The Risk for Dementia in Older Adults with Attention Deficit/Hyperactivity Disorder (ADHD): Does Cognitive Reserve Affect Time to Dement in Adults with ADHD Symptoms?

by

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We acknowledge and respect the Lək̓ wəŋən (Songhees and Esquimalt) Peoples on whose territory the university stands, and the Lək̓ wəŋən and W̱SÁNEĆ Peoples whose historical relationships with the land continue to this day.

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Abstract

As the population over 65 continues to grow, the number of older adults with attention deficit/hyperactivity disorder (ADHD) is also likely to increase. While dementia risk increases after age 65, previous research suggests that adults with ADHD have a higher risk for dementia than their neurotypical peers. The purpose of this research was to investigate how the Cognitive Reserve (CR) theory of ageing relates to the risk for dementia associated with ADHD symptoms (ADHD-sx). Given that impairments in the domains typically used as proxies of the CR (i.e., education, occupation and social participation) persist across the lifespan for individuals with ADHD, it was first predicted that individuals with ADHD-sx would have lower CR than individuals without ADHD-sx. Secondly, to extend previous research, it was predicted that individuals with ADHD-sx would have a higher risk for dementia than individuals without ADHD-sx. Finally, given the variability in outcomes associated with ADHD, it was predicted that the risk for dementia associated with ADHD-sx would depend on CR. In 2008/2009, 986 participants from the Longitudinal Aging Study Amsterdam were followed until either a diagnosis of dementia was observed or the last assessment point, 8 years (two additional assessments) later. Based on currently reported ADHD-sx and childhood onset of attention problems, participants were assigned to either an ADHD-sx group *(n*= 147) or a non-ADHD group *(n*= 839). The results revealed no significant differences between groups on CR ($\chi^2(1)$ = .14, p = .71). A Cox-proportional hazard analysis reported no significant risk for dementia associated with ADHD-sx (HR: 1.29, 95% CI [.43, 3.88], p = .65). Finally, the moderating effect of CR could not be estimated due to insufficient data. These results reveal important considerations when studying older adults with neurodevelopmental disorders and provide future directions for research on the CR theory of ageing.

Keywords: ADHD; cognitive reserve; ageing; dementia

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Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-V) as a persistent pattern of inattention and/or hyperactivity-impulsivity which: appears before the age of 12 (criterion B), causes impairment in two or more settings (criterion C), interferes with functioning or development (criterion D), and cannot be better explained by another mental disorder (criterion E; e.g., schizophrenia, mood disorder, substance intoxication) (American Psychological Association, 2013). To meet the symptom criterion for ADHD according to the DSM-V, an individual must manifest at least 6/18 symptoms listed according to either self-report or informant report. If an individual meets the threshold for diagnosis and endorses most of their symptoms in the domain of inattention, they are categorized as having the predominantly inattentive presentation of ADHD (ADHD-I). On the other hand, if an individual endorses most of their symptoms in the hyperactive-impulsive dimension, they are categorized as having the predominantly hyperactive-impulsive presentation of ADHD (ADHD-H/I). Finally, endorsing a significant number of symptoms in both domains categorizes them with the combined presentation of ADHD (ADHD-C).

Among children under 12, the prevalence of ADHD ranges between 6.1%-9.4% (Salari et al., 2023), Access to diagnostic assessment and treatment varies by region, socioeconomic status and race/ethnicity, however, the prevalence of ADHD is a worldwide phenomenon (Thapar & Cooper, 2015). Despite its ubiquity, there is heterogeneity in terms of sex. According to a recent cross-sectional study using data from the National Health Interview Survey in the United States,

ADHD is two times more prevalent in males than females (Li et al., 2023). Furthermore, according to a review by Thapar and Cooper (2015), males are treated eight times more often than females.

