of studies reviewed on mental health.

Study authors	Sample size	Mental health measure	Sample age at mental health measure	Outcome measure	Sample age at outcome measure	Outcome
Gallacher et al. (2009)	1160	Spielberger State Trait Anxiety Inventory	48–67	Dementia	17 years later	Trait anxiety predicts dementia.
Peikus et al. (2016)	1082 (63 discordant twin pairs)	STPI, anxiety subscale	60.86 (mean age)	Dementia	28 years later	Anxiety predicts dementia, but common genetic factors partially mediate
Green et al. (2003)	4046	Single question assessing experience of episodic depression; APOE genotype	1 to 25 years prior to AD diagnosis	AD	70.2 (mean age)	Depression predicts AD decades later. Stratification by APOE genotype did not modify results
Geerlings et al. (2008)	486	Self-reported history of depression requiring counseling or medical treatment	45.8	AD	Up to 8 years later	History of depression predicts AD
Dotson et al. (2010)	1239	Depression assessed with the Center for Epidemiologic Studies Depression Scale	55.5 (mean age)	MCI and dementia	24.7 years later (on average)	History of depression predicts dementia but not MCI
Kessing and Andersen (2004)	22,974	Bipolar diagnosis, number of episodes	52.0 (mean age)	Dementia	N/A	Bipolar episodes predict dementia
Wu et al. (2013)	64,804	Bipolar disorder diagnosis	N/A	Dementia	74.1 (mean age)	Bipolar disorder predicts dementia, often with onset before age 65
Zilkens, G Bruce, Duke, Spilsbury, and B Semmens (2014)	27,136	Schizophrenia diagnosis	30–65 (48.6 = mean age)	Dementia	65–84	Midlife schizophrenia predicts dementia in late life
Ribe et al. (2015)	> 2.8 million	Schizophrenia diagnosis	44.6	Dementia	80.6	Midlife schizophrenia predicts dementia in late life and before age 65
Burke et al. (2016)	8762	Self-reported depression more than 2 years prior; APOE genotype	N/A	AD	71.2	There was no interaction between lifetime history of depression and APOE genotype

explored such an interaction in patients with anxiety, bipolar disorder, or schizophrenia. See [Table 3](#) for a summary of studies on mental health.

Physical health

A large portion of the research on midlife risk factors has focused on physical health. Several domains have emerged as robust predictors of cognitive decline, notably nicotine and alcohol use, BMI, physical activity, and vascular health.

Nicotine use

[Galanis et al. \(1997\)](#) followed a sample of Japanese-American men from the Honolulu Heart Program from 1965 until 1993. Participants who had smoked continuously from the beginning of the study until the second follow-up between 1971 and 1974, during which the mean age was 58.6, scored significantly lower on the CASI at the final examination between 1991 and 1993. Scores on the CASI range from 0 to 100; participants scoring below 82 were classified as cognitively impaired. Using this dichotomous classification and comparing to a reference group of never-smokers, the OR associated with continuous smoking during midlife was 1.36, after controlling for age, education, and midlife alcohol consumption. The OR in smokers who quit during midlife was also 1.36. In a model that adjusted for BMI and several vascular covariates, the relationship was attenuated but remained significant in continuous smokers (OR = 1.29). In the fully adjusted model, long-term quitters were at lower risk compared to a reference group of continuous smokers, with respective ORs of 0.65 and 0.60 in participants who had quit smoking 11–20 years and more than 20 years before the second follow-up. Analyses using pack-years, or the average number of packs smoked per day multiplied by the number of years spent smoking, did not find a significant relationship with CASI scores, though a trend emerged such that those with 26–50 pack-years were at greater risk than those with 1–25 or greater than 50 pack-years.

In a follow-up analysis of data from the Honolulu Heart Program, [Tyas et al. \(2003\)](#) found that midlife smoking status, defined by pack-years, predicted incidence of AD, diagnosed by a series of exams administered to participants with low or declining scores on the CASI. Light smoking was defined as less than or equal to 26.7 pack-years, medium as 26.7–40.5, heavy as 40.5–55.5, and very heavy as up to 156 pack-years. As in [Galanis et al. \(1997\)](#), data on smoking were collected 25–30 years before administration of the CASI. While smoking status, defined as never, current, or former, did not predict AD, quantity and duration of smoking did. Using light smokers as a reference group, medium and heavy smokers had ORs of 2.55 and 2.93, respectively. Very heavy smokers were not at greater risk, a finding that the authors attribute to a survivor effect. In an autopsied subset of 218 former participants, medium and heavy smokers had significantly more neocortical neuritic plaques than light and very heavy smokers did, with respective count ratios of 2.12 and 2.09, suggesting a molecular basis for the relationship between smoking and AD.

[Whitmer, Sidney, Selby, Johnston, and Yaffe \(2005\)](#) assessed the sequelae of four midlife cardiovascular risk factors over a 26-year follow-up. One was smoking status, defined dichotomously as having never or ever smoked. Aged 40–44 at baseline, participants who had smoked had an HR of 1.26 of developing dementia after adjusting for education and sex. Dementia diagnoses came from medical records obtained when participants were in their late 60s and 70s.

