Everyday Physical Activity and Mobility Affect Executive Function Performance and Change in Older Adults: Evaluating Independent and Moderating Effects of Genetic Risk for Alzheimer's Disease

by

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Abstract

Objective: Among older adults, everyday physical activity (EPA) and mobility (MOB) are important contributors to age-related variability and change in executive functioning (EF). However, the role of these health and lifestyle influences may be moderated by genetic factors, especially those known to be risk factors for neurodegenerative disease. The goals of this research were to (a) confirm a single-factor EF latent variable fit this sample of participants and maintained measurement invariance, (b) determine the best fitting latent growth models for EF, EPA, and MOB, (c) examine how EPA, MOB and four genetic factors independently affect EF performance and change, (d) test moderating effects of the four genetic factors on EPA-EF relationships, and (e) test moderating effects of the four genetic factors on MOB-EF relationships. **Method**: The sample consisted of genotyped older adults (*N*=577, *M* age = 70.47 years) over three waves (9 years) of the Victoria Longitudinal Study. The four genetic factors were *Apolipoprotein E* (*APOE* rs7412 and rs429358) *Clusterin* (*CLU* rs11136000), *Complement receptor 1* (*CR1* rs6656401), and *Phosphatidylinositol binding Clathrin Assembly Protein* (*PICALM* rs541458). Analyses included (a) confirmatory factor analysis establishing a single latent EF factor from four standard EF tasks, (b) latent growth modeling (Mplus 7.0) over a 40-year band of aging (ages 53-95), and (c) path analyses to investigate the independent and interactive effects of *APOE*, *CLU, CR1, PICALM*, EPA and MOB on EF. **Results**: First, the single factor EF latent variable fit the sample of participants and had configural, metric and partial scalar invariance. Second, older adults significantly differed in both MOB and EF performance, exhibited significant 9-year EF and MOB change and individual variability in rate of MOB and EF decline. Third, higher levels of EPA were associated with better EF performance at the centering age (75 years) and less EF decline. In addition, higher levels of MOB were associated with better EF performance. Fourth, within the *APOE* ε3 (non-risk) and

the CLU risk (C+) groups, those with higher EPA exhibited better EF performance and more gradual change over time than those with lower EPA. Also, when *APOE* and *CLU* were used to create a risk score, higher levels of EPA were associated with higher levels of EF performance for the low-risk group, and more gradual 9-year change for both the low and mid-risk groups. Fifth, the effect of level of mobility on level of EF was stronger for both the *APOE* ε4 (risk) and *CLU* risk carriers than their non-risk peers. However, although this pattern of results was similar when *APOE* and *CLU* were combined into a risk score, moderation was not evidenced.

Conclusion: For individuals with low genetic risk for AD, participating in higher levels of EPA was beneficial to EF performance and change. In addition, level of mobility was strongly related to level of EF performance for individuals with high genetic risk for AD.

Keywords: everyday physical activity, executive function, mobility, *APOE*, *CLU*, *CR1*, *PICALM*, Victoria Longitudinal Study

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List of Abbreviations

EF. . . . . Executive Function

EPA. . . . . .Everyday Physical Activity

MOB. . . . . Mobility

AD. . . . . .Alzheimer's disease

APOE . . . . . Apolipoprotein E

CLU. . . . . .Clusterin

PICALM.. . . . .Phosphatidylinositol Binding Clathrin Assembly Protein

CR1. . . . . Complement Component (3b/4b) Receptor 1

BIN1 . . . . . .Bridging Integrator 1

QIAgen . . . . . .QIAgility robotic system

VLS . . . . . Victoria Longitudinal Study

S1 . . . . . Sample (number)

W1. . . . . Wave (number)

CFI . . . . . Comparative fit index

RMSEA . . . . . .Root Mean Square Error of Approximation

SRMR . . . . . Standardized root-mean-square residual

RG1 . . . . . Research goal (number)

Introduction

Physical activity and mobility are two important influences on cognitive decline that occurs as a function of both normal aging and neurodegenerative disease. However, non-modifiable factors, such as genetic risk, may also exert influence on cognitive aging decline, both independently and through moderating effects. The first aim of this research is to test independent effects of two factors on executive function (EF) performance and 9-year change with aging. The two factors are (a) everyday physical activity (EPA), which refers to leisure participation in a wide variety of activities, and (b) mobility (MOB), a composite measure comprised of indicators of gait and balance. The second aim is to examine whether these two influences are moderated by genetic risk, represented by four genotypes associated with cognitive decline and Alzheimer's disease. The research background supporting these aims is presented in this section.

Background

Research examining the variability in decline in cognitive aging has identified several independent components of influence, including biological, health, genetic, and lifestyle factors (Baltes, 1987; Dixon, Small, MacDonald, & McArdle, 2012; Fotuhi, Hachinski, & Whitehouse, 2009). However, examining singular influences on complex cognitive function and change is no longer ideal, as many sources are operating interactively to influence cognitive outcomes and trajectories. Accordingly, dynamic models representing networks of influence have been applied both conceptually and methodologically within aging research (e.g., Anstey, 2014). Recent investigations have confirmed lifestyle, health, and genetic factors operate interactively to exert risk-elevating or protective influences (Ferencz et al., 2014; McFall et al., 2014) leading to the

wide range of cognitive outcomes associated with aging, from healthy aging to neurodegenerative decline.

Alzheimer's disease (AD), the leading cause of dementia, is a progressive, complex, multi-factorial neurodegenerative disease accounting for 60 - 80 percent of all cases of dementia (Barnes & Yaffe, 2011). Currently, there are over 500 000 people living with AD or related dementia in Canada, and it is projected the prevalence of AD will double by 2038 (Alzheimer's Society of Canada, 2010). Pharmacological treatments have been ineffective at treating or preventing dementia, having only limited success for symptom management (Erickson, Weinstein, & Lopez, 2012; Mangialasche et al., 2010). Consequently, attention has focused on examining the role of modifiable, non-pharmaceutical components of influence (such as physical activity) in order to develop effective strategies for disease prevention (Barnes & Yaffe, 2011; Erickson et al., 2012; Farina, Tabet, & Rusted, 2014).

Physical activity is a modifiable lifestyle factor defined as any skeletal muscle movement which results in energy expenditure. It can be categorized in several ways, including subgroups such as aerobic exercise, resistance training, and leisure physical activity (Caspersen, Powell, & Christenson, 1985). The benefits of controlled exercise interventions and fitness training to brain and general health are well known (Erickson et al., 2010, 2011; Kelly et al., 2014; Voss et al., 2013). However, there are several barriers to daily implementation of high intensity physical activity for older adults, including health comorbidities which restrict participation in higher intensity exercise and fitness training (Schutzer & Graves, 2004). As such, there has been growing interest in EPA, a modifiable lifestyle factor which encompasses everyday leisure participation in a wide variety of activities available to older adults in voluntary moderate doses. Examples include walking, tennis, exercise, and gardening. Longitudinal research has found

beneficial cognitive effects of participating in leisure physical activity. Specifically, higher baseline EPA is associated with better scores and less decline in multiple cognitive domains, such as reasoning and memory, episodic memory, verbal fluency, and executive function (Blasko et al., 2014; Lindwall et al., 2012; Thibeau, McFall, Wiebe, Anstey, & Dixon, in press; Wang et al., 2013). EPA may be measured by self-report (Lindwall et al., 2012; Woodard et al., 2012) or accelerolmeter (actigraphy; John & Freedson, 2012; Strath, Pfeiffer, & Whitt-Glover, 2012), both of which can produce useful information. Research has indicated that these procedures produce correlated information across multiple populations (Freene, Waddington, Chesworth, Davey, & Cochrane, 2013; Gosney, Scott, Snook, & Motl, 2007; Jacobi et al., 2009; Kwak, Kremers, Brug, & Van Baak, 2007).

In older adults, a physically active lifestyle has been found to improve body composition, mobility, and cognitive function (Chodzko-Zajko et al., 2009; Tremblay et al., 2011). Physical activity is likely to directly influence musculoskeletal and neuromuscular systems which can be observed through performance on measures of mobility, such as gait speed and balance (Gregg, Pereira, & Caspersen, 2000). It is well established that the incidence of mobility limitations increases with age and there is notable variability in the rate of such decline (Diehr, Thielke, Newman, Hirsch, & Tracy, 2013; White et al., 2012). Mobility declines are thought to be an early predictor of both cognitive and physical decline (Allali et al., 2014; de Vries et al., 2012; Mielke et al., 2013; Yogev, Hausdorff, & Giladi, 2008). However, the relationships among physical activity, mobility and cognitive aging are not fully understood. A recent review has indicated that participation in physical activity has been found to reduce functional limitations (as quantified by objective measures including gait speed; Paterson & Warburton, 2010). In addition, Berryman and colleagues (2013) reported that individuals who perform better on tests

of mobility demonstrate higher neuromuscular performance, higher aerobic capacities and have better cognitive flexibility. Therefore, as mobility is highly related to physical activity, objective measures of mobility could be used in addition to self-reported physical activity for a more robust measure of physical fitness. Also, it is plausible that maintaining mobility through physical activity could be beneficial to cognitive performance.

Mobility (MOB) is a key functional health biomarker which has been associated with cognitive decline across many cognitive domains, including EF (Atkinson et al., 2010; Deary, Whalley, Batty, & Starr, 2006; Gale, Allerhand, Sayer, Cooper, & Deary, 2014). Notably, recent evidence suggests EF may play a pivotal role in the regulation of gait and mobility in older adults (Buracchio et al., 2011; Gothe et al., 2014; McGough et al., 2011; Mielke et al., 2013). In addition, declines in gait speed have been found to be predictive of cognitive decline, mild cognitive impairment and dementia (Mielke et al., 2013; van Kan et al., 2015; Waite et al., 2005). Recently, higher levels of physical functioning (as measured by a composite of indicators of mobility and muscle strength) were found to be associated with better EF performance (Desjardins-Crepeau et al., 2014). Taken together, these studies add to the mounting evidence demonstrating that the effect of MOB on EF is relevant to both non-demented aging and the onset of dementia.

Executive function (EF) encompasses higher-level cognitive processes required to make and execute plans, solve problems, set goals, shift between stimulus and response, and inhibit responses (e.g., Luszcz, 2012; West, 1996). These complex processes, mediated by the prefrontal cortex, are often categorized into three dimensions, namely, updating, shifting, and inhibition (Miyake et al., 2000). EFs are thought to be among the most age-sensitive cognitive functions (de Frias, Dixon & Strauss, 2006; Glisky, 2007; McFall et al., 2013, Raz, Dahle, Rodrigue,

Kennedy, & Land, 2011) due to significant age-related neurodegeneration occurring in the prefrontal cortices (Raz & Rodrigue, 2006). However, not all individuals show the same decline in EF performance as they age. Substantial individual differences suggest other factors, such as lifestyle, genetics, or health, may influence age-related EF decline. Therefore, age-related prefrontal volume loss and subsequent decline in cognitive performance may be exacerbated by genetic risk, lack of participation in leisure pursuits such as physical activity, and functional health declines (Ferencz et al., 2014; Hultsch, Hertzog, Small, & Dixon, 1999; Small, Dixon, McArdle, & Grimm, 2011; Solé-Padullés et al., 2009; Whalley, Deary, Appleton, & Starr, 2004). A number of genes have been associated with cognitive changes with aging (Harold et al., 2009; Harris & Deary, 2011; Lambert et al., 2009; Laukka et al., 2013; Mengel-From, Christensen, McGue, & Christiansen, 2011). Among these, *APOE* (rs7412*;* rs429358), *CLU* (rs11136000), *CR1* (rs6656401), and *PICALM* (rs541458) have been identified as among the top genetic risk factors for AD (Corneveaux et al., 2010).