Due to the higher prevalence of ADHD in males and the apparent treatment bias, concern has been raised that the symptom criterion is gender biased. However, Collett et al. (2000) demonstrated that ADHD had partial measurement invariance between sexes. Specifically, there were no differences between sexes in which indicators loaded onto the latent constructs of inattention and hyperactivity/impulsivity (Collett et al., 2000). Furthermore, the relative factor loading weights were not significantly different between sexes, indicating that, when endorsed, symptoms in males and females shared the same relationship to each latent construct (Collett et al., 2000). Finally, the correlations between the latent constructs (i.e., inattention and hyperactivity/impulsivity) were the same between the sexes (Collett et al., 2000). Therefore, sex differences in prevalence may be due to the mean level of symptoms or variance in symptoms between the sexes.

In fact, Arnett et al. (2014) demonstrated that mean scores were higher in males than females and symptom variance was larger such that males were more prevalent in the extreme ends of the symptom distribution than females (Arnett et al., 2014). Therefore, the results by Arnett et al. (2014) suggest that the ADHD phenotype is more severe in males than females and for this reason, males reach diagnostic significance more often than females. Additionally, since symptoms are more severe in males, hyperactivity/impulsivity in males is likely more disruptive and consequently, recognized more easily than symptoms in females (Arnett et al., 2014; Willcutt et al., 2012; Young et al., 2020). Therefore, one explanation for the treatment bias is that symptoms in males may attract diagnosis and treatment more often than in females due to

symptom severity. Unfortunately, delayed diagnosis and treatment has significant consequences such as academic and occupational underachievement, substance use, social difficulties and mortality (Chen et al., 2022; Cherakasova et al., 2022; Zalsman & Shilton, 2016).

Impairment Related to ADHD

The two dimensions of ADHD (i.e., inattention and hyperactivity-impulsivity) are differentially related to impairments and comorbidities. In children and adolescents/adults (17 years and older), the inattentive symptom dimension better accounts for impaired academic functioning, lower life satisfaction, peer neglect, and shy or passive behavior (Willcutt et al., 2012). In contrast, the hyperactive/impulsive dimension is more related to peer rejection, relational aggression, and accidents or injuries (Willcutt et al., 2012). In terms of comorbidities, ADHD is frequently concurrent with behavioral disorders, such as conduct disorder (CD), or psychiatric disorders, such as mood disorders or anxiety disorders, which complicates diagnosis and treatment (Frank-Briggs, 2010; Ottosen et al., 2019). Internalizing disorders, such as mood disorders and anxiety disorders, occur most frequently with inattentive symptoms, whereas hyperactive/impulsive symptoms more commonly co-occur with externalizing disorders, such as CD (Willcutt et al., 2012). Furthermore, the inattentive presentation is more likely to co-occur with learning disorders than the hyperactive presentation (Willcutt et al., 2012). In adolescents and adults (17 years and older), ADHD is often concurrent with substance abuse or dependency and antisocial personality disorder, along with CD, depression and anxiety disorders (Biederman et al., 1993; Murphy et al. 1996).

The concomitance of ADHD with other psychiatric or behavioural disorders presents a challenge for accurately diagnosing the source of impairment. According to Sibley et al. (2017), repeated assessments of 239 adults over 14 years revealed that of the 47 participants who

screened positively for ADHD in adulthood (18 years or older) over the course of the study, only 2 were veridical cases of ADHD, as symptoms emerged in the majority of the participants concurrently with substance use disorder. Furthermore, none of the cases identified in adulthood occurred independently of other psychiatric symptoms (Sibley et al., 2017). The Sibley et al. (2017) study emphasizes the importance of comprehensive assessment for eliminating other possible explanations for symptoms that may resemble those of ADHD. Furthermore, their results highlight the development of other psychiatric disorders over time which complicate the diagnosis of ADHD and its treatment in adulthood.