In a prospective study of middle-aged men and women, heavy smoking at baseline, defined as more than two packs daily, predicted subsequent AD ([Rusanen, Kivipelto, Quesenberry, Zhou, & Whitmer, 2011](#)). Diagnoses were derived from medical records at a mean of 23 years after baseline measures were taken. Adjusting for education, BMI, alcohol consumption, and vascular risk factors, the HR in reference to non-smokers was 2.57. The same trend was observed but not significant in those smoking between 0.5 and two packs daily. Smoking prior to baseline did not predict AD. No interactions involving race or sex were identified.

Alcohol use

The relationship between alcohol consumption and cognitive decline has consistently been identified as nonlinear, with low levels of consumption associated with lower incidence of impairment compared to both abstinence and heavy consumption. [Christian et al. \(1995\)](#) assessed cognitive performance using the TICS-m from 1990 to 1991 in a sample of 4739 U.S. veteran male twins from the NAS-NRC registry born between 1917 and 1927. Participants reported their weekly alcohol use during the 1970s and 1980s. 352 participants did not drink. Among those who did, alcohol consumption was divided into quintiles. All analyses controlled for age and education. The overall mean score on the TICS-m was 33.16 (SE = 0.055). Diagnosed alcoholics scored significantly lower at 31.67 (SE = 0.469). Those who averaged less than one drink per week and those who averaged more than 16 scored significantly lower than those averaging between 8.2 and 16. Respective scores were 32.97 (SE = 0.132), 33.0 (SE = 0.136), and 33.49 (SE = 0.132). Analyses were repeated in monozygotic twins discordant for alcohol consumption, eliminating potential genetic confounding. Participants consuming between 8.2 and 16 drinks per week scored, on average, 0.94 points higher than their co-twins who consumed between less than one and 8.1 drinks per week. In a dichotomous measure among drinkers, participants who consumed less than 16 drinks weekly scored 0.61 points higher than their heavy-drinking co-twins.

A similar pattern was identified in a population-based study in Finland. [Anttila et al. \(2004\)](#) assessed 1018 participants aged 65–79 years for MCI and dementia roughly 23 years after obtaining self-reports of alcohol consumption. Participants who drank less than once per month were half as likely to develop MCI as those who never drank and those who drank several times per month, adjusting for education, smoking, BMI, and vascular health factors. Dementia risk did not differ by alcohol consumption, though the frequent drinking category may have been defined too broadly for an association between heavy drinking and dementia to become apparent.

In a 34-year longitudinal study of Swedish women aged 38–60 years at baseline, those who drank wine during midlife were less likely to develop dementia ([Mehlig et al., 2008](#)). For each type of alcohol, participants were classified dichotomously: current

drinking (at baseline) or former/never drinking. Two models were used; one included covariates such as education, BMI, and health factors that were measured at baseline, while the other used the same covariates but with updated values obtained over the course of the study. The HR associated with wine consumption in the updated model was 0.56. The same trend was evident but nonsignificant in the baseline model. The opposite pattern emerged for consumption of spirits. Consumption was associated with an increased risk of dementia but was only significant in the baseline, unadjusted model (HR = 1.59). These results point to opposing effects of wine and spirit consumption, indicating a need to stratify by type of alcohol in addition to quantity. At a mechanistic level, wine may carry a neuroprotective effect through resveratrol, a component of red wine that has been found to exert anti-oxidative effects and maintain cell viability. Its properties may act in opposition to the cell death caused by amyloid β build-up (Savaskan et al., 2003).

Handing, Andel, Kadlecova, Gatz, and Pedersen (2015) assessed the long-term correlates of drinking in a 43-year follow-up study of participants from the Swedish Twin Registry. The mean age at baseline was 54.2. Alcohol consumption was divided into five categories based on grams of ethanol consumed per day. Participants were classified as nondrinkers, light (0–5 g), moderate (5–12 g), heavy (12–24 g), or very heavy (> 24 g) drinkers. Using light drinkers as the reference group and adjusting for sex, education, smoking, and health factors, heavy drinkers and very heavy drinkers were at greater risk of dementia, with respective HRs of 1.10 and 1.18. Consistent with Mehlig et al. (2008), spirit consumption was associated with dementia (HR = 1.03), while wine consumption was slightly protective (HR = 0.98). Analyses of the 177 dementia-discordant monozygotic twin pairs revealed that moderate to very heavy drinkers were three times more likely than their light-drinking co-twins to develop dementia, pointing to an effect of alcohol use independent of genetic and familial factors. Among the twins, nondrinkers and light-drinkers did not significantly differ in their risk. The authors characterized the relationship between alcohol use and dementia as J-shaped given the greater risk associated with heavy drinking compared to non-drinking.

Body mass index (BMI)

BMI, a ratio of weight in kilograms to height in square meters, is defined as normal when it is between 18.5 and 25, and obese when it is greater than 30. Midlife obesity has consistently been identified as a risk factor for cognitive decline. In the population-based Finnish study, participants with a mean age of 50.6 at baseline were assessed for dementia status after an average of 21 years (Kivipelto et al., 2005). Adjusting for vascular risk factors, participants who were obese at baseline had an OR of 2.10 of developing dementia. BMI between 25 and 30, the overweight range, did not predict dementia. The reference group was comprised of participants with BMI less than or equal to 25. Height and weight were measured at the baseline visit.