ApoE is a lipoprotein involved in lipid metabolism and transportation. The *APOE g*ene has three allelic variations, ε2, ε3 and ε4, yielding six possible genotypes: ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4 (Lahiri Sambamurti, & Bennett, 2004). *APOE* has been associated with multiple trajectories and clinical outcomes of aging, including normative cognitive decline, MCI, and AD (Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Small, Rosnick, Fratiglioni, & Backman, 2004; Wisdom, Callahan & Hawkins, 2011). Specifically, the risk for AD increases according to the *APOE* genotype, such that *APOE* ε2 may be relatively protective, ε3 is neutral (neither risk increasing nor protective), and ε4 increases the risk substantially (Corder et al., 1994; Lahiri et al., 2004). In addition, ε4 carriers performed significantly worse than ε4 non-carriers on measures of cognitive functioning, including executive function (Wisdom et al., 2011).

CLU encodes the protein clusterin, which inhibits complement activation and prevents β-amyloid from aggregating into fibrils, by increasing clearance of Aβ across the blood-brain barrier. It is also associated with apoptosis, inflammation, the cell cycle, cholesterol traffic, and lipid metabolism (Lambert et al., 2009; Nuutinen, Suuronen, Kauppinen & Salminen, 2009; Sweet et al., 2012). Increased plasma clusterin levels have been associated with, AD severity, brain atrophy and disease progression (Thambisetty et al., 2010; Thambisetty et al., 2012). In addition, the *CLU* C allele has been associated with increased brain ventricular expansion, regardless of clinical status (Roussotte, Gutman, Madsen, Colby, & Thompson, 2014) as well as more rapid cognitive decline for individuals with and without cognitive impairment (Sweet et al., 2012), while the T allele has been associated with better cognitive performance (Mengel-From et al., 2011) in very old adults of varying cognitive status from the Danish 1905 Cohort Study.

PICALM encodes phosphatidylinositol-binding clathrin assembly protein, is involved in vesicle formation (Hollingworth, Harold, Jones, Owen, & Williams, 2010) and amyloid precursor protein metabolism, and therefore may affect clearance of β-amyloid in the brain (Lambert & Amouyel, 2011). According to Hollingworth and colleagues (2010), it is also possible that *PICALM* contributes to neurodegeneration by causing dysfunction at the synapse. Recently, the *PICALM* T allele was associated with a lower age at midpoint of cognitive decline (Sweet et al., 2011), and was associated with susceptibility for AD (Gharesouran, Rezazadeh, Khorrami, Ghojazadeh, & Talebi, 2014).

CR1 is thought to impact the development of AD through its role of regulating complement activity and is thought to promote clearance of Aβ particles, which can aggregate to form amyloid plaques (Lambert et al., 2009; Lambert & Amouyel, 2011). The *CR1* rs6656401 polymorphism has two alleles, an A and a G, which yield three allelic variations, A/A, A/G and

G/G. Recent research has indicated that rates of decline on measures of global cognition increase with the addition of each A (risk) allele (Chibnik et al., 2011), which has also been associated with an increased risk for AD (Zhang et al., 2010).

Although several studies identify the effects of single genes on the development of neurodegenerative disease and declines in cognitive function, recent research has indicated that candidate genes may operate additively or interactively to influence cognitive outcomes (Dixon et al., 2014; Sapkota, Vergote, Westaway, Jhamandas, & Dixon, 2015). In fact, research has shown that various genotype composites, including combinations of *PICALM*, *CLU*, *CR1* and *APOE* are associated with memory performance for older adults (Barral et al., 2012; Keenan et al., 2012; Verhaaren et al., 2012). Moreover, genetic effects on cognitive aging may be magnified when additional environmental risk factors are considered (Lindenberger et al., 2008; Nagel et al., 2008), such as low physical activity (Papenberg, Lindenberger, & Bäckman, 2015). Notably, Ferencz and colleagues (2014) confirmed the negative effect of high genetic risk score (a composite measure comprised of *PICALM*, *CLU*, and *BIN1)* on episodic memory performance was attenuated by participation in physical activity. We expand this research by examining whether genes or combinations of genes associated with an increased risk of AD moderate the effect of everyday physical activity or mobility on executive functioning in older adults.

Research Goals

The overall purpose of this study is to examine concurrent and longitudinal relationships between EPA, MOB and EF as potentially moderated by genes associated with AD genetic risk. We assembled a 3-wave (up to 9 years) VLS data set, covering a 40-year age span (55 – 95 years), which included manifest measures of the key constructs, EF, EPA, MOB, and four theoretically selected genetic polymorphisms (i.e., *APOE* rs429358 and rs7412, *PICALM*

rs541458, *CR1* rs6656401, and *CLU* rs11136000*)*. We used structural equation modeling to investigate five research goals. Research goal 1 was to confirm (a) that a single-factor EF latent variable model used in previous research (McFall et al., 2014; Thibeau et al., in press) applied to this slightly different sample of participants and (b) longitudinal measurement invariance of the EF latent variable model across three waves. Research goal 2 was to determine the best fitting latent growth models for EF, EPA and MOB. Research goal 3 was is to use conditional growth models to explore how (a) EPA and MOB independently affect level and change in EF, and (b) the genetic factors independently affect level and change in EF. Research goal 4 was to determine whether the genetic predictors or combinations of the genetic predictors moderate the association between EPA and EF performance and 9-year change in older adults. Research goal 5 was to determine whether the genetic predictors or combinations of the genetic predictors moderate the association between MOB and EF performance and 9-year change.

Method

Participants

Participants were community dwelling older adults drawn from the Victoria Longitudinal Study (VLS). The VLS is a Canadian large-scale, long-term investigation of neurocognitive aging as influenced by biological, medical, health, lifestyle, environmental and other factors (Dixon & de Frias, 2004). Three main sequential samples (initially aged 55-95 years) are followed at about 4-year intervals ($M = 4.4$). As the focus of this study is to examine change in EF as predicted by genetic variants, participants were limited to a source subsample of approximately 683 participants (bridging all three main VLS core samples). This source sample provided biofluid for genotyping between 2009 and 2011. Following previous protocols within the VLS (Dixon et al., 2012; McFall et al., 2014), a longitudinal data set from the same time

frame was assembled, with a total individualized duration of up to 9 years. Specifically, the present study consisted of Sample 1 (S1) waves 6, 7 and 8, Sample 2 (S2) waves 4 and 5, and Sample 3 (S3) waves 1, 2, and 3. For efficiency, the first wave in each sample will be henceforth termed as W1, the second W2, and the third W3.

Exclusionary criteria were applied, including: (a) a diagnosis of AD or other forms of impairment and dementia, (b) Mini Mental State Exam score of < 24 (Folstein, Folstein & McHugh, 1975), (c) a self-report of "severe" for conditions such as high blood pressure, low blood pressure, epilepsy, spinal or thyroid conditions, depression, head injury, (d) reported alcohol or drug dependence, (e) reported use of anti-psychotic medications, (f) self-reported "moderate" cases of neurological conditions (Parkinson's or stroke), (g) reported or identified cases of diabetes (e.g., with the VLS multilevel diagnostic criteria), and (h) participants with no EF, MOB or EPA data. A total of 145 participants were excluded.

The final sample contained $N = 538$ individuals ($n = 357$ females) all of whom contributed data to W1 (M age = 70.29 $SD = 8.57$, range 53.24 – 95.25). W2 consisted of $n = 456$ adults (M age = 74.51, $SD = 8.48$, range 57.27 – 94.53, $n = 301$ females). W3 consisted of $n = 291$ adults (M age = 76.12, $SD = 8.02$, range 62.44 – 94.90, $n = 205$ females). Table 1 presents basic demographic information. The design stipulated that S1 and S3 participants could contribute data to all three waves, but S2 participants contributed data to W1 and W2 (the third wave not available). All missing data were estimated by multiple imputations using Mplus 7 (Enders, 2011; Little, 2013; Muthén & Muthén, 2010). By prevailing convention 20 or more imputations are recommended (e.g., Enders, 2011; Graham, Olchowski, & Gilreath, 2007; Rubin, 1987). We included 50 imputations, as we have done in previous studies (see McFall et al., 2014).

Measures

Executive Function (EF). Four neuropsychological measures were used to represent two dimensions of EF, with two measures each of shifting, and inhibition, (Miyake et al., 2000). All four measures have all been used in standard form with older adults in VLS studies reporting psychometric (Bielak, Mansueti, Strauss & Dixon, 2006), structural and neuropsychological (de Frias et al., 2006, 2009), genetic (Sapkota et al., 2014), health (McFall et al., 2013, 2014), and lifestyle (de Frias & Dixon, 2014) factors.

Shifting. (1) Brixton Spatial Anticipation Test (Burgess & Shallice, 1997) indexed shifting by measuring rule-attainment. The Brixton test consists of a 56-page stimulus booklet, each page showing the same display of 10 circles, with each circle numbered from 1 to 10. On each page, one of the circles is filled with a blue color. The position of this filled circle changes from one page to the next. The changes in position are governed by a series of simple rules that vary without warning. Participants were required to predict the blue circle placement based on previous presented patterns. Responses were considered correct if the response followed the current pattern, or when the trials changed, if it would have been correct had the pattern remained the same. The total errors were recorded (on a maximum of 54 trials) and converted to scaled scores. An overall standardized scaled score based on a scale ranging from 1 (*impaired*) to 10 (*very superior*) was used for analysis. (2) The Color Trails Test (D'Elia, Satz, Uchiyama, & White, 1996) was designed to measure shifting. Color trails test Part 2 showed numbers from 1 – 25 twice (each sequence has either a yellow or pink background) and required the participant to connect numbers in numerical order alternating between pink and yellow circles, disregarding the numbers in circles of the alternate color. A reverse coded latency score was used for analysis to be commensurate with all other tasks, thus higher scores indicate better performance.

Inhibition. (1) The Hayling Sentence Completion test was developed to index inhibition by measuring initiation speed and response suppression. It consists of two sections of 15 sentences, each missing the last word. Section 1 requires the participant to quickly and correctly complete the sentence, and measures response speed. Section 2 requires completing the sentence quickly with an unconnected word, and measures response suppression. Response latencies on both sections and errors on Section 2 are used to derive an overall scaled score for each participant on a scale ranging from 1 (*impaired*) to 10 (*very superior*). (2) The Stroop test measures inhibitory processes by requiring the respondent to name the color of the ink a word is printed in and supress the automatic response of reading the word itself (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997). The performance score is the interference index and reflects slowing in response to interference in Part C ([Part C time – Part A time]/Part A time). The interference index was reverse coded for the analyses to be commensurate with the other executive functioning tasks; therefore higher scores indicate better performance.

Everyday Physical Activity (EPA). The measure is the four-item physical activity subscale from the VLS-Activity Lifestyle Questionnaire (Hultsch et al., 1999; Small et al., 2011; see Appendix C). Each item indexed frequency of participation in everyday physical activities (e.g., jogging, walking,tennis,swimming, biking, gardening) over a period of two years on a scale of 0 (never) to 8 (daily). Responses were totalled, producing a continuous measure with scores ranging from 0 – 32. Higher scores indicate more participation in everyday leisure physical activities.

Mobility (MOB). The composite was formed with unit-weighted z-scores of the following indicators of mobility. Scores were reverse coded; therefore, a higher mobility score indicated better mobility performance.

Timed Walk. This task was designed to measure a person's walking speed over a distance of 20 feet. Participants were instructed to walk in a straight line as quickly and safely as possible just past the tape on the floor at a distance of 10 feet, turn around and walk as quickly and safely as possible back to the starting position. The amount of time taken to perform this task was recorded in seconds.

Timed Turn. This task was designed to assess the ability to move using the legs. This is accomplished by assessing a person's ability to make a complete circle from a standing position. Participants were instructed to stand directly behind a white line on the floor, with their toes lined up along the line and feet slightly apart, then asked to make one complete turn in place, returning to the starting position with the toes lined up once again directly behind the white line. Time taken to complete the task was measured in seconds.