Cognitive Profiles of ADHD

ADHD is not defined by a specific neurocognitive profile. According to studies by Halleland et al. (2019) (n = 79) and Biederman et al. (2006) (n = 145), only 31% of their participants with ADHD had impaired executive functioning, defined by scores 1.5 SD below the mean on two or more tests of executive function. At the group level, those with executive dysfunction and ADHD performed worse on cognitive tests than controls with executive dysfunction, indicating that although executive dysfunction is not characteristic of ADHD, cognitive performance was more impaired when executive dysfunction co-occurred with ADHD (Biederman et al., 2006; Halleland et al., 2019). In adults with average intelligence and no evidence of executive dysfunction, group differences reveal that ADHD continues to impair cognitive performance compared to neurotypical controls (Biederman et al., 1993; Bridgett et al., 2006). However, in contrast to the results for adults with average and below average IQs, Milioni et al. (2017) found that the cognitive performance of ADHD adults with above average intelligence was indistinguishable from high IQ controls.

Group differences in cognition between controls and individuals with ADHD are typically observed on tests of reaction time variability, vigilance, working memory and response inhibition (Pievsky et al., 2018; Young et al., 2020). According to Bridgett et al. (2006), differences between controls and ADHD depend on the age of onset (i.e., those with a childhood diagnosis typically perform worse than healthy controls), comorbid disorders (i.e., adults without comorbidities perform comparably to healthy controls), education (i.e., similar levels of education moderated IQ differences), and head trauma (i.e., ADHD adults without head trauma perform comparably to healthy controls).

However, the mean difference between groups is small. In the review by Pievsky et al. (2018), the standard mean difference between groups across 34 meta-analyses was .45. Relative to the large effect size between groups in terms of symptoms (2.5-4.0), the standard mean difference in cognition indicated that large cognitive deficits do not characterize ADHD. Likewise, with respect to IQ, Bridgett et al. (2006) observed that the differences in IQ between controls and ADHD were not clinically significant; adults with ADHD score on average 2.94 IQ points below neurotypical adults (Bridgett et al., 2006). Therefore, although cognition seems to be affected by ADHD in adults with average and below average intelligence, the difference is minimal overall.

The Life Course of ADHD

When the diagnostic criteria for ADHD were originally presented in the third edition of the DSM (1980), it was assumed that the disorder was exclusive to childhood (APA, 1980). However, it has since become apparent that the disorder persists into adulthood for approximately 60% of childhood cases (Faraone et al., 2006; Semeijn et al., 2016; Song et al., 2021). Therefore, it is estimated that 2.5% of children diagnosed with ADHD continue to meet

its criteria in adulthood (Faraone et al., 2006; Song et al., 2021). Interestingly, there are also individuals without a childhood onset who meet the criteria for ADHD in adulthood. According to Song et al. (2021), the global prevalence of these symptomatic adults over 18 is 6.76%. In a follow-backward design, Moffitt et al. (2015) discovered that only three out of 31 participants with ADHD in adulthood manifested the diagnosis in childhood. In the same study, only 3 of the 61 children who were diagnosed with ADHD in childhood continued to meet criteria in adulthood.

The prevalence of symptomatic adults observed by Moffitt et al. (2015) and Song et al. (2021) could be explained by masking behaviour, or the developmental course of ADHD. It is possible that the symptoms of these adults may have been masked in their childhood through compensatory behaviours or due to their interaction with their environment (Mitchell et al., 2021). Symptoms and the impairment caused by them may not have appeared for symptomatic adults until responsibilities and changes in their environment outweighed their ability to compensate for their symptoms (Turgay et al., 2012).

The prevalence of children whose symptoms seem to remit in adulthood could also be explained by the normative developmental course of ADHD symptoms. In general, assessments using DSM-V criteria show that the hyperactive presentation wanes from childhood (prevalence: 30.3%) into adolescence (23.1%), whereas inattentive and combined presentations remain stable from childhood (inattentive presentation prevalence: 33.2%; combined presentation prevalence: 31.4%) into adolescence (inattentive presentation prevalence: 37.3%; combined presentation prevalence: 31.1%) (Salari et al., 2023). For instance, in a sample of 1450 children who underwent repeated assessment from age 8 to 17, Larsson et al. (2011) demonstrated that scores on the hyperactive dimension decreased whereas inattentive scores increased over time.