In a study of participants from the Swedish Twin Registry ranging from 45 to 65 years old at baseline, those in the top 25% of the sample's self-reported BMI distribution (BMI \geq 26.5) had adjusted ORs of 1.55 and 1.68 of developing dementia and AD, respectively, compared to those with BMI less than 26.5 (Hassing et al., 2009). The model was adjusted for education, nicotine and alcohol use, and vascular risk factors. Analyses were conducted between, not within, twin pairs. The mean age at dementia diagnosis was 83. Although the dichotomous classification of BMI used in this study prevents us from disentangling the effects of BMI in the overweight and obese ranges, less than 5% of the sample were obese, suggesting an elevated risk in individuals who are overweight but not obese. The study accounted for the correlation within twin pairs but did not employ a traditional twin model to control for genetic confounds.

Xu et al. (2011) controlled for genetic effects in twin pairs discordant for dementia using a sample from the Swedish Twin Registry. Twin pairs older than 65 were screened using the TELE questionnaire and the BDRS; those whose cognitive performance showed evidence of impairment underwent a clinical examination for dementia. Midlife BMI, at a mean age of 43.4, was based on self-report and obtained from the twin registry. After adjusting for education and vascular risk factors, increasing BMI, coded as a continuous variable among all participants, predicted dementia, with an OR of 1.08. Treated categorically and analyzed between twin pairs, BMI between 25 and 30 had an OR of 1.71 and BMI greater than 30 had an OR of 3.88, in comparison to a reference group with BMI between 20 and 25. Those with BMI less than 20 were not at greater risk. Within dementia-discordant twin pairs, there was a trend such that midlife BMI in the overweight and obese ranges predicted dementia, but the association was no longer significant, indicating genetic and/or familial confounding. However, only 44 of the 137 discordant pairs were monozygotic; the dizygotic pairs are not free from genetic confounding. Future research should explore the association in larger samples of discordant monozygotic twin pairs.

In a sample of 1394 participants from the Baltimore Longitudinal Study of Aging, 142 developed AD (Thambisetty et al., 2015). Each unit increase in midlife BMI, measured at age 50, predicted a six to seven month earlier age of onset. Participants were unimpaired at baseline, and the average follow-up period was 13.9 years. In an autopsied subsample of 191 participants, higher midlife BMI was associated with a greater number of neurofibrillary tangles but not neuritic plaques, offering preliminary evidence of a molecular basis for the association between BMI and cognitive impairment.

Physical activity

Midlife physical activity has been found to play a protective role in subsequent cognitive performance. Given its correlation with BMI, we note whether studies of physical activity control for midlife adiposity. The longitudinal Finnish study discussed throughout this paper obtained self-reports of leisure-time physical activity when participants were at a mean age of 50 (Rovio et al., 2005). Participants were classified as active if they participated in physical activity lasting at least 20–30 min two or more times per week, and sedentary if they did not. After a mean follow-up period of 21 years, participants completed the MMSE and were assessed for dementia and AD if their performance indicated cognitive impairment. In the fully adjusted model, which controlled for education, midlife BMI, vascular risk factors, smoking, and alcohol use, the active participants had ORs of 0.47 and 0.35 for dementia and AD, respectively, compared to the reference group of sedentary participants.

Similar results were found in a sample from the Swedish Twin Registry, although physical activity level was classified differently (Andel et al., 2008). Participants in their late 40s reported their engagement in physical activity between the ages of 25 and 50. They were divided into four categories: hardly any exercise, light exercise, regular exercise, and hard physical training. Follow-up assessments for dementia occurred, on average, 31 years later. The researchers completed case-control and co-twin control analyses. Controlling for education, fruit and vegetable consumption, smoking, alcohol use, and BMI, case-control analyses found that, compared to participants who engaged in hardly any exercise, those who engaged in light or regular exercise were 37% and 66% less likely to develop dementia, respectively. Participants who exercised regularly were also 66% less likely to develop AD. The same trend was observed but not significant for participants in the light exercise category. Participants who engaged in hard physical training were not at lower risk of dementia or AD. Controlling for the same covariates, co-twin control analyses in 90 dementia-discordant twin pairs identified a trend such that, within pairs, the twin who exercised more was less likely to develop dementia, with an OR of 0.66. The trend was nonsignificant, which the authors attribute to the small sample. The pattern was similar for AD. 32 of the twin pairs were monozygotic.

Using a co-twin control design, Carlson et al. (2008) assessed midlife physical, cognitive, and social activity levels in relation to dementia diagnosis. Born between 1917 and 1927, participants were 147 veteran male twin pairs, 84 of whom were monozygotic, from the NAS-NRC registry. They completed a questionnaire in 1967 regarding participation in leisure activities and were assessed for dementia 28 years later using the TICS-m, Dementia Questionnaire, and in-person clinical evaluation. Midlife physical activity was unrelated to incidence of dementia in old age in dementia-discordant twin pairs. Physical activity level was based on reported participation in outdoor activities, gardening, sports, home improvement, and exercise after age 35. Because activities ranging in physical demand were considered together, the analyses may have been unable to detect the associations found in other studies between moderate levels of physical activity and subsequent cognitive performance. The study did not control for BMI.

Chang et al. (2010) evaluated the association between midlife physical activity, when participants were at a mean age of 51, and cognitive performance 26 years later in a sample from the Age Gene/Environment Susceptibility (AGES)—Reykjavik Study. Physical activity level was divided into three categories: no physical activity, less than or equal to five hours per week, and greater than five hours per week. Cognitive ability was assessed using a battery of tests measuring processing speed, memory, and executive function. Controlling for education, BMI, systolic blood pressure, smoking, and cholesterol, participants in both groups that exercised performed better on all three measures of cognitive performance than did those who were inactive at midlife. Compared to inactive participants, those who exercised less than or equal to five hours per week had an OR of 0.60 of developing dementia. Those with greater than five hours per week had an OR of 0.80, but the association was not significant. Taken together, these studies suggest a protective role of midlife physical activity in maintaining cognitive ability and reducing subsequent risk of dementia and AD.