DNA Extraction and Genotyping

Saliva was collected according to standard procedures from Oragene-DNA Genotek and stored at room temperature in the Oragene disks until DNA extraction. DNA was manually extracted from the saliva sample mix using the manufacturer's protocol and quantified using a NanoDrop ND-1000 Spectrophotometer (Wilmington, DE). Genotyping was carried out by using a PCR-RFLP strategy to analyze the allele status for *APOE* (determined by the combination of the single nucleotide polymorphisms (SNPS) rs429358 and rs7412), *CR1* (rs6656401), *CLU* (rs11136000) and *PICALM* (rs541458). Briefly, SNP-containing PCR fragments were amplified from 25 ng of genomic DNA using specific primers (*APOE*: Fwd: 5'-GGCACGGCTGTCCAAGGA-3', Rev: 5'-GCCCCGGCCTGGTACACTGCC-3'; *CLU*: Fwd: 5'-AAAGCAGGCTGCAGACTCC-3', Rev: 5'-AGTGCTGGGATTACAGGTGTC-3'; *CR1*: Fwd: 5'-CTCCAGGCTTCCTTCCAGT-3', Rev: 5'-TTAATGATCTCGAGCTGTGACC-3';

PICALM: Fwd: 5'-AAACCACAGATGAACTGATGTAACTG-3', Rev: 5'-GGCATTAGGACCTGCCATC-3'). Reactions were set up in 96-well plates using the QIAgility robotic system (QIAgen). RFLP analysis was performed on a high resolution DNA screening cartridge on a QIAxcel capillary electrophoresis system (QIAgen) using the protocol OL700 after digestion of the PCR amplicons with the restriction enzymes (all from NE Biolabs) of *APOE*: HhaI for 16 hours at 37°C. The analysis was confirmed upon migration of the restriction fragments on 10 or 15% acrylamide gels for the SNP.

Genetic analyses included genotype categorization based on the presence or absence of the risk allele. *APOE* genotype was divided into three categories: ε2+ (protective) consisted of ε2/ε2 and ε2/ε3 combinations, ε3 (non-risk) consisted of ε3/ε3, and ε4+ (risk) consisted of ε4ε4 and ε3/ε4 allele combinations. For all analyses including *APOE,* standard practice is to remove the genotype which combines the risk and protective alleles (ε2ε4; n = 28), in order to assess the independent effects of ε2 and ε4 (McFall et al., 2014). For the other three AD risk genes, the following rules were applied: (a) the *CLU* genotype was divided into two categories, C- (non-risk) consisted of the T/T allele combination, C+ (risk) consisted of the T/C and C/C allele combinations (Bertram, McQueen, Mullin, Blacker & Tanzi, 2007; Harold et al., 2009; Lambert et al., 2009); (b) the *CR1* genotype was divided into two categories, A+ (risk) consisted of the A/A and A/G allele combinations, A- (non-risk) consisted of the G/G allele combination (Chibnik et al., 2011; Jin, Li, Yuan, Xu, Cheng, 2012; Lambert et al., 2009); and (c) the *PICALM* genotype T+ (risk) consisted of the T/T and T/C allele combinations, T- (non-risk) consisted of the C/C allele combination (Schjeide et al., 2011).

To examine interactions with genetic risk score, we followed a series of steps for genotype categorization. First, risk scores were calculated for *APOE* by assigning a score of "0" for an ε2

allele, a score of "1" for an ε3 allele and a score of "2" for an ε4 allele. Therefore, ε2 homozygotes were given a score of "0", ε2ε3 heterozygotes were given a score of "1", ε3 homozygotes were given a score of "2", ε3ε4 heterozygotes were given a score of "3", and ε4 homozygotes were given a score of "4". Second, genetic risk scores were calculated based on the presence or absence of a risk allele for *CLU*. A score of "0" was assigned if no risk allele was present, "1" if one risk allele was present and a "2" if both risk alleles were present. Therefore, for *CLU* C-allele homozygotes were assigned a score of "2", heterozygotes a score of "1" and T-allele homozygotes a score of "0". Third, cumulative genetic risk scores were calculated for the gene combination of *APOE* and *CLU*. Fourth, a tertile split was conducted on the genetic risk score, resulting in three groups (i.e., low, mid, and high genetic risk; see Appendix B).

Statistical Analyses

Structural equation modeling was conducted using Mplus 7 (Muthén & Muthén, 2010). Confirmatory factor analysis and latent growth modeling were used to test the five research goals. Model fit for all analyses was determined using standard indices: (a) χ^2 for which a good fit would produce a non-significant test ($p > .05$), indicating the data are not significantly different than the model estimates, (b) comparative fit index (CFI) for which $\geq .95$ was judged a good fit and between .90 and .94 was judged an adequate fit, (c) root mean square error of approximation (RMSEA), for which $\leq .05$ would be judged good and between .06 and.08 would be judged adequate, and (d) standardized root-mean-square residual (SRMR) for which good fit is judged by a value of $\leq .08$ (Kline, 2011; Little, 2013). To test longitudinal measurement invariance, the confirmatory factor analysis models with free and constrained parameters were compared using a chi-square-based likelihood ratio test ($\Delta\chi^2$). However, as this test is sensitive to over-identifying lack of invariance in large sample sizes, it is recommended to use the ΔCFI test

(cut-off = .01; Cheung & Rensvold, 2002; Little, 2012) as well as the aforementioned standard fit indices (Kline, 2011; Meade, Johnson & Braddy, 2006).

Analyses for RG 1: Verification of EF latent model and measurement invariance. We used a standard procedure to verify previously observed psychometric characteristics of EF**.** First, confirmatory factor analysis was performed to verify that a single latent EF factor (previously observed: McFall et al., 2013, 2014) fit this particular sub-sample of participants. Second, longitudinal measurement invariance was tested using (a) configural invariance, for which the same indicator variables load onto the latent variable to determine if the same EF measures represent the latent variable at each wave of data collection, (b) metric invariance, for which factor loadings are constrained to be equal for each latent variable indicating that each latent variable was measuring the same construct, and (c) scalar invariance, for which indicator intercepts are constrained to be equal allowing mean differences to be evident at the latent mean level. Third, EF factor scores were estimated in MPlus and used in all subsequent growth models. Multiple imputations were used for missing EPA, age, MOB, and EF factor score data.

Analyses for RG2: Latent growth modeling for EF, EPA and MOB. Consistent with other VLS research, age was coded as a continuous factor. Age was centered at age 75, the approximate mean of the 40-year span of data. This is a commonly observed inflection period in cognitive aging (e.g., Dixon et al., 2012; Schaie, 2013; Small et al., 2011) and has been used in previous related research (McFall et al., 2014). Latent growth modeling was performed to establish the functional form of change for EF, EPA and MOB. Models tested include: (a) a fixed intercept model, which assumes no inter- or intraindividual variation (b) a random intercept model, which models interindividual variability in overall level but no intraindividual change (c) a random intercept fixed slope model, which allows interindividual variability in level but

assumes all individuals exhibit the same rate of change and (d) a random intercept, random slope model which allows interindividual variability in level and change (Singer & Willett, 2003).

Analyses for RG 3: Independent effects of EPA, MOB, *APOE*, *CLU*, *CR1*, and *PICALM* on the EF growth model. The best unconditional EF growth model was used as the baseline against which conditional growth models with the independent predictors of change in two clusters (EPA, MOB; *APOE*, *CLU*, *CR1*, *PICALM*) were tested (Little, 2013). Path analyses was used to determine the effect of each predictor on level of EF performance at age 75 and 9-year EF change.

Analyses for RG 4: Interactive effects of the individual genes x EPA on the EF growth model (RG 4a); Interactive effects of the genetic risk score x EPA on the EF growth model (RG 4b). To examine the genetic-EPA interactions, a series of steps were followed. First, a model which tested the effect of EPA on level of EF performance and 9-year EF change was estimated, with all the parameter estimates constrained to be equal across genetic groups. Second, the parameters were free to vary between genetic groups to examine moderation. These steps were completed for each genetic predictor (*APOE*, *CLU*, *CR1* and *PICALM*). Evidence of moderation was indicated by a significant difference test which compared the fully constrained to the unconstrained model (Kline, 2011). Third, education, gender, vascular health, (measured by pulse pressure, a proxy measure of arterial stiffness PP; Benetos et al., 2010; see McFall et al., 2014, 2015; Raz et al., 2011) and body mass index (BMI) were separately and simultaneously included as covariates, as these factors have been associated with executive functioning in older adults.

To examine whether an AD genetic risk score (i.e. *APOE* and *CLU*) altered the pattern of results seen in RG4a, the same procedure was followed.

Analyses for RG 5: Interactive effects of the individual genes x MOB on the EF growth model (RG5a); Interactive effects of the genetic risk score x MOB on the EF growth model (RG5b). To examine genetic-mobility interaction effects on the EF growth model a series of steps were followed. First, a parallel process model was estimated for the entire sample, with all the parameter estimates constrained to be equal across genetic groups. Second, regressions among latent growth factors were free to vary between genetic groups in order to compare differences in the predictive strength of mobility across genetic groups. Third, the latent growth factors for mobility were regressed on each of the covariates (Gender, PP, BMI, Education and PA). These steps were completed for each genetic predictor (*APOE*, *CLU*, *CR1* and *PICALM*). Moderation was evidenced by a significant difference test which compared the constrained model to the model where the associations varied across genetic groups.

Results

RG1: EF Latent Model and Invariance Verification

We first confirmed that a single-factor model consisting of the four EF indicators fit this sub-sample of participants (see Table 2 for all goodness of fit indices). Second, we used overall model fit and $\Delta\chi^2$ tests to confirm measurement invariance, including the sequence from (a) configural invariance ($\chi^2 = 33.68$ $df = 35$, $p = .53$), (b) metric invariance ($\Delta\chi^2 = 8.149$, $\Delta df = 6$, $p = .23$, ΔCFI = .001), and (c) scalar invariance ($\Delta\chi^2 = 152.37$, $\Delta df = 8$, $p < .001$, ΔCFI = .08). The significant effect for the latter indicated this criterion was not met, and thus we proceeded to test a model with partial scalar invariance ($\Delta\chi^2 = 21.341$ $\Delta df = 4$, $p < .001$, ΔCFI = .01). Despite a significant decrease in model fit, we retained the partial scalar model with intercepts constrained to be equal across time for Stroop and Brixton, given the observation of a larger pattern of good fit indices and the acceptable ΔCFI (i.e., RMSEA = .027, CFI = .99, SRMR = .06, ΔCFI = .01).

Two indicator variables (i.e., Hayling, Color Trails) exhibited mean differences outside of the latent variable. The invariance testing results indicated that the EF model measured the same construct over time, the same indicator variables marked EF at each wave, and partial scalar invariance allowed us to compare latent variable means (Kline, 2011).

RG2: Latent growth modeling for EF, PA, and MOB

The best fitting unconditional growth model for EF was established as a random intercept, random slope model (see Table 3). First, at age 75, older adults varied significantly in level of EF performance (b = 1.05, p < .001). Second, there was significant decline in EF performance (M = -.016, p = .003). Third, there was significant individual variability in the rate of decline (b = .003, p < .001).

Next for EPA, the preferred model was a random intercept, fixed slope model (see Table 3). First, at age 75, there was significant variability in level of EPA (b = .156, p < .001). Second, older adults exhibited significant decline in EPA level (M = -.015, p < .003), but without individual differences in rate as evidenced by the non-significant random slope (p > .05) in the random intercept, random slope model.

For mobility, the preferred model was a random intercept, random slope model (see Table 3). First, at age 75, there was significant variability in level of MOB (b = .557, p < .001). Second, older adults exhibited significant decline in MOB level (M = -.061, p < .001). Third, there was significant individual variability in the rate of decline (b = .002, p = .001).

RG3: Independent effects of EPA, MOB, *APOE*, *CLU*, *CR1*, and *PICALM* on the EF growth model

We tested two growth models with EPA as a predictor of EF level and change. The first model used the EPA growth model in parallel process with the EF growth model. Time-varying

EPA did not predict EF performance at age 75 (b = -.002, p >.05) nor 9-year EF change (b = .529, p >.05). The second time-invariant model with initial (W1) level of EPA revealed significant predictions for both EF performance at age 75 (b= .340, p <.001) and 9-year change (b = .016, p = .002; see Figure 1). Specifically, at W1 lower levels of EPA were associated with significantly worse EF performance (M = -.347) than were higher levels of EPA (M = -.007). Moreover, lower initial levels of EPA were associated with greater 9-year EF decline (M = -.042) than were higher levels (M = -.026). Thus, the time-invariant EPA (W1) model was used in subsequent analyses.