Likewise, Willcutt et al. (2012) found that across five studies examining symptom stability over 5-9 years after the initial diagnosis, 59% of children continued to meet criteria for diagnosis but only 35% of these children continued to endorse the ADHD-H/I presentation. Both studies suggest that symptoms change over time and that the hyperactive-impulsive presentation best describes the symptom presentation of ADHD in childhood whereas adolescence and adulthood may be better characterized by inattention (Larsson et al., 2011; Willcutt et al., 2012).

The changing profile of symptoms over development has important implications for impairment. According to Zoromski et al. (2015), impairments in academic, social and behavioral functioning were related to hyperactive symptoms in young children whereas impairments in these domains were better accounted for by inattentive symptoms in adolescents. Similarly, impairment in adulthood is best accounted for by inattentive symptoms (Chandra et al., 2021; Matte et al., 2015). Interestingly, the sex differences in prevalence normalize in adulthood (i.e., 1.6:1, male to female; APA, 2013), suggesting that the inattentive symptoms become a significant source of impairment in the context of adulthood responsibilities and expectations. Therefore, the cause of impairment shifts from the hyperactive-impulsive dimension in childhood to the inattentive dimension in adolescence/adulthood.

Critically, the remission of the disorder from childhood to adulthood often observed in the literature (Faraone et al., 2006; Moffitt et al., 2015) also suggests that the diagnostic criteria used to evaluate ADHD in adulthood may not be developmentally sensitive. In a meta-analysis by Faraone et al. (2006), 32 follow-up studies were analyzed to determine the prevalence of ADHD in adulthood. The analysis estimated that, by the age of 25, 40-60% of children who previously met the diagnostic criteria for ADHD continued to experience symptoms below the threshold for diagnosis (Faraone et al., 2006). Similar results were found in a review of seven

longitudinal cohort studies of children with ADHD by Cherkasova et al. (2022). Therefore, the apparent decline of symptoms in adulthood has important implications for diagnostic prevalence.

Gordon et al. (2006) demonstrates that the number of symptoms endorsed by an individual does not necessarily correspond to the amount of impairment the individual experiences. According to four large American and Canadian studies, the observed correlation between symptoms and impairment was moderate: impairment accounted for only 10% of the variance in symptoms, on average (Gordon et al., 2006). Therefore, someone with a full range of symptoms can be minimally impaired whereas someone with very few symptoms can be very impaired. Although adults may not endorse enough symptoms to meet diagnostic criteria, the Gordon et al. (2006) results suggest that impairment may persist, despite diagnostic remission.

Given that the current construct of ADHD was not defined until publication of the DSM-III in 1980, many adults might not have knowledge of their disorder. In fact, although research using validated scales finds that the prevalence of persistent ADHD in adults over 50 is 2.5%, only .23% have obtained a clinical diagnosis and only .09% receive treatment (Dobrosavljevic et al., 2020). Prior to the DSM-V, ADHD symptoms had to be present before the age of 7. Although the purpose of the age of onset criterion was to reduce false positives when symptoms could be better explained by another cause, determining the presence of symptoms prior to 7 likely excluded individuals unnecessarily due to the fallibility of their memory and the impairment of episodic memory and knowledge-of-self often observed for individuals with ADHD (Sharma et al., 2021). For this reason, the diagnostic criteria in the DSM-V iteration were changed to permit symptoms present by age 12 (APA, 2013).

However, Faraone et al. (2006) found that differences were negligible between adults who met the age-of-onset criterion and those who did not: both groups exhibited the same risk

for comorbid psychiatric conditions, psychosocial impairments, and familial transmission. Results such as these, coupled with evidence that symptoms remit while impairment persists, called into question the validity of the DSM-IV/III criteria for assessing ADHD in adults (Sharma et al., 2021).