Vascular risk factors

Blood pressure. Blood pressure has two components, systolic and diastolic; the former is consistently tied to late-life cognitive performance. Launer, Masaki, Petrovitch, Foley, and Havlik (1995) followed a sample of Japanese-American men from the Honolulu Heart Program for roughly 25 years. Participants were in their early 50s at baseline. Each 10-mm HG increase in systolic blood pressure at baseline (mean age = 52.7) conferred a 5% increase in risk of poor cognitive function at follow-up (mean age = 77.8). Cognitive function was classified according to performance on the CASI; a score below 82 was deemed poor. Analyses were adjusted for education, stroke, heart disease, and atherosclerosis. No relationship was identified between diastolic blood pressure and performance on the CASI.

In the same population-based Finnish sample discussed earlier, there was a nonsignificant association between elevated systolic blood pressure in midlife (mean age = 50) and subsequent MCI, diagnosed at a mean age of 71 (Kivipelto et al., 2001). High systolic blood pressure was defined as greater than or equal to 160 mm Hg. A separate study of the same sample, however, found that elevated systolic blood pressure at midlife predicted AD (Kivipelto et al., 2002). Comparing to a reference group with systolic blood pressure less than 140 mm Hg and adjusting for education, smoking, and alcohol use, the OR was 2.6. Diastolic blood pressure did not predict AD.

The study discussed earlier of four midlife cardiovascular risk factors found that midlife hypertension, defined as elevated systolic (≥ 140 mm Hg) and/or diastolic (≥ 90 mm Hg) blood pressure, predicted dementia when participants were reassessed in their late 60s and 70s (Whitmer et al., 2005). Adjusted for education and sex, the HR was 1.42. The mean age at baseline was 42. The study design does not allow us to disentangle the effects of systolic and diastolic blood pressure, but there is little research to suggest that elevated diastolic blood pressure in midlife predicts cognitive decline.

Diabetes. In a retrospective study of male civil servants from the Israeli Ischemic Heart Disease study, those who had been diagnosed with diabetes during their 40s were more likely to have dementia during follow-up, occurring at a mean age of 82 (Beeri et al., 2004). Participants were assessed for cognitive ability using the TICS-m; those with low scores underwent a diagnostic interview. Adjusting for demographic and cardiovascular factors, including BMI, cholesterol level, blood pressure, and history of smoking, the OR was 2.83. The reference group was comprised of individuals identified as cognitively unimpaired.

In their study of cardiovascular risk factors, Whitmer et al. (2005) found that midlife diabetes, diagnosed in participants aged 40 to 44, predicted dementia 26 years later. Adjusting for education and demographic factors, the HR for the comparison of diabetic and non-diabetic participants was 1.46. Of the four cardiovascular factors (smoking, hypertension, diabetes, and cholesterol) included in the study, diabetes was most predictive of dementia, a finding that the authors attribute to vascular changes in the brain that often accompany diabetes.

Using retrospective reports from elderly members of the Swedish Twin Registry, Xu et al. (2009) assessed the relationship

between midlife diabetes, with onset before age 65, and dementia. The mean participant age was 74.4. The ORs for dementia and AD were 2.76 and 2.25, respectively, after adjusting for demographic and cardiovascular factors, including hypertension, BMI, heart disease, and stroke. In a subsample of 210 dementia-discordant twin pairs, diabetes with midlife onset predicted dementia, with an adjusted OR of 2.41. 46 of the twin pairs were monozygotic. The co-twin analyses support the role of midlife diabetes as a direct risk factor, independent of familial confounds. Future studies should seek to further reduce the possibility of genetic confounding by assessing the relationship in larger samples of monozygotic twins. The association was not significant when diabetes onset occurred at age 65 or older, implicating duration of illness as a relevant factor.

Consistent with this notion, [Tuligenga et al. \(2014\)](#) linked duration of the illness as well as glycemic control to rate of cognitive decline in a sample from the Whitehall II study of British civil servants. Participants aged 39 to 64 were screened for diabetes between 1991 and 1993 before undergoing three cognitive assessments between 1997 and 2009. The cognitive assessments measured memory, reasoning ability, and verbal and semantic fluency. A composite ability measure was calculated from performance on the four tests. Participants with diabetes at baseline experienced a more rapid decline in cognitive abilities over a 10 year period than those without diabetes and those who were diagnosed during the course of the study. Specifically, diabetic participants experienced declines in composite ability, memory, and reasoning scores that were, respectively, 24%, 45%, and 29% more rapid than those experienced by normoglycemics. Glycemic control, defined by mean glycated hemoglobin (HbA_{1c}) level, was associated with memory decline, with a one percentage point increase predicting a significantly faster decline in participants diagnosed with diabetes at baseline. Management of diabetic symptoms, therefore, may reduce the risk of rapid cognitive decline.