We tested a model using the MOB growth model in parallel process with the EF growth model. Level of mobility at age 75 predicted level of EF performance at age 75 (b = .798, p =.003), but not 9-year change (b = .010, p =.81). In addition, change in mobility over 9 years did not predict change in EF over 9-years (b = .31, p > .70). Moreover, we examined possible bi-directionality and results were similar. Specifically, level of EF performance at age 75 predicted level of mobility at age 75 (b = .252, p < .001) but not 9-year change (b = -.006, p = .80). Also, change in EF over 9 years did not predict change in mobility (b = .645, p = .27).

For EF, we tested four models with *APOE*, *CLU*, *CR1,* and *PICALM* as independent predictors of EF level and change. No independent effects were found, as none of the four genes tested predicted level of EF performance at age 75, or 9-year EF decline.

RG 4a: Interactive effects of *APOE* x EPA, *CLU* x EPA, *CR1* x EPA, *PICALM* x EPA and on the EF growth model

We conducted four sets of two-model comparisons to examine whether *APOE*, *CLU*, *CR1,* or *PICALM* moderated the effect of EPA on EF.

For *APOE*, an interaction was evidenced by the fully constrained model producing a significantly worse fit than the unconstrained model (D = 28.24, $\Delta df = 14$, $p = .013$; see Table 4 for model comparisons). Specifically, level of EPA at W1 predicted both level of EF performance at age 75 ($b = .391$ $p < .001$) and 9-year EF change ($b = .021$, $p = .001$; see Figure 2) for the *APOE* ε3/ε3 group only. Within the *APOE* ε3/ε3 group, older adults with low levels of EPA at W1 exhibited poorer EF performance ($M = -.407$) and steeper 9-year decline ($M = -.049$) than did their peers with high levels of EPA ($M = -.016$ and $M = -.028$, respectively; see Figure 2b). This pattern was not present for the ε2/ε2 ε2/ε3 (protective) or the ε3/ε4 ε4/ε4 (risk) group, as level of EPA did not alter level of EF at age 75 ($b = .454$, $p = .108$; $b = .122$, $p = .538$, respectively) nor the 9-year EF change ($b = .013$, $p = .416$; $b = .007$, $p = .492$, respectively; see Figure 2a and 2c).

When the covariates (gender, education, PP and BMI) were included in the analyses, education and PP exhibited significant effects on level of EF performance and 9-year decline for the *APOE* ε3 homozygote (non-risk) and *APOE* ε4+ (risk) group. Specifically, for the ε3 and ε4+ groups, higher education was associated with higher level of EF performance at age 75 and more gradual 9-year decline, and higher levels of PP (poorer vascular health) was associated with lower levels of EF performance at age 75 and steeper EF decline over 9 years. Gender exhibited significant effects on 9-year decline for the *APOE* ε3 homozygote (non-risk) group only. Specifically, higher levels of EPA at W1 were associated with less decline over 9 years for female ε3 carriers only. BMI did not exhibit significant effects on level of EF performance or 9-year change for any of the ApoE groups. Notably, despite education, gender and PP having significant effects, no changes in the main results were observed.

A significant interaction was indicated for *CLU* (see Figure 3 for model fit indices). Moderation was evidenced by a significantly worse fitting constrained model when compared to the unconstrained model (D = 14.76, $\Delta df = 7$, $p = .03$). Specifically, for the risk (C+) group, level of EPA at W1 predicted both the level of EF performance ($b = .316$, $p < .001$) and 9-year EF change ($b = .016$, $p = .006$). Within the risk group, older adults with lower levels of EPA at W1 exhibited poorer EF performance at age 75 ($M = -.298$) and steeper 9-year EF decline ($M = -.049$) than their peers with higher EPA levels at W1 ($M = .018$ and $M = -.026$, respectively; see Figure 3a). In contrast, for the *CLU* C- non-risk group, level of EPA at W1 affected only level of EF performance ($b = .480$, $p = .013$) not 9-year EF change ($b = .018$, $p = .136$; see Figure 3b).

When the covariates were included in the analyses, BMI and gender did not exhibit significant effects on either level of EF performance or 9-year change. Education and pulse pressure both exhibited significant effects on level of EF performance and 9-year decline for only the *CLU* risk group. Specifically, within the *CLU* C+ group, higher education was associated with higher level of EF performance at age 75 and less 9-year decline, and higher levels of pulse pressure (poorer vascular health) was associated with lower levels of EF performance at age 75 and steeper EF decline over 9 years. In addition, the pattern of main results for the non-risk group changed with the inclusion of these covariates. Specifically, when education was added, the effect of EPA at W1 on level of EF performance at age 75 for the CLU C- (non-risk) carriers became non-significant ($b = .414$, $p = .053$). However, none of the other covariates (i.e., BMI, gender, or pulse pressure) changed the patterns of main results.

For *CR1* and *PICALM,* the constrained models did not provide a significantly worse fit than the unconstrained models, therefore there was no evidence for moderation (D = 9.8, $\Delta df = 7$, $p = .20$; and D = 7.98, $\Delta df = 7$, $p = .33$, respectively; see Table 4 for model comparisons).

RG 4b: Interactive effects of AD genetic score x EPA on the EF growth model

Based on the results of RG4a, we examined whether there was genetic moderation by genetic risk score comprised of both *APOE* and *CLU*. We tested the effect of EPA, measured at W1, on level of EF performance at age 75 and 9-year change based on a tertile split of the cumulative genetic risk score of *APOE* and *CLU* (see Figure 4; Appendix B). The constrained model provided a significantly worse fit (D = 26.88, $\Delta df = 14$, $p = .02$), providing evidence of moderation by the genetic risk score. First, for the low-risk group, level of EPA at W1 significantly predicted level of performance ($b = .574$, $p = .003$) but not 9-year change ($b = .019$, $p = .099$, see Figure 4a). Specifically, within the low-risk group, older adults with lower levels of EPA at W1 exhibited poorer EF performance at the age of 75 ($M = -.820$) than did their genetically corresponding peers with higher levels of EPA at W1 ($M = -.246$). Second, for the mid-risk group, level of EPA at W1 significantly predicted 9-year change ($b = .020$, $p = .019$, see Figure 4b). Specifically, within the mid-risk group, older adults with lower levels of EPA at W1 exhibited steeper EF decline ($M = -.05$) than their genetically corresponding peers with higher levels of EPA at W1 ($M = -.03$, respectively). EPA at W1 did not predict EF performance or 9-year change for the high-risk group (see Figure 4c).

All of the covariates exhibited significant effects on EF, with the exception of gender. Education and pulse pressure predicted EF level and change for the mid- and high-risk groups, and BMI predicted level of EF performance at age 75, and 9-year decline for the low-risk group. In addition, the pattern of main results changed with the inclusion of BMI, but did not change with the addition of education, gender, or pulse pressure. Specifically, when BMI was added, EPA at W1 also predicted 9-year decline in EF for the low-risk group ($b = .002$, $p = .042$).

RG 5a: Interactive effects of *APOE* x MOB, *CLU* x MOB, *CR1* x MOB, and *PICALM* x MOB on the EF growth model

We conducted four sets of two-model comparisons to examine whether *APOE*, *CLU*, *CR1,* or *PICALM,* moderated the effect of MOB on EF.

For *APOE*, an interaction was evidenced by the significant difference test between the constrained model and the model in which the regressions between latent growth factors were free to vary (D = 16.16, $\Delta df = 6$, $p = .013$; see Table 5 for model comparisons). Specifically, level of mobility at age 75 was most strongly predictive of level of EF at age 75 for ε4 carriers ($b = .844$, $p < .001$). Level of mobility at age 75 was also predictive of level of EF at age 75 for ε3/ε3 carriers ($b = .450$, $p < .001$) but not for the ε2 carriers ($b = .292$, $p > .05$).

When covariates were added into this model, PP exhibited significant effects on mobility. Specifically, better vascular health was associated with less 9-year decline for the *APOE* ε3/ε3 carriers. However, the inclusion of the covariates did not change the main results, level of mobility at age 75 remained a stronger predictor of level of EF at age 75 for the risk group than the non-risk group.

For *CLU*, an interaction was evidenced by the significant difference test between the constrained model and the model in which the regressions between latent growth factors were free to vary (D = 9.56, $\Delta df = 3$, $p = .022$; see Table 5 for model comparisons). Specifically, level of mobility at age 75 was strongly predictive of level of EF at age 75 for risk (C+) carriers ($b = .532$, $p < .001$). Level of mobility at age 75 was not predictive of level of EF at age 75 for non-risk (C-) carriers ($b = .428$ $p = .05$).

When covariates were added to this model, BMI, PP and EPA exhibited significant effects on mobility, but gender and education did not. Specifically, lower BMI and higher levels of

physical activity were associated with higher levels of mobility at age 75 for only the CLU risk carriers. Better vascular health was associated with higher mobility at the age of 75, and less 9-year decline for the CLU risk group. However, the inclusion of these covariates did not change the main results.

For *CR1* and *PICALM,* the constrained models did not provide a significantly worse fit than the unconstrained models, therefore there was no evidence for moderation (D = 4.40, $\Delta df = 3$, $p = .22$; and D = 1.16, $\Delta df = 3$, $p = .76$, respectively; see Table 5 for model comparisons).

RG 5b: Interactive effects of the AD risk composites x MOB on the EF growth model

Based on the results of RG 5a, we examined whether there was genetic moderation by a composite comprised of *APOE* and *CLU*. We conducted a two-model comparison to examine whether a genetic risk score moderated the effect of MOB on EF, based on a tertile split of the cumulative genetic risk score of *APOE* and *CLU.* The pattern of results were similar to previous analyses, level of mobility at age 75 was a stronger predictor of level of EF at age 75 for the high-risk group than the mid or low-risk groups, however, the difference test between the constrained and partially constrained models was not significant (D = 12.06, $\Delta df = 6$, $p = .06$; see Table 5 for model comparisons).

Discussion

The overall purpose of this research was to examine concurrent and longitudinal associations among a lifestyle factor (EPA), a mobility factor (MOB), and four genetic polymorphisms (*APOE, CLU, CR1* and *PICALM*) as they are related to performance and change in EF. We distributed this aim into five goals.

For Research Goal 1 (EF latent model and invariance verification) confirmatory factor analysis verified that a single-factor model fit the data well. This model demonstrated metric and

partial scalar invariance, indicating the EF latent variable was unified and stable across the three waves. The single-factor EF latent variable has been reported in other recent VLS research with different samples, including normal aging (de Frias et al., 2006), mild cognitive impairment (de Frias et al. 2009), diabetes patients (McFall et al., 2013), as well as a similar sample of normal aging participants (McFall et al., 2014; Thibeau et al., in press).

For Research Goal 2 (latent growth models for EF, EPA and MOB) we expected results similar to previous VLS research for the growth models of EPA and EF (McFall et al., 2014; Thibeau et al., in press). For EPA, we observed (a) significant variability in performance and (b) significant decline in EPA (but without interindividual variability). For EF, we observed (a) significant performance variability, (b) significant 9-year decline, and (c) significant interindividual variability in decline. A novel finding occurred for MOB. We observed (a) significant performance variability, (b) significant 9-year decline, and (c) significant interindividual variability in decline. These results add to emerging literature which has identified differing trajectories of mobility decline in well-functioning older adults (Diehr et al., 2013; White et al., 2013). The observed variability in performance and decline in EF is central to our subsequent research goals.