The following revisions were made to the adult ADHD diagnostic criteria in the DSM-V: the threshold was lowered to 5/9 symptoms in either dimension, and the age of onset criterion was raised from 7 to 12 (APA, 2013). Still, some authors have suggested that a 4/9 symptom threshold is more appropriate for adults over 60 (Kooji et al., 2005). Therefore, the debate on age-appropriate symptom thresholds continues. Regardless, the revised criteria lowered the threshold for diagnosis and justified life-changing treatment for individuals who would have otherwise not met criteria for diagnosis.

The adjustments to the criteria have increased the prevalence of adult diagnosed ADHD: according to a field study in a sample of 4000 young adults aged 18-19, the prevalence of persistent ADHD was 2.9% based on the DSM-IV criteria (Matte et al., 2015). In comparison, using the DSM-V, the prevalence was 3.8% (Matte et al., 2015). Therefore, the prevalence of diagnosed ADHD in adulthood has increased based on the newest edition of the DSM.

ADHD and Aging

Since ADHD persists into adulthood, there inevitably exists a population of adults with ADHD who are approaching old age. According to a recent meta-analysis of 20 studies, the estimated pooled prevalence of persistent ADHD in adults over 50 was 2.5% (Dobrosavljevic et al., 2020). The prevalence of adults who have ADHD without a childhood onset is 4.51% (Song et al., 2021). Therefore, as the population of adults over 65 continues to grow across the globe

(Beard et al., 2016; Livingston et al., 2017), it is likely that the number of adults over 65 with persistent and symptomatic ADHD will also increase in the coming decades. Critically, considering the growing population over 65, the prevalence of dementia in older adulthood is increasing.

Dementia (currently classified by the DSM-V in the category of major neurocognitive disorders) is defined primarily by its main clinical feature: an acquired cognitive dysfunction (APA, 2013). In addition to this primary feature, dementia is also defined by cognitive decline that interferes with independent functioning, that occurs outside the context of delirium, and that cannot be better explained by another mental disorder (APA, 2013). Dementia can be further specified by its etiology (if known), the presence of behavioral disturbances, such as apathy or mood disturbances, and by its severity (i.e., mild, moderate or severe) (APA, 2013).

The prevalence of dementia increases exponentially after 65 (Wolters et al., 2020; Plassman et al., 2007; Prince et al., 2013). At 65, its prevalence is between 1-2%, whereas by 85, the number of individuals affected by dementia rises to 21% (Prince et al., 2013). Likewise, the incidence rate increases dramatically with age such that, in any given year, 1.6 to 8.6 in every 1000 persons 60-65 are diagnosed with dementia, whereas 42.2 to 97.0 in every 1000 persons are diagnosed with dementia among 85–89-year-olds (Wolters et al., 2020). Given the incidence rate and the growing population of adults over 65, the prevalence of dementia is expected to rise dramatically in the coming decades.

According to the *World Alzheimer Report* (2022), 55 million people were living with dementia (diagnosed or undiagnosed) in 2019. Critically, the prevalence of dementia is expected to affect 139 million adults worldwide by 2050 (*World Alzheimer Report*, 2022). The prevalence of dementia in Canada parallels the global trend. Approximately 600,000 Canadians were living

with dementia in 2020, and by the year 2030, it is estimated that close to one million Canadian adults will have dementia (*The Landmark Study*, 2022; Chambers et al., 2016). Due to the high cost to both the economy and the family (Livingston et al., 2017; Chambers et al., 2016), delaying the onset of dementia is imperative.