Cholesterol. The population-based Finnish studies of blood pressure in midlife (mean age = 50) also assessed serum cholesterol levels. Elevated cholesterol, defined as greater than or equal to 6.5 mmol/L, predicted MCI 21 years later ([Kivipelto et al., 2001](#)). Compared to a reference group of participants with cholesterol less than 6.5 mmol/L, the OR was 1.9, adjusted for age and BMI. Using the same dichotomous classification of cholesterol levels, [Kivipelto et al. \(2002\)](#) found that elevated cholesterol predicted AD, with an OR of 2.8 after adjusting for demographic and health-related factors, including smoking and alcohol use.

[Whitmer et al. \(2005\)](#) identified elevated cholesterol as one of four midlife cardiovascular risk factors relevant to late-life dementia. Among participants in their early 40s, elevated cholesterol, defined as greater than or equal to 240 mg/dL (or 13.3 mmol/L), predicted dementia diagnosis 26 years later. Compared to those without high cholesterol, the adjusted HR was 1.42. Participants with all four risk factors, smoking, hypertension, diabetes, and high cholesterol, were at significantly greater risk of developing dementia, with an HR of 2.37. The factors appeared to act in a dose-dependent manner; no interactions were reported.

Interaction with APOE genotype

Studies of smoking and the APOE genotype have yielded mixed results. In a study by [Ott et al. \(1998\)](#), elderly participants (mean age = 66.4) who smoked at baseline were at greater risk of AD only if they did not carry an APOE4 allele. Among non-carriers, the OR was 4.6; in carriers, the OR was nonsignificant at 0.6. Among former smokers, who are more relevant to our midlife focus, the same trend was observed but was not significant. In two studies of the population-based Finnish sample discussed earlier, the opposite pattern was identified. [Rusanen et al. \(2010\)](#) found that, among carriers, the ORs associated with smoking for dementia and AD were 4.93 and 6.56, respectively, but midlife smoking did not increase risk in non-carriers. Participants were classified as smokers if they had smoked within a year prior to baseline measurement. Using a dichotomous classification of never or ever smoking, [Kivipelto et al. \(2008\)](#) identified the same pattern, but the interaction term was not significant. By contrast, [Tyas et al. \(2003\)](#) found no significant interactions between the genotype and midlife smoking status or amount smoked in pack-years.

With respect to alcohol use, [Anttila et al. \(2004\)](#) found an interaction such that risk of dementia increased alongside midlife alcohol consumption in APOE4 carriers only. Compared to those who never drank, the ORs for carriers who drank infrequently (less than once a month) and frequently (several times a month) were 4.08 and 7.07, respectively. Risk of dementia did not change significantly for non-carriers based on frequency of drinking. Similar results were found in an elderly sample; non-carriers who consumed up to three drinks of wine per day were at lower risk of AD, while the protective association was not observed in carriers ([Luchsinger, Tang, Siddiqui, Shea, & Mayeux, 2004](#)).

There is little research to suggest an interaction between BMI and APOE genotype. [Tolppanen et al. \(2014\)](#) found no moderation by genotype of the association between midlife BMI (mean age = 50.2) and dementia 26 years later in a population-based Finnish sample.

Mixed results have been reported in studies of physical activity and APOE genotype. In the Finnish sample, the association between physical activity and subsequent dementia/AD diagnosis was significant in APOE4 carriers but not in non-carriers ([Rovio et al., 2005](#)). The AGES—Reykjavik Study identified the opposite pattern, such that APOE4 carriers who exercised during midlife were not at lower risk of dementia than their inactive counterparts, while exercise showed a protective association in non-carriers ([Chang et al., 2010](#)). Future research is needed to clarify the moderating role of APOE genotype in relation to physical activity.

There does not appear to be an interaction between midlife hypertension and carrier status. Defining midlife hypertension as a blood pressure greater than 140/90 mmHg between the ages of 48 and 63, [Carmelli et al. \(1998\)](#) found no interaction with the APOE genotype in predicting decline on a battery of cognitive tests 10 years later. [Kivipelto et al. \(2002\)](#) also identified elevated systolic blood pressure in midlife and APOE4 carrier status as independent risk factors for AD.

[Carmelli et al. \(1998\)](#) did find an interaction between midlife hyperglycemia, defined as blood glucose level > 200 mg/dL, and APOE genotype. Participants with both risk factors experienced a greater decline in cognitive performance than predicted if the relationship were additive. The same pattern was identified in a sample of elderly Japanese-American men from the Honolulu Heart Project, although diabetic status was assessed during old age, not midlife ([Peila, Rodriguez, & Launer, 2002](#)).

Few studies of cholesterol and APOE genotype have been conducted in midlife samples. Kivipelto et al. (2002) found that APOE4 carrier status and high systolic blood pressure in midlife were independent risk factors for AD. There is little research thus far to suggest an interaction.