Research Goal 3 (unconditional growth models using EPA and MOB) revealed two main results. First, for EPA, results verified that older adults with higher baseline levels of EPA had better initial EF performance and more gradual decline over the three waves. This is consistent with recent research (e.g., Bielak, Cherbuin, Bunce, & Anstey, 2014; Blasko et al., 2014; Buchman et al., 2012; Ferencz et al., 2014; Hamer, Lavoie & Bacon, 2013; Lindwall et al., 2012; Rovio et al., 2005; Wang et al., 2013; Woodard et al., 2012) indicating higher levels of EPA may attenuate cognitive decline. Also, of note is that the VLS measure of EPA encompasses a wide

scope of dosage, duration, and type of physical activity, including engagement in low to moderate intensity activities, therefore broadening the scope of physical activity known to be beneficial to cognitive function (Thibeau et al., in press). In fact, a recent meta-analysis of prospective studies examining the relationship between physical activity and cognitive decline has confirmed even low to moderate levels of physical activity provide significant protection against cognitive impairment for non-demented older adults (Sofi et al., 2010). A recent review of the literature has indicated moderate physical activity is liked with more efficient patterns of brain activity during tasks of executive control (Voelcker-Rehage & Niemann, 2013). Moreover, novel community-based lifestyle interventions are being developed to promote health for older adults by increasing participation in social, cognitive and physical activities (Varma et al., in press). Thus, engagement in low to moderate levels of physical activity may be a relatively accessible strategy for older adults to protect against cognitive decline associated with dementia.

This benefit to cognition could occur through increased brain volume as a result of participation in EPA. Recently, Tamura and colleagues (2014) found that a mild-intensity calisthenics program was associated with prefrontal volume preservation, and that changes in attention and memory were positively correlated with the prefrontal volume change. Additionally, Erickson and colleagues (2010) indicated that greater amounts of walking predicted greater gray matter volume over a period of 9 years. As walking is an everyday activity included in the range represented in the construct of EPA, it is conceivable that participation in other forms of low to moderate intensity EPA benefits prefrontal gray matter volume, thereby favorably influencing EF in non-demented older adults.

Second, for MOB, we tested time-varying MOB in parallel process with the EF latent growth model. Results indicated that level of mobility at age 75 predicted level of EF at age 75,

but not decline in EF performance. Bi-directionality was examined, and results were similar, level of EF at age 75 predicted level of mobility at age 75. These results are supportive of research associating executive function and mobility in older adults (Ble et al., 2005; Doi et al., 2014; Watson et al., 2010). Of note, however, is that mobility performance at age 75 did not predict EF decline over time. Although the absence of this association was also indicated by Payette and colleagues (2011), as a follow-up analysis we examined whether initial level of mobility was predictive of either EF performance, or 9-year decline. Results indicated that individuals with better initial levels of mobility had better EF performance and less 9-year decline than their peers with poor initial mobility. Although it was expected that similar results would be seen when mobility was used as a time-varying predictor, the absence of this association could be due in part to the relatively healthy, active sample of participants within the VLS. It is possible that these relatively active individuals do not experience the EF decline associated with mobility decline, as a function of physical inactivity. Physical activity has been found to increase gray matter volume in the prefrontal cortex (Colcombe et al., 2006), an area which mediates processes associated with EF. Therefore, while still exhibiting mobility decline, this may not reflect EF decline, possibly due to level of engagement in protective lifestyle factors which increase brain matter volume. In fact, when EPA was examined as a predictor of mobility, higher levels of EPA were significantly associated with higher levels of mobility, and less mobility decline over time. This relationship was also shown by Berryman and colleagues (2013). Specifically, individuals with higher performance on measures of gait and balance had better EF performance and higher physical fitness levels.

In addition, it has been shown that the association between mobility performance and EF decline is stronger if there is already evidence of mobility impairment due to a neurodegenerative

disease, or if the locomotor task is highly challenging (Yogev, Hausdorff, & Giladi, 2008). Therefore, it is possible we did not find evidence of an association between mobility performance and EF decline because (a) the sample was non-demented, normally aging participants or (b) the relatively straightforward mobility tasks did not require intense dual-processing. To obtain more information about the processes of mobility involved within non-demented older adult populations, future research could examine the EF-MOB relationship using mobility tasks with differing levels of cognitive load (Gill et al., 2015).

The subsequent analyses of the genetic factors as independent predictors of EF level and change did not reveal notable results. Mixed results are evident in the literature for non-demented older adults. Although *APOE* has been associated with some declines in cognitive function (Caselli et al., 2009; Yaffe et al., 2009), there are a few possible explanations for the absence of evidence of an independent effect of *APOE*. First, as one of the exclusionary criteria was a MMSE score indicative of impairment (< 24), it is possible carriers of the ε4 allele who are at higher risk of becoming impaired had already developed cognitive impairment and therefore were not included in the study. As mobility impairment could also be a phenotype of cognitive impairment, this exclusion could result in a sample of higher physically functioning *APOE* ε4 carriers who are protected from the risks associated with this gene. In fact, of the three genetic groups, the *APOE* ε4 group had the highest mean level of EPA. Although the groups were not significantly different from each other in EPA level, this marginally higher level of physical activity would be dependent upon a high level of mobility or other protective factors. Interestingly, when considering both the absence of (a) a relationship between mobility decline and EF decline and (b) an independent effect of *APOE* on EF, these results could provide a possible explanation as to why the ε4 carriers assumed to be at higher risk for negative cognitive

outcomes do not show detrimental cognitive performance or decline within this non-demented sample. Second, it has been suggested that *APOE* operates in combination with other risk and protective factors to influence cognitive outcomes (Bender & Raz, 2012; Runge, MacDonald, McFall, & Dixon, 2014). Therefore, higher levels of mobility at the age of 75 could be a considerable protection factor against further cognitive decline. This explanation is further examined in RG5.

For Research goal 4a, we tested genetic moderation effects on the EPA-EF relationship. *APOE* and *CLU* both exhibited significant moderation effects, whereas *CR1* and *PICALM* did not. *APOE* ε3 carriers who had high levels of EPA outperformed and exhibited less 9-year EF decline than their genetically corresponding peers with lower levels of EPA. This effect was not seen within the ε2 or ε4 groups. This effect remained when other factors known to influence EF performance (education, PP, BMI, and gender) were considered. Interestingly, results of previous research on the interaction between physical activity and *APOE* status for risk of cognitive decline and dementia have proven to be inconsistent. Various studies have indicated a positive association for only the risk (ε4) carriers (Ferencz et al., 2014; Rovio et al., 2005; Woodard et al., 2012), whereas others have not found a significant association (Lindsay et al., 2002; Luck et al., 2014; Paillard-Borg, Fratiglioni, Xu, Winblad, & Wang, 2012). Our current results extend research by Podewils and colleagues (2005), who observed that engaging in higher levels of physical activity reduced the dementia risk only for *APOE* ε4 non-carriers. Of note, most of the recent research that examines *APOE* does so by comparing the risk (ε4+) and non-risk groups (ε4-), thus grouping together the ε2/ε2, ε2/ε3 and ε3/ε3 carriers (Ferencz et al., 2014; Luck et al., 2014; Paillard-Borg, et al., 2012; Woodard et al., 2012). Therefore, little is known about a gene x EPA interaction for the ε2 carriers. Although the current results did not indicate an effect of EPA

for the *APOE* ε2 carriers, further research is needed to examine any potential synergistic effect of having the protective allele status (ε2) for *APOE* and participating in a risk-reducing lifestyle activity such as physical activity.

Regarding possible mechanisms, recent work has indicated that higher levels of physical activity are associated with lower levels of beta-amyloid, insulin, triglycerides, and higher levels of high density lipoprotein (Brown et al., 2013). In fact, lower plasma Aβ levels as a result of physical activity, have been found for only the *APOE* ε4 non-carriers (Brown et al., 2013). In addition, higher plasma Aβ has been associated with more cognitive decline (Cosentino et al., 2010). Therefore, as seen in the current study, ε4 non-carriers may exhibit the cognitive benefits of engaging in physical activity through reduced circulating levels of Aβ.

For the *CLU* risk carriers, participation in EPA attenuated the effect of genetic risk on EF performance and decline over three waves. This pattern was not seen within the *CLU* non-risk group after adjusting for education. Recently, Ferencz and colleagues (2014) found that physical activity attenuated the risk of episodic memory decline for individuals who had higher scores on a genetic risk composite comprised of *CLU*, *PICALM* and *BIN1*. In their study, the *CLU* T allele was used as the risk allele, due to previous associations with episodic memory decline (Barral et al., 2012). In contrast, our research was guided by GWAS and other literature which indicated the C allele confers risk for AD and has been associated with decrements in cognitive function (Bertram et al., 2007; Harold et al., 2009; Lambert et al., 2007; Lambert et al., 2011; Mengel-From, Christensen, McGue, & Christiansen, 2011). To our knowledge, this is the first study examining the relationship between *CLU* and EF in older adults.

Interestingly, our findings indicated higher levels of EPA diminished the effect of the *CLU* genetic risk on EF performance and decline. This could be potentially due to EPA induced

structural changes in the brain, such as increased brain volume and angiogenesis (Boyle et al., 2014; Bullitt et al., 2009; Lista & Sorrentino, 2009). Physical activity is known to increase blood flow and increase hippocampal and medial temporal lobe volumes in the brain (Bugg & Head, 2011; Erickson et al., 2009; Erickson et al., 2011) which potentially could attenuate the brain atrophy normally associated with the *CLU* gene (Thambisetty et al., 2012). Future research should examine structural brain changes as a function of physical activity stratified by genotypes associated with risk for AD.

When we combined *APOE* and *CLU* into a genetic risk score the results indicated that the risk score significantly moderated the EPA-EF association. Specifically, individuals with lower risk and high levels of EPA had better EF performance at age 75 than individuals with lower genetic risk and low levels of EPA. In addition, the mid-risk group with high levels of EPA also demonstrated a cognitive benefit, as they experienced less decline over the 9 years than those in the mid-risk group with lower levels of EPA. There was no benefit of EPA participation for the high-risk group. When BMI was accounted for, the low-risk group also indicated a benefit of EPA on EF decline, as those with higher levels of EPA at W1 had less decline over the 9 years than their genetically corresponding peers with lower levels of EPA.

This observed pattern of results gives further support to a synergistic relationship between protective factors (i.e., genetic and lifestyle factors) associated with non-demented cognitive aging. These results complement recent literature (e.g., Papenberg, Lindenberger, & Bäckman, 2015); specifically, genetically advantaged individuals are also responsive to modifiable lifestyle and environmental factors. Of note is the fact that the effect of EPA on EF was not seen in the high risk carriers. Interestingly, fMRI research recently indicated a detrimental additive effect of the *CLU* C risk allele and *APOE* ε4 risk allele on brain activity during an executive attention task

in young adults (Green et al., 2014). This effect of genetic risk on brain activation has also been seen in older adult carriers of the *APOE* ε4 risk allele (Bookheimer et al., 2000). Specifically, non-demented ε4 carriers have greater patterns of brain activation during episodic memory performance, suggestive of a higher cognitive burden when completing the task. Taken together, it is possible these results may indicate that any potential protective effect on EF associated with physical activity is not enough to overcome the effect of a high multi-gene AD-risk score.

For research goal 5, we tested the genetic moderation effects on the MOB-EF relationship. Moderation was observed for two of the four genes, *APOE* and *CLU*, but not for the genetic risk score. For *APOE*, level of mobility was the strongest predictor of EF performance at the centering age of 75 for the risk allele carriers (ε4), but was also a predictor of EF performance for the ε3 carriers. It is interesting to consider the present results in the context of literature which links the three variables: genetics, mobility and EF. There has been an invested effort in the expansion of reserach examining the association between *APOE* and EF. It is now widely accepted that the *APOE* ε4 allele is associated with greater risk of EF decline (Wisdom, Callahan, & Hawkins, 2011). In addition, EF has been consistently associated with mobility across normally aging populations, as well as MCI (Gothe et al., 2014; Holtzer, Mahoney, & Verghese, 2013; Martin et al., 2013; McGough et al., 2011). However, there have been very few studies examining the association between *APOE* and mobility, and results within these studies have been mixed. Specifically, *APOE* ε4 has been associated with poor performance on measures of gait speed at baseline (Melzer et al., 2005), faster rates of mobility decline in men (Verghese et al., 2013), and faster rates of gait speed decline in only one of four longitudinal studies of aging (Alfred et al., 2014). In contrast, the ε4 allele was not associated with mobility decline (Blazer, Fillenbaum, & Burchett, 2001). Our results, which combine all three variables (i.e.,

MOB, *APOE* and EF), indicate the relationship between mobility and EF is stronger for the *APOE* risk carriers than the non-risk carriers. This highlights the importance for further research on the relationship between *APOE* and mobility, and consideration of the implications for cognitive decline.