Neurodevelopmental Disorders and Dementia

Although the research is currently scarce, there is evidence to suggest that the risk for dementia may be significantly elevated across the category of neurodevelopmental disorders in the DSM, including diagnoses such as ASD, Intellectual Disability, and ADHD. Using the U.S. Medicaid insurance registry, Vivanti et al. (2021) found that the prevalence of early onset dementia in adults with autism spectrum disorder (ASD) was 4.04% compared to .97% for neurotypical adults, after controlling for significant confounders such as cardiovascular disease. The incidence rate for early onset dementia was two times higher for adults with ASD than controls (Vivanti et al., 2021). The potential mediating role of depression or other psychiatric disorders did not contribute significantly to explaining the relationship between ASD and early onset dementia (Vivanti et al., 2021). Although this research was exclusive to early onset dementia, the prevalence and incidence among those with ASD suggests that early onset dementia is a risk for adults with ASD.

Critical to the risk for dementia in ASD is controlling for other neurodevelopmental disorders that are comorbid with ASD, such as intellectual disability (ID). Vivanti et al. (2021) explored the differential risk for early onset dementia in adults with only ID and found that their adjusted risk was three times higher relative to controls. Similarly, the risk for early onset dementia in those with ASD and ID was 2.8 times higher than controls (Vivanti et al., 2021). Strydom et al. (2013) also observed that adults over 60 with ID had a risk five times higher than

that of controls without ID. Therefore, ID also shares a significant relationship to the prevalence of and risk for dementia.

The risk for dementia may also be a significant concern for adults with diagnosed ADHD. In a study by Dobrosavljevic et al. (2022), 3.5 million adults over 50 were followed for 12 years. Diagnosed ADHD was recorded in 9532 (0.3%) participants. Each year of the study, the presence of dementia or mild cognitive impairment (MCI) was assessed. At the end of data collection, 2.1% of the sample developed MCI or dementia (Dobrosavljevic et al., 2022). Using a Cox proportional hazard model, the age of dementia diagnosis was significantly lower and the risk for dementia was three times higher in people with diagnosed ADHD compared to participants without ADHD (Dobrosavljevic et al., 2022). Associations between ADHD and dementia have been observed in other studies (Fluegge & Fluegge, 2018; Golimstok et al., 2011; Tzeng et al., 2019; Zhang et al., 2022) leading to the speculation that dementia may occur more frequently in people with ADHD than those without the disorder.

The Cognitive Reserve Theory of Ageing. An explanation for the relationship between dementia and neurodevelopmental disorders has yet to be made clear. In the case of ADHD, one possible explanation could be the cascading effect of ADHD-symptoms on impairment over the lifespan (Callahan et al., 2017). This explanation may also be relevant for an increased risk of dementia in adults with other neurodevelopmental disorders (see Appendix A). The Cognitive Reserve theory provides a useful lens through which to study the cascading effect of impairment caused by neurodevelopmental disorders.

In neurotypical adults, age-related neuropathology does not necessarily result in clinical symptoms related to dementia. Several studies have observed that up to 25% of elderly participants who perform within the normal range on various cognitive tests prior to death, met

the full pathological criteria for Alzheimer disease at autopsy (Ince, 2001). This seemingly contradictory observation of pathology in the absence of cognitive impairment can be at least partially explained by the Cognitive Reserve theory of ageing.

Accordingly, individual differences in the functional connectivity of neural networks and synaptic density of neural substrates to cognition afford resilience against cognitive impairment despite accumulating neuropathology (Stern, 2009). Although the exact mechanisms through which compensation occurs are not yet understood (Steffener & Stern, 2012), it is theorized that individuals with more neural capacity, efficiency, flexibility are better equipped to maintain normal cognitive performance for longer, thereby delaying the manifestation of cognitive impairment (Steffener & Stern, 2012; Stern, 2009). The theory implies two major sources of resilience: the brain reserve and the cognitive reserve[1]. Brain reserve refers to individual differences in the quantitative volume and structural integrity of the brain. For instance, previous research has found that larger brains are able to sustain more injury prior to presenting clinical manifestations of impairment (Stern, 2009). Therefore, more brain matter provides cognitive resilience despite injury/neuropathology.