Summary

Several indices of midlife physical health predict cognitive performance decades later. Moderate and heavy smoking at midlife predict dementia and AD (Galanis et al., 1997; Tyas et al., 2003; Whitmer et al., 2005; Rusanen et al., 2011), although the studies we discussed did not include twin pairs. Alcohol consumption appears to relate to dementia in a nonlinear pattern, with low to moderate levels of drinking predicting better cognitive outcomes than either abstinence or heavy drinking (Anttila et al., 2004; Mehlig et al., 2008). Two twin studies point to a causal role of heavy drinking in the development of dementia (Christian et al., 1995; Handing et al., 2015). Obesity predicts cognitive decline; there may be a direct effect, as suggested by the greater number of neurofibrillary tangles associated with high midlife BMI in an autopsied sample (Thambisetty et al., 2015), but a twin study indicates some degree of genetic and/or familial confounding (Xu et al., 2011). Consistent with the role of BMI, midlife physical activity has a protective association with cognitive decline (Rovio et al., 2005; Chang et al., 2010), although twin studies offer mixed results as to whether the relationship is causal (Andel et al., 2008; Carlson et al., 2008). Several aspects of vascular health, including elevated systolic blood pressure (Launer et al., 1995; Kivipelto et al., 2002; Whitmer et al., 2005), diabetes (Beeri et al., 2004; Whitmer et al., 2005; Tuligenga et al., 2014), and cholesterol (Kivipelto et al., 2001, 2002; Whitmer et al., 2005), also predict decline. Only diabetes has been implicated as causally related to dementia (Xu et al., 2009). BMI (Tolppanen et al., 2014), hypertension (Carmelli et al., 1998; Kivipelto et al., 2002), and cholesterol (Kivipelto et al., 2002) appear to act independently of APOE genotype as risk factors, while results are mixed as to whether smoking (Ott et al., 1998; Rusanen et al., 2010; Kivipelto et al., 2008; Tyas et al., 2003) and physical activity (Rovio et al., 2005; Chang et al., 2010) interact with carrier status. APOE4 carriers who drank (Anttila et al., 2004) or developed diabetes (Carmelli et al., 1998) during midlife were at significantly higher risk of dementia. See Table 4 for a summary of studies on physical health.

Social support

The bulk of the research on social support in relation to cognitive decline has focused on elderly populations. Because decline in cognitive ability often impedes the maintenance of social connections (Kensinger & Gutchess, 2017), these studies do not provide evidence of social support as a protective factor in late-life cognitive performance. A small line of research, however, has established a link between midlife social network and subsequent cognitive ability.

In a 12-year longitudinal study of adults aged 50 and older at baseline, Holtzman et al. (2004) found that social network participation predicted performance on the MMSE, scored from 0 to 30. Social network size was defined as the number of people with whom a participant maintained contact. Controlling for alcoholism, cerebrovascular disease, education, age, and gender, there was a small but significant relationship between baseline network size and MMSE score at follow-up. Participants with a given social network size were 84% as likely as those with one less social connection to score at or below the lowest quartile in the population on the MMSE, a finding that the authors propose may be due to the increased intellectual stimulation and/or decreased stress that accompany social interaction.

Saczynski et al. (2006) also defined social engagement primarily by quantity of connections. Middle-aged, Japanese-American men from the Honolulu Heart Program answered five yes/no questions about their marital status, living arrangement, and social participation. One question regarding the existence of a confidant relationship addressed relationship quality; the others assessed amount of social contact. Midlife social engagement did not significantly predict performance on the CASI after a mean follow-up period of 27.5 years. Declining social engagement between midlife and late life did, although this may be indicative of a prodromal phase of dementia rather than a direct effect of social network.

In the study of physical, cognitive, and social activity in the NAS-NRC twin sample, Carlson et al. (2008) found a relationship between midlife social activity and subsequent incidence of dementia. In 84 dementia-discordant MZ twin pairs, midlife activity score, based on self-reported frequency of participation, predicted dementia status at follow-up 28 years later. The activities most closely associated with reduced incidence of dementia were social by nature, including family activities and visits with friends. The OR associated with these activities was 0.60. In this longitudinal male sample, midlife social activity appeared to carry a protective effect on cognition.

In the population-based Finnish sample discussed throughout this paper, marital status, assessed at a mean age of 50, predicted incidence of MCI and AD 21 years later (Håkansson et al., 2009). Adjusting for age, education, sex, APOE status, depression, and midlife health factors, participants not living with a partner at midlife had ORs of 2.14 and 2.06 of developing MCI and AD, respectively. The reference group was comprised of participants who were married/cohabiting at midlife. Among those not cohabiting, participants who were widowed at midlife were at greatest risk of MCI and AD, with respective ORs of 3.30 and 2.52 compared to cohabiting participants. Participants who were single or divorced at midlife were not at significantly greater risk of MCI or AD than those who cohabited were. The study points to a protective function of social support specific to cohabiting couples.

Interaction with APOE genotype

Carlson et al. (2008) found no significant interaction between APOE genotype and social, cognitive, or physical activity level. By contrast, Håkansson et al. (2009) found that APOE4 carriers who were widowed or divorced at midlife and follow-up were at greater risk of AD, with an OR of 25.55 compared to a reference group of cohabiting non-carriers. The interaction was less pronounced for

Table 4
Summary of studies reviewed on physical health.