Interestingly, our results indicated *CLU* also moderated the association between level of mobility and level of EF, as level of mobility was a predictor of level of EF at age 75 for only genetic risk (C+) carriers. To our knowledge there is no previous research on the relationship between *CLU* and mobility, nor *CLU* and EF. This highlights the need for further research to replicate these results,and to indicate possible biological mechanisms involved in this relationship. Speculatively, a pathway which may be implicated is the *CLU*-lipid association. Moderate physical activity is known to increase high-density lipoprotein (HDL) levels (Crichton & Alkerwi, 2015). HDL removes cholesterol from the artery wall, reducing the risk of cardiovascular disease (Rader, 2006) which is associated with increased brain activation and poor EF performance (Chuang et al., 2014) and is a major risk factor for AD (Newman et al., 2005). As plasma clusterin levels have been positively correlated with HDL levels (Won et al., 2014), and clusterin has been implicated in HDL's cardioprotective effects (Hoofnagle et al., 2010, it is possible that *CLU* may moderate the effects of mobility and physical activity on EF through its relation to HDL.

Notably, *APOE* and *CLU* moderate the EPA-EF and MOB-EF relationships in a similar manner, suggesting mobility and physical activity are strongly related. Additionally, Best and colleagues (2015) found that mobility and physical activity were both positively correlated with improvements in EF over a 12-month period. Therefore, it is possible that various biological pathways and mechanisms responsible for these effects would be similar. In fact, a recent study

has implicated insulin-like growth factor (IGF-1) as a biomarker in older adults at risk for mobility limitations (Lippi, Sanchis-Gomar, & Montagnana, 2014). IGF-1 declines with age and mediates exercise induced neurotrophic changes in the brain (Voss, Vivar, Kramer, & van Praag, 2014). It also plays a role in increasing bone mass and density, muscle angiogenesis, muscle cell growth, muscle protein synthesis, brain synaptogenesis and neuronal growth (Lippi, Sanchis-Gomar, & Montagnana, 2014). Therefore, it is possible that age-related declines in the production of IGF-1 could influence mobility and cognitive declines as a function of muscle strength, bone health and neuronal reductions.

Another mechanism which has been linked with the EPA-EF association is brain volume (Colcombe et al., 2006; Erickson et al., 2010). Likewise, slower gait speed has been linked with smaller prefrontal cortex volumes (Rosano et al., 2012). As the prefrontal cortex mediates EF processes, it is possible that level of mobility has an effect on level of EF as a function of prefrontal brain volume. Moreover, *APOE* ε4 has been associated with reduced prefrontal volumes (Bender & Raz, 2012) and *CLU* C+ has been associated with brain atrophy (Thambisetty et al., 2012). Therefore, it is possible that atrophy as a result of genetic risk exacerbates the relationship between mobility and brain volume. It is evident further research is needed in this area.

There are several limitations to this study. First, the participants of the VLS are initially selected to be relatively healthy, free of neurodegenerative disease and may possess several risk-reducing factors, such as access to national health care, above-average in years of education, and community-dwelling status. As a group, they may not be representative of the broadest population of older adults; however, they could reflect a growing proportion of older adults in western countries. Second due to the design of the VLS, W3 data had not been collected for the

second sample contributing to this study. Therefore, only participants from the first and third VLS sample contributed to W3. A more complete design would have included participants from all three samples in W3. Third, we use a self-report measure of EPA and thus not all aspects of the construct domain are represented or observed. Future research may consider including both observational and self-report indicators in order to establish validity and create composite indicators. Fourth, *APOE* ε3/ε4 carriers were combined into a genetic group with ε4/ε4 carriers. In this relatively large sample, only 12 participants were ε4 homozygotes. As research has indicated the effect of the *APOE* risk allele could be a function of the number of alleles present (Corder, Saunders, & Risch, 1994), a larger representation of ε4 homozygotes could have affected *APOE* related mobility and cognitive decline results.

There are also several strengths associated with this study. First, we used a modern statistical approach to systematically analyze five research goals. Second, we had a relatively large and well-characterized sample (W1 $n = 538$) which comprised a span of 40 years of aging. Third, age was measured as a continuous variable through an accelerated longitudinal design which allowed us to examine a change period of 9 years. Fourth, we included four standard, reliable neuropsychological manifest variables in our EF latent variable. In addition, for this study we used mobility as a time-varying predictor in parallel process with EF. Although much of the recent research has used regression modelling to determine whether mobility levels at baseline are predictors of cognitive performance (Doi et al., 2014; Melzer et al., 2005), the use of time-varying predictors allows for (a) examination of both level and change in mobility and (b) estimation of possible long-term associations with EF.

In conclusion, our results indicate that cross-domain risk and protective factors operate interactively to contribute to the variability observed for EF performance and change in non-

demented older adults. This highlights the importance of examining multiple influences on cognitive performance and change in aging. We examined the relationships between lifestyle (EPA), physical health (MOB) and cognition (EF) in older adults, as moderated by genetic factors associated with AD. The current results indicated that the role of genetic risk is marked when examined interactively with lifestyle and physical health factors, as two genetic factors associated with AD (i.e., *APOE*, *CLU*) independently and synergistically moderated the EPA-EF and MOB-EF relationships Clinically, developing interventions which increase everyday physical activity may be an accessible strategy through which genetically advantaged older adults can garner cognitive benefits, potentially reducing the risk of dementia.

Table 1

Descriptive Statistics for Sample by APOE Genotype and Longitudinal Wave

APOE	ε2ε2/ε2ε3			ε3ε3			ε3ε4/ε4ε4		
	W1	W2	W3	W1	W2	W3	W1	W2	W3
n	69	56	36	313	269	152	132	110	62
Age	70.58 (8.84)	75.08 (8.59)	74.69 (6.53)	70.53 (8.70)	74.78 (8.59)	75.16 (7.54)	69.71 (8.27)	73.61 (8.27)	74.02 (6.75)
Range	53.24 - 86.87	57.27 - 86.87	63.84 - 87.17)	54.13 - 95.25	58.11 - 94.53	62.44 - 94.90	54.63 - 87.36	58.93 - 90.41	63.22 - 92.59
Gender (% female)	66.6	66.6	67.7	60.5	56.7	68	60.5	56.7	68

Note. Results presented as Mean (Standard Deviation). W1 = Wave 1; W2 = Wave 2; W3 = Wave 3. The genotypic distribution for APOE is in Hardy-Weinberg equilibrium, $\chi^2 = .84$.

Table 2

Goodness of Fit Indices for Executive Function Confirmatory Analysis Models and Measurement Invariance Testing

Model	AIC	BIC	χ2	df	*p*	RMSEA	CFI	SRMR	Δχ2	Δdf
One Factor EF (W1)	8513.16	8564.63	3.13	2	.29	.03 (.00 - .10)	0.99	0.02		
One Factor EF (W2)	7389.46	7438.75	.02	2	0.99	.00 (.00 - .00)	1	0.001		
One Factor EF (W3)	4078.43	4121.30	3.26	2	.20	.05 (.00 - .14)	0.98	0.25		
Configural Invariance	19493.12	19729.16	35.55	35	.44	.01 (.00 - .03)	1	0.03		
Metric Invariance	19042.86	19253.05	41.83	41	.043	.01 (.00 -. 03)	.99	0.05	8.15	6
Scalar Invariance	19137.40	19313.28	152.37	49	<.001	.06 (.05 - .07)	0.92	0.10	110.54*	8
Partial Scalar Invariance[a]	**19056.20**	**19249.23**	**63.17**	**45**	**0.038**	**.03 (.01 -.04)**	**0.99**	**0.06**	**21.34***	**4**

Note. EF = Executive Function; W1 = Wave 2; W2 = Wave 2; W3 = Wave 3; AIC = Akaike information criterion; BIC = Bayesian information criterion; RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; * $p < .001$

[a] Best fitting model used for Factor Score Analysis.

Table 3

Goodness of Fit Indices for EF, EPA and MOB Latent Growth Models

Model	-2LL	Parameters Free	AIC	BIC	D	Δdf
Executive Function (EF)						
Fixed intercept	5184.44	2	5188.45	5197.02		
Random intercept	3120.45	3	3126.45	3139.32	2064.00*	1
Random intercept, fixed slope	2840.41	4	2848.41	2865.57	280.04*	1
Random intercept, random slope[a]	**1781.95**	**6**	**1793.95**	**1819.69**	1058.46*	2
Everyday Physical Activity (EPA)						
Fixed intercept	2478.5	2	2482.5	2491.08		
Random intercept	1855.22	3	1861.22	1874.09	623.28*	1
Random intercept, fixed slope[a]	**1734.95**	**4**	**1742.95**	**1760.11**	120.27*	1
Random intercept, random slope[b]	1732.95	6	1744.95	1770.69	1.998	2
Mobility (MOB)						
Fixed intercept	5351.34	2	5355.34	5363.92		
Random intercept	4808.27	3	4818.27	4827.14	543.06*	1
Random intercept, fixed slope	4376.88	4	4384.88	4402.04	431.39*	1
Random intercept, random slope[a]	**4198.15**	**6**	**4210.15**	**4235.89**	178.73*	2

Note. -2LL = -2 log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; D = difference statistic; * $p < .001$

[a] Preferred model. [b] This model was not retained as the variance of the slope was not significant

Table 4

Difference tests for genetic predictors as moderators of EPA on EF level and change

Model	-2LL	Parameters free	D	Δdf	*p*
Individual Moderators					
APOE Constrained	1703.12	8			
APOE* Unconstrained	**1674.88**	**22**	**28.24**	**14**	**< .001**
CLU Constrained	1766.2	8			
CLU* Unconstrained	**1751.44**	**15**	**14.76**	**7**	**0.039**
PICALM Constrained	1764.44	8			
PICALM Unconstrained	1747.14	22	17.3	14	0.24
CR1 Constrained	1766.4	8			
CR1 Unconstrained	1758.22	15	8.18	7	0.32
Genetic Risk Score					
APOE CLU Constrained	1681.88	8			
APOE CLU* Unconstrained	**1655**	**22**	**26.88**	**14**	**0.02**

Note. -2LL = -2 log likelihood; D = difference statistic; *indicates significant moderation

Table 5

Difference tests for genetic predictors as moderators of MOB on EF level and change

Model	-2LL	Parameters free	D	Δdf	*p*
Individual Moderators					
APOE Constrained	5643.12	15			
APOE* Regression paths free	**5626.96**	**21**	**16.16**	**6**	**.013**
CLU Constrained	5922.10	15			
CLU* Regression paths free	**5912.54**	**18**	**9.56**	**3**	**.022**
PICALM Constrained	5914.94	15			
PICALM **Regression paths free**	5913.78	18	1.16	3	.76
CR1 Constrained	5922.10	15			
CR1 **Regression paths free**	5917.70	18	4.40	3	.22
Genetic Risk Score					
APOE CLU Constrained	5629.44	15			
APOE CLU **Regression paths free**	5617.38	21	12.06	6	.06

Note. -2LL = -2 log likelihood; D = difference statistic; *indicates significant moderation