Study authors	Sample size	Physical health measure	Sample age at physical health measure	Outcome measure	Sample age at outcome measure	Outcome
Galanis et al. (1997)	3429	Smoking status and pack-years	58.6	CASI	77.7	Continuous smoking predicts lower CASI scores; smoking defined by pack-years does not
Tyas et al. (2003)	3734	Smoking by pack-years	Early 50s	AD	Late 70s (25 to 30 years after baseline)	Medium and heavy smokers are at greater risk of AD. No interaction between smoking and APOE genotype was identified
Whitmer et al. (2005)	8845	Smoking, hypertension, diabetes, high cholesterol	40–44	Dementia	26.67 years (mean follow-up)	All 4 cardiovascular risk factors predict dementia dose-dependently
Rusamen et al. (2011)	21,123	Smoking by packs daily	58.01	AD	81.45	Smoking more than 2 packs daily predicts AD
Christian et al. (1995)	4739	Weekly alcohol consumption	40–60s	TICS-m	63–73	The 1st and 5th quintiles of alcohol consumption are associated with lower scores on the TICS-m compared to the 4th quintile. Alcoholics scored below the sample mean
Anttila et al. (2004)	1018	Frequency of drinking per month, APOE genotype	47.94 (mean age)	MCI and dementia	65–79 (mean age of 71.49)	Infrequent drinking was associated with lower risk of MCI than nondrinking and frequent drinking. Drinking pattern was not associated with dementia. Dementia risk increased in carriers with increasing consumption of alcohol
Mehlig et al. (2008)	1462	Type of alcohol consumed	38–60	Dementia	34 years later	Wine consumption predicted lower incidence of dementia
Handing et al. (2015)	12,326 (177 dementia-discordant MZ twin pairs)	Quantity of alcohol consumed per day	54.2	Dementia	Up to 43 years later	Moderate to heavy drinking in dementia-discordant MZ twin pairs predicted dementia
Kivipelto et al. (2005)	1449	BMI	50.6	Dementia	Mean of 21 years later	Midlife obesity but not overweight predicted dementia
Hassing et al. (2009)	1152	BMI	45–65 (mean age of 52.5)	Dementia, AD	83 (mean age)	Midlife overweight predicted dementia and AD
Xu et al. (2011)	8534 (137 dementia-discordant twin pairs)	BMI	43.4 (mean age)	Dementia	74.4 (mean age)	Midlife overweight and obesity predicted dementia. Underweight did not. The relationship was not significant in discordant twin pairs
Thambisetty et al. (2015)	1394	BMI	50	AD	13.9 years later (mean)	Higher BMI in midlife predicts earlier age of AD onset and more neurofibrillary tangles, post-mortem
Rovio et al. (2005)	1449	Frequency of engagement in leisure-time physical activity	50	Dementia, AD	21 years later (mean)	Participating in leisure-time physical activity at least twice weekly predicted lower incidence of dementia and AD. The role of physical activity may be greater in APOE4 carriers
Andel et al. (2008)	3134 case controls, 90 dementia-discordant twin pairs	Intensity of exercise between ages 25 and 50	48.1 (mean)	Dementia	31 years later (mean)	Case-control analyses revealed a protective relationship between physical activity and dementia. Co-twin control analyses approached significance
Carlson et al. (2008)	147 twin pairs	Participation in 5 types of physical activity	40–50	Dementia	28 years later (average follow-up)	Midlife physical activity did not predict dementia incidence in dementia-discordant twin pairs
Chang et al. (2010)	4945	Number of hours of physical activity per week	51 (mean)	Cognitive performance, Dementia	26 years later	Participants with midlife physical activity scored better on the cognitive test battery. Those with moderate levels of physical activity were less likely to develop dementia. Risk did not differ among APOE4 carriers based on physical activity

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Table 4 (continued)

Study authors	Sample size	Physical health measure	Sample age at physical health measure	Outcome measure	Sample age at outcome measure	Outcome
Launer et al. (1995)	3735	Systolic and diastolic blood pressure	52.7	Cognitive impairment based on CASI performance	77.8	Elevated systolic, but not diastolic, blood pressure at midlife predicted cognitive impairment
Kivipelto et al. (2001)	1449	Systolic blood pressure, serum cholesterol	50	MCI	71	There was a nonsignificant association between elevated systolic blood pressure and MCI. Elevated cholesterol predicted MCI
Kivipelto et al. (2002)	1449	Systolic and diastolic blood pressure, serum cholesterol, APOE genotype	50	AD	71	Elevated systolic, but not diastolic, blood pressure at midlife predicted AD. Elevated cholesterol predicted AD. Neither factor interacted with APOE genotype
Beeri et al. (2004)	1892	Diabetes	44.5	Dementia	82	Midlife diabetes predicted dementia
Xu et al. (2009)	13,693 (210 dementia-discordant twin pairs)	Diabetes	< 65	Dementia, AD	74.4	Midlife diabetes predicted dementia in discordant twin pairs
Tuigenga et al. (2014)	5653	Diabetes, glycemic control	39 to 64	Cognitive test battery measuring memory, reasoning, and verbal and semantic fluency	55 to 79 (at final cognitive assessment)	Midlife diabetes and poor glycemic control predict accelerated cognitive decline
Ott et al. (1998)	6870	Smoking (never, former, and current)	55 and older	AD	2.1 years later (mean follow-up)	Former and current smoking were associated with greater risk of AD in non-carriers only
Rusnan et al. (2010)	1449	Smoking	50 (mean age)	Dementia, AD	21 years later (mean follow-up)	Smoking was associated with greater risk of dementia and AD in carriers only
Kivipelto et al. (2008)	1449	Smoking (never or ever)	50 (mean age)	Dementia	21 years later (mean follow-up)	Midlife smoking was associated with greater risk of dementia in carriers, but the interaction term was nonsignificant
Tolppanen et al. (2014)	1304	BMI, APOE genotype	50.2 (mean age)	Dementia	26 years later	There was no interaction between BMI and APOE genotype
Carmelli et al. (1998)	410	Hypertension, hyperglycemia, APOE genotype	48–63	Performance on cognitive test battery	63–73	There was no interaction between hypertension and APOE genotype. Carriers with hyperglycemia experienced a more rapid cognitive decline than predicted in an additive relationship

Table 5
Summary of studies reviewed on social support.