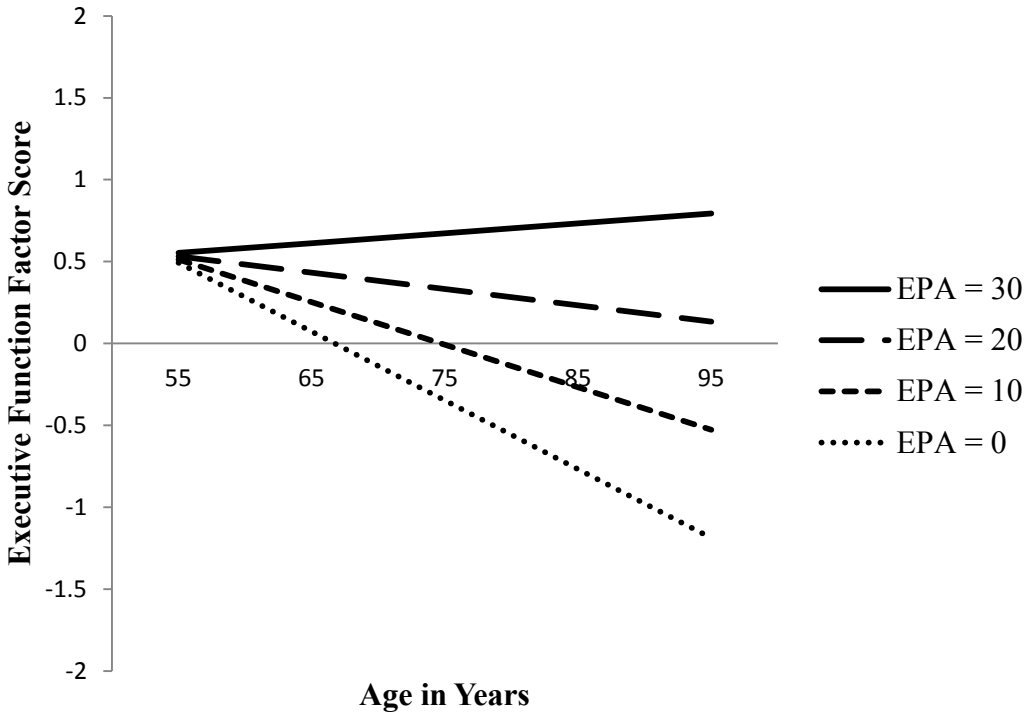
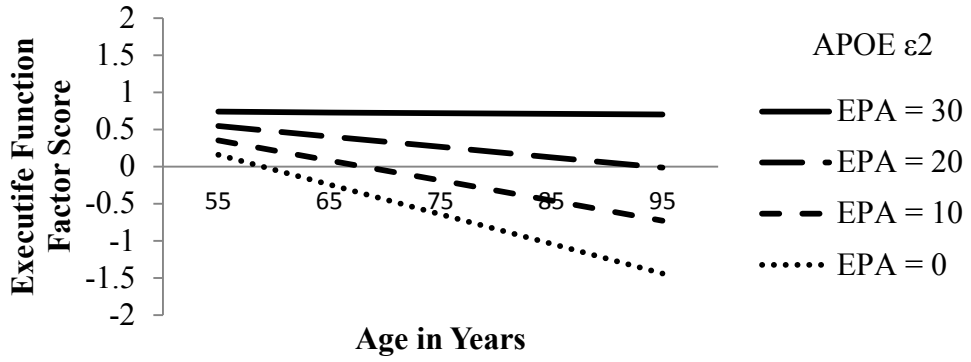


*Figure 1.*Predicted growth curve for executive function factor scores using everyday physical activity (EPA) at W1 as a predictor with age as a continuous variable centered at 75 years. -2 log likelihood = 1766.19 Akaike information criterion = 1782.19; Bayesian information criterion = 1816.51

A



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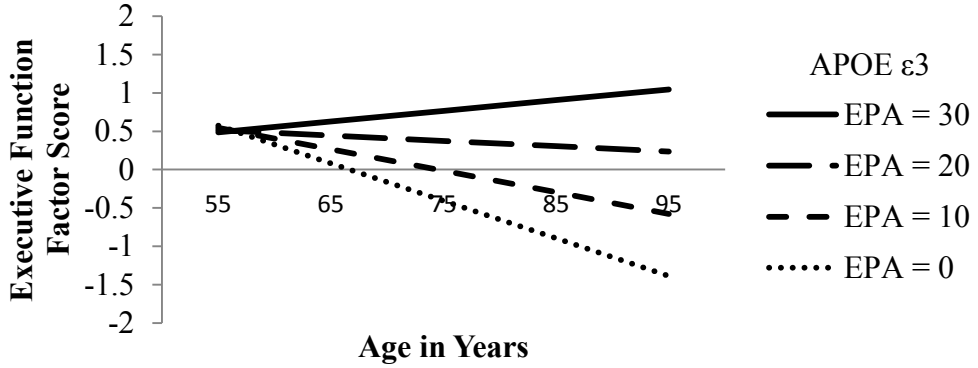
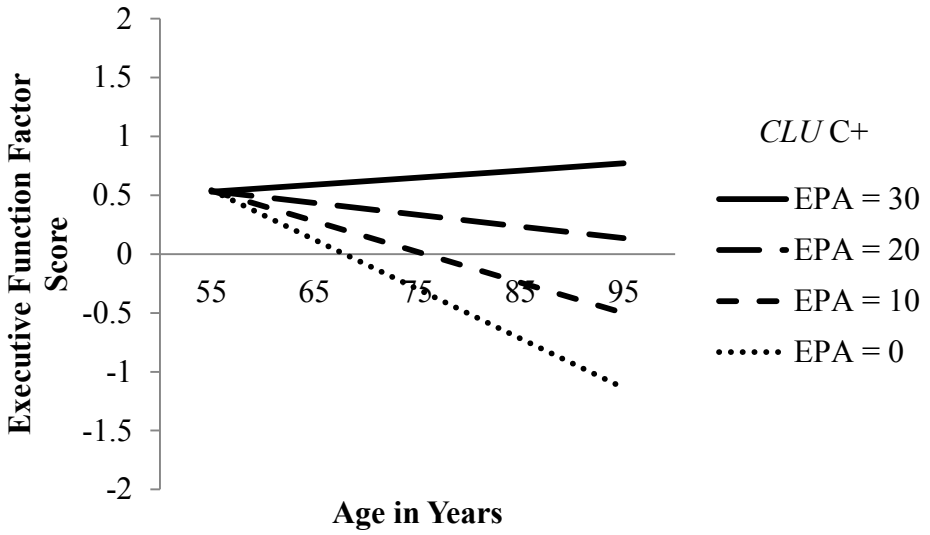


C

Figure 2. Predicted growth curve for executive function factor scores by *APOE* allele status using everyday physical activity (EPA) as a predictor with age as a continuous variable centered at age 75. -2 log likelihood = 1695.30; Akaike information criterion = 1727.29; Bayesian information criterion = 1795.17. Figure 2(A) is *APOE* ε2 (i.e., ε2/ε2, ε2/ε3). Figure 2(B) is *APOE* ε3 (i.e., ε3/ε3). Figure 2(C) is *APOE* ε4 (i.e., ε3/ε4, ε4/ε4).

A



B

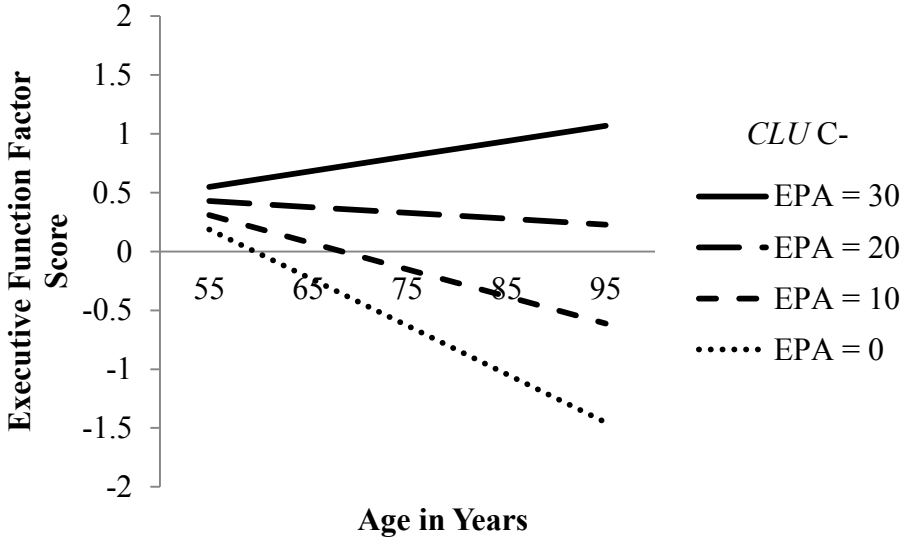
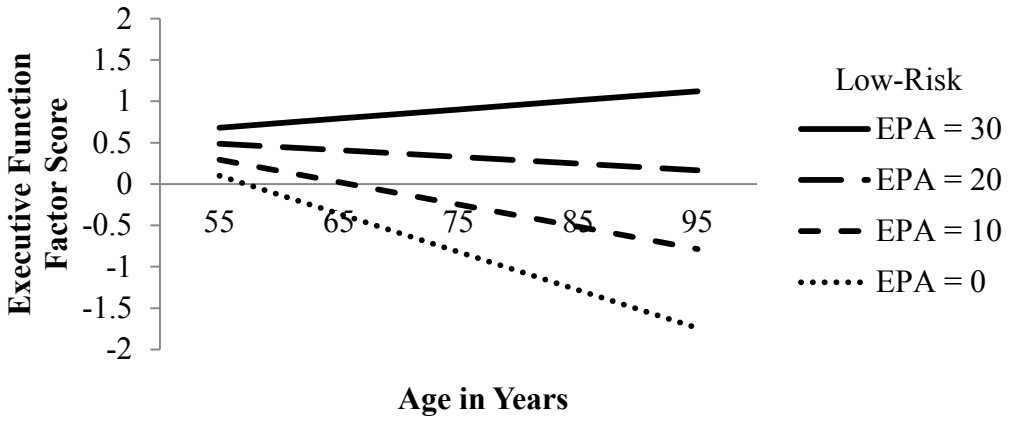


*Figure 3.*Predicted growth curve for executive function factor scores by *CLU* allele status using everyday physical activity (EPA) as a predictor with age as a continuous variable centered at age 75. -2 log likelihood = 1751.44; Akaike information criterion = 1781.43; Bayesian information criterion = 1798.16. Figure 3(A) is *CLU* C+ (i.e., C/C, C/T). Figure 3(B) is *CLU* C- (i.e., T/T).

A



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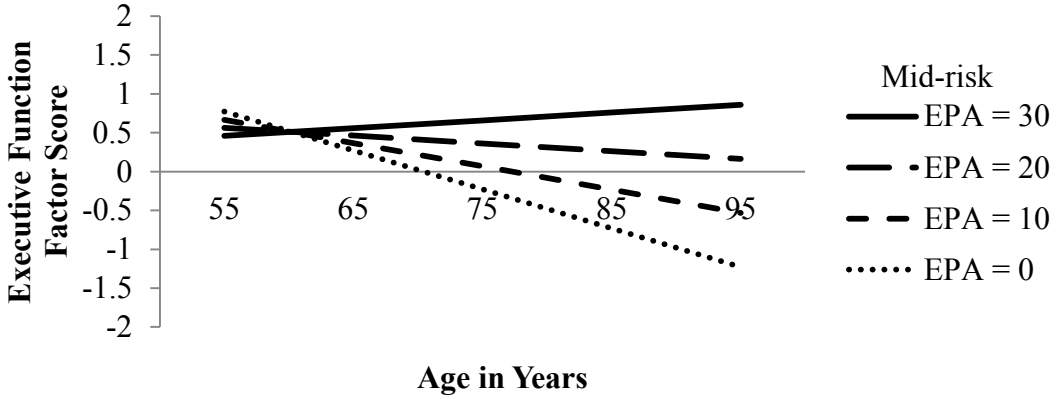

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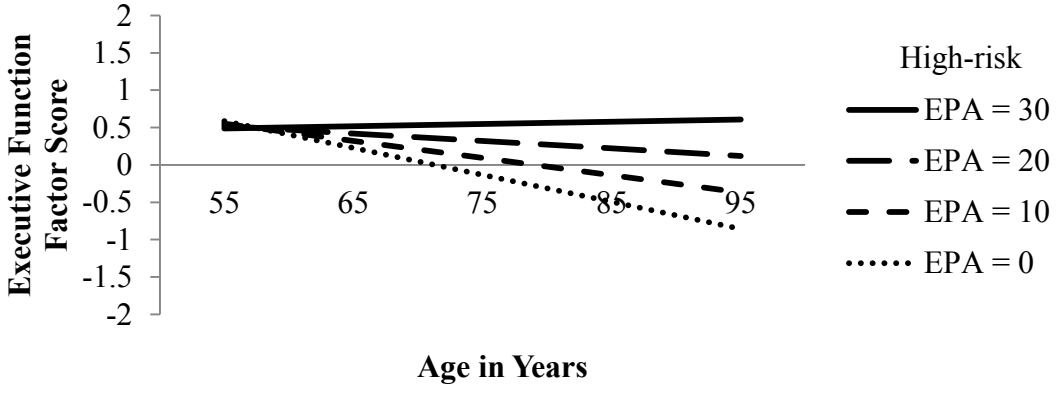

Figure 4. Predicted growth curve for executive function factor scores by AD genetic risk score (comprised of *APOE* and *CLU*) using everyday physical activity (EPA) as a predictor with age as a continuous variable centered at age 75. -2 log likelihood = 1655.0; Akaike information criterion = 1699.00; Bayesian information criterion = 1792.33. Figure 4(A) is the low risk group. Figure 4(B) is the mid-risk group. Figure 4(C) is the high risk group.