Study authors	Sample size	Social support measure	Sample age at social support measure	Outcome measure	Sample age at outcome measure	Outcome
Holtzman et al. (2004)	354	Social network size	50+ (mean age = 61.3)	MMSE	12 years later	Larger social network size was associated with slightly higher MMSE scores
Saczynski et al. (2006)	2513	Social engagement	53.8 (mean age)	CASI	27.5 years later (average follow-up)	Midlife social engagement did not significantly predict CASI performance
Carlson et al. (2008)	147 twin pairs	Social activity	40–50	Dementia	28 years later (average follow-up)	Midlife social activity predicted incidence of dementia in dementia-discordant monozygotic twins
Håkansson et al. (2009)	1449	Marital status	50.4 (mean age)	MCI, AD	21 years later (mean follow-up)	Midlife marital status predicted incidence of MCI and AD. APOE4 carriers who were widowed in midlife were at particularly high risk of AD

MCI. Future studies of social support as a protective factor in conjunction with APOE genotype should assess outcomes in participants who differ by marital status, as this appears to be an aspect of social network with long-reaching consequences.

Summary

Although most often studied in older samples, the quantity and quality of social relationships in midlife have been linked to cognitive performance in old age. Number of social contacts yielded mixed results, with one study reporting an association with cognitive performance in old age (Holtzman et al., 2004) and another study finding no relationship (Saczynski et al., 2006). A study of male twins provided support for a causal role of frequency of social participation in preventing dementia (Carlson et al., 2008). Midlife relationship status also predicted cognitive performance; cohabiting was associated with lower incidence of MCI and AD, while those who were widowed in midlife were at greater risk (Håkansson et al., 2009). There is preliminary evidence to support an interaction between midlife marital status and APOE genotype, with widowed or divorced APOE4 carriers at significantly greater risk of AD than cohabiting non-carriers (Håkansson et al., 2009). See Table 5 for a summary of studies on social support.

Discussion

Cognitive decline occurs as part of the typical aging process in healthy adults. Individual variation is considerable, with some adults exhibiting clinical levels of impairment in the form of MCI and/or dementia and others maintaining cognitive functioning well into old age. Variation in outcome is driven by the presence of risk and protective factors decades before decline becomes apparent. Research consistently demonstrates a link between several key areas of functioning in midlife and subsequent cognitive wellbeing. Relevant factors range from malleable lifestyle components to facets of the individual, such as personality and biological pathways, that differentially increase or decrease risk, often in interaction with one's APOE genotype. In particular, studies based on samples from the Swedish Twin Registry and the NAS-NRC Twin Registry point to a direct effect of certain risk factors on late-life cognitive performance, independent of genetic and familial confounding. Evidence was particularly strong for occupational complexity, alcohol consumption, and diabetes. The most consistent evidence of interaction with the APOE genotype was found in studies of physical health, with APOE4 carriers who drank heavily or developed diabetes during midlife demonstrating high rates of cognitive impairment.

It is worth noting the extent to which the factors discussed in this review tend to be correlated. For example, educational attainment predicts health behavior, such that fewer years of education are associated with higher BMI and greater consumption of tobacco (Kubzansky, Berkman, Glass, & Seeman, 1998), and hypertension is associated with elevated levels of anxiety (Baer, Collins, Bourianoff, & Ketchel, 1979). Likewise, high systolic blood pressure has been found to predict high cholesterol intake (Sakurai et al., 2011), both of which, as discussed earlier, independently increase risk of AD (Kivipelto et al., 2002). Such correlations render it likely that, in some individuals, many risk factors will be present.

Evidence for the role of the risk and protective factors discussed in this paper also comes from the results of interventions and public health strategies designed to promote late-life health. These target the midlife risk factors considered most malleable, which are outlined in a review by Hughes and Ganguli (2009). Obisesan et al. (2008) found that controlling blood pressure reduced the degree of cognitive loss typically seen in hypertensive individuals, and another study reported that participants randomly assigned to a program of physical activity showed moderate cognitive improvement when assessed 18 months later (Lautenschlager et al., 2008). Moreover, a recent decline in incidence of cardiovascular risk factors in wealthy countries has been accompanied by a decline in dementia risk, implicating interventions related to cardiovascular health as a potential strategy to promote cognitive functioning (Qiu & Fratiglioni, 2015).

Despite evidence of declining incidence in developed countries (Matthews et al., 2013; Schrijvers et al., 2012), dementia remains a major public health concern, with particularly large increases in prevalence predicted to occur in low and middle-income countries (Prince et al., 2013). The increase in dementia cases in developing countries, coupled with the aging population in certain developed countries (Anderson & Hussey, 2000), point to the importance of interventions that address the midlife risk factors discussed in this review.

Conclusion

The five domains of midlife functioning discussed in this paper predict cognitive performance decades later. While some risk and protective factors independently predict performance, others interact with the APOE genotype to shape cognitive change in old age, ranging from mild, age-related declines in fluid abilities to clinical impairments resulting from dementia. A comprehensive understanding of the factors contributing to late-life cognitive impairment is necessary for the development of interventions to reduce the prevalence of dementia in the aging global population.

Conflicts of interest

None.

Funding

This work was supported by the John Templeton Foundation through the Genetics and Human Agency project at the University of

Virginia.

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