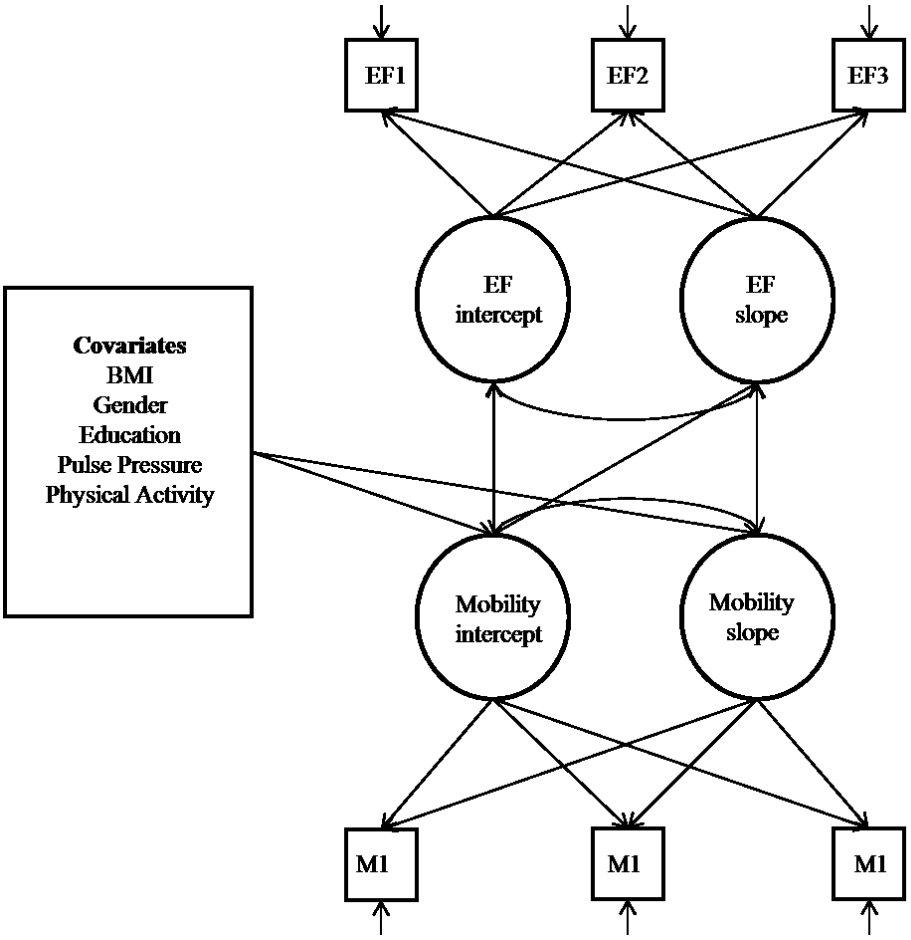

Figure 5. Parallel process latent growth model of executive function and mobility across three measurement occasions in the Victoria Longitudinal Study. This model is described notationally in the text. Latent variable intercepts and slopes for mobility are regressed on the covariates. Residual variances for mobility latent variables are shown by smaller arrows going toward the latent variables. EF = Executive function factor score at a measurement occasion. M = Observed composite mobility score at a measurement occasion.

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Appendix A

Descriptive Statistics for Sample by Genotype and Longitudinal Wave

CLU	C+ (risk)			C-		
	W1	W2	W3	W1	W2	W3
n	448	386	223	91	69	40
Age	70.26 (8.73)	74.53 (8.64)	74.59 (7.10)	70.41 (7.77)	74.30 (7.61)	75.94 (7.83)
Range	55.36 - 90.79	57.27 - 94.53	62.44 - 94.90	55.36 - 90.79	59.94 - 87.83	64.24 - 92.59
Gender (% female)	66.6	66	68.6	63.7	63.7	67.5
PICALM	T+ (risk)			T-		
	W1	W2	W3	W1	W2	W3
n	405	333	190	133	121	72
Age	70.70 (8.58)	74.98 (8.53)	75.18 (7.35)	69.11 (8.42)	73.26 (8.23)	73.67 (6.77)
Range	53.24 - 95.25	57.27 - 94.53	62.44 - 94.40	54.67 - 90.73	59.06 -90.41	63.36 - 89.69
Gender (% female)	67.1	66.6	71	63.9	62.8	61.1
CR1	A+ (risk)			A-		
	W1	W2	W3	W1	W2	W3
n	356	285	163	183	170	100
Age	70.52 (8.56)	74.54 (8.58)	75.07 (7.58)	69.82 (8.59)	74.42 (8.34)	74.36 (6.59)
Range	53.24 - 95.25	57.27 - 91.88	62.81 - 92.89	54.13 - 90.73	58.11 - 94.53	62.44 - 94.90
Gender (% female)	68.8	67.7	73	61.7	62.3	61

Note. Results presented as Mean (Standard Deviation). W1 = Wave 1; W2 = Wave 2; W3 = Wave 3. The genotypic distribution for *CLU* is in Hardy-Weinberg equilibrium, $\chi^2 = .55$. The genotypic distribution for *CR1* is not in Hardy-Weinberg equilibrium, $\chi^2 = .02$. The genotypic distribution for *PICALM* is not in Hardy-Weinberg equilibrium, $\chi^2 = .01$.

Appendix B

Descriptive Statistics for Sample by Genetic Risk Score and Longitudinal Wave

Genetic Risk Score	Low Risk			Medium Risk			High Risk		
	W1	W2	W3	W1	W2	W3	W1	W2	W3
n	105	85	52	192	168	91	217	182	107
Age	70.17 (8.49)	74.03 (8.22)	74.74 (7.03)	70.97 (8.88)	75.37 (8.81)	75.53 (7.97)	68.82 (8.39)	73.94 (8.32)	74.22 (6.58)
Range	53.24 - 90.79	57.27 - 89.71	63.84 - 89.79	54.13 - 95.25	58.44 - 91.88	62.44 - 94.90	54.63 - 90.73	58.93 - 94.53	63.22 - 92.89
Gender (% female)	63.8	62.3	69.2	64.5	64.2	62.6	67.2	66.4	71.9

Note. Results presented as Mean (Standard Deviation). W1 = Wave 1; W2 = Wave 2; W3 = Wave 3. Low-risk group consisted of *APOE*/*CLU* combinations ε2ε2/CC, ε2ε2/TC, ε2ε2/TT, ε2ε3/TT, ε2ε3/TC, ε3ε3/TT. Mid-risk group consisted of *APOE*/*CLU* combinations ε2ε3/CC, ε3ε3/TC, ε3ε4/TT. High-risk group consisted of *APOE*/*CLU* combinations ε3ε3/CC, ε3ε4/CC, ε3ε4/TC, ε4ε4/CC, ε4ε4/TC, ε4ε4/TT.

Appendix C

VLS Activity Lifestyle Questionnaire- Physical Activity (VLS-ALQ)

Date: _____ / _____ / _____ Participant #: _____

d m y Scorer's Initials: _____

ACTIVITIES QUESTIONNAIRE

Our lives are organized to a great extent by the types of activities we participate in. In this questionnaire, you will find a list of activities that different people do in their everyday lives.

You may never have participated in some of these activities. Others you may have participated in several years ago. In this questionnaire, we would like you to tell us how many of these activities you have participated in within the last two years.

You will be asked to indicate about how often you engage in each activity. Do not worry if you cannot give an exact figure. **Circle** the letter that **MOST NEARLY** describes the frequency with which you have done the activity during the past two years. Here is an example:

I go shopping at a mall or downtown:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

Let's assume that you go to a mall or downtown once or twice a month most of the time. There may have been a month when you did not go at all, or there may have been a month when you went more often. But once or twice a month most nearly describes what you usually have done over the last two years. Thus alternative **f** is circled.

In addition to estimating how often you do them, there are two other things we would like you to tell us about the activities you have participated in over the last two years.

First, we would like you to tell us whether you participated in an activity for the very first time within the last two years. Here is an example:

I travel in a foreign country:

a.	Never	e.	About once a month	__ I did this for
b.	Less than once a year	f.	2 or 3 times a month	the **"very first time"** within the last two years
		g.	About once a week	
c.	About once a year	h.	2 or 3 times a week	
d.	2 or 3 times a year	i.	Daily	

Let's assume that you travelled to a foreign country once within the last two years. Thus, alternative **c** is circled. But let's assume this was the very first time you had taken such a trip. Thus an **X** is placed in the front of the "very first time" statement.

Second, we would like you to tell us whether you did something new or different related to an activity during the last two years. Here is an example:

a.	Never	e.	About once a month	_ I did this for
b.	Less than once a year	f.	2 or 3 times a month	the **"very first time"** within the last two years
		g.	About once a week	
c.	About once a year	h.	2 or 3 times a week	
d.	2 or 3 times a year	i.	Daily	

_ I did something **"new and different"** related to this activity within the last 2 years

Let's assume you play cards about once a week. Thus, alternative **g** is circled. Let's also assume that you have been playing cards for a number of years. Thus, the "very first time" statement is **NOT** checked. But, finally, let's assume that in addition to playing the game you usually play, you were introduced to a new card game within the last two years. This represents a departure from the routine of your participation in card playing. It would be something new and different related to an activity you have been doing within the past two years. Thus, an **X** is placed in front of the "new and different" statement.

For each of the activities listed on the following pages, please **circle** the number that most nearly describes the frequency with which you have participated in them during the last two years. Also, for those activities you have participated in place an **X** beside the "very first time" or "new and different" statements if these describe your experience with the activity within the last two years.

21. I garden indoors or outdoors:

a.	Never	e.	About once a month	_"very first time"
b.	Less than once a year	f.	2 or 3 times a month	
c.	About once a year	g.	About once a week	
d.	2 or 3 times a year	h.	2 or 3 times a week	_"new and different"
		i.	Daily	

22. I engage in exercise activities such as jogging, swimming, bicycling, or walking:

a.	Never	e.	About once a month	_"very first time"
b.	Less than once a year	f.	2 or 3 times a month	
c.	About once a year	g.	About once a week	
d.	2 or 3 times a year	h.	2 or 3 times a week	_"new and different"
		i.	Daily	

23. I engage in outdoor activities such as sailing, fishing, or backpacking:

a.	Never	e.	About once a month	_"very first time"
b.	Less than once a year	f.	2 or 3 times a month	
c.	About once a year	g.	About once a week	
d.	2 or 3 times a year	h.	2 or 3 times a week	_"new and different"
		i.	Daily	

24. I engage in recreational sports such as tennis, bowling, or golf:

a.	Never	e.	About once a month	_"very first time"
b.	Less than once a year	f.	2 or 3 times a month	
c.	About once a year	g.	About once a week	
d.	2 or 3 times a year	h.	2 or 3 times a week	_"new and different"
		i.	Daily	