Cognitive reserve specifically refers to the theory that individual differences in life experiences afford cognitive resilience despite neuropathology. Typically, the CR is represented by the following life experiences, in no particular order: SES, income or occupational status, educational attainment, leisure activity, social participation, physical activity and premorbid IQ (Howard et al., 2023; Opdebeeck et al., 2016). The most robust measures of CR are those that consider more than one life experience (Howard et al., 2023; Nogueira et al., 2022).

[1] These reserves are not mutually exclusive since life experiences can shape both the structure and function of the brain while brain structure and function can simultaneously influence life experiences (Reuter-Lorenz & Park, 2014; Stern, 2009).

Questionnaires that produce a total score are commonly used to quantify the extent of enriching experiences across domains (Nogueira et al., 2022). Strengths of this approach to measuring CR are that questionnaires represent the extent of exposure an individual has to multiple enriching life experiences and produce a single score which simplifies analysis and between study comparisons. However, this approach is limited by its reliance on self-report data which may be biased. Furthermore, given that life experiences are usually quantified on ordinal scales, variance is limited. Critically, to properly test the CR theory, a measure of brain status must be available to demonstrate that despite similar levels of neuropathology, individuals with higher CR are cognitively unimpaired for longer compared to those with lower CR (Stern, 2009). Unfortunately, few studies have included a measure of brain status when testing the CR theory (Howard et al., 2023).

Studies that substantiate the CR theory are those that have explored the association between dementia and education, complex occupation, social participation or engagement in leisurely activities (Kuiper et al., 2015; Valenzuela & Sachdev, 2006). A systematic review by Valenzuela and Sachdev (2006) examined the incidence rate of dementia, in participants who were cognitively normal at baseline, with respect to education, occupation and leisure activities, in 22 longitudinal studies. For education, 10 out of 15 studies demonstrated that individuals with high education had a 47% decreased risk for dementia compared to those with low education (Valenzuela & Sachdev, 2006). Likewise, 9 out of 12 studies found that participants with a history of “complex” occupation had a 44% decreased risk for dementia. Finally, all six studies investigating the effect of current leisure activities found a significant, protective effect such that participants who regularly participated in leisure activities had a 50% reduced risk for dementia compared to those who currently engaged infrequently with leisure activities (Valenzuela &

Sachdev, 2006). With respect to social engagement, Kuiper et al. (2015) reviewed 19 longitudinal studies and found participants who reported lower levels of social participation had a 41% higher risk for developing dementia compared to participants with higher levels of social participation. Therefore, more enriching life experiences in the domains of education, occupation, social participation and leisure activity seem to offer protection against the risk of a dementia diagnosis. Complementary to these observations, fewer enriching life experiences relate to higher risk for dementia (Opdebeeck et al., 2016; Valenzuela & Sachdev, 2006).

The probability of accumulating fewer enriching life experiences may share a common factor: adverse childhood experiences (ACEs). Previous research has observed that the context in which a child develops influences their subsequent educational, occupational and cognitive outcomes over their lifespan (Richards & Sacker, 2003). Therefore, ACEs may play an important role in developing cognitive reserve. ACEs refer to negative life events that occur prior to 18 years and have a lasting impact on a person's life (Merrick et al., 2018; Swedo et al., 2023). ACEs are often assessed in four domains: child maltreatment, parental maladjustment (i.e., psychopathologies, substance use, domestic violence), exposure to violence, and parental loss (i.e., death or separation/divorce). According to Swedo et al. (2023), over 60% of adults in the United States have experienced at least one ACE, whereas only 17% report four or more ACEs. Four or more ACEs were most common among individuals who were unemployed, whose household earned less than $15,000 USD and who attained less than a high school education (Swedo et al., 2023). Therefore, although childhood adversities are common in a population, the accumulation of four or more ACEs may play a role in compromising the development of the cognitive reserve.

Collectively, enriching life experiences are thought to offer resilience in the form of the cognitive reserve (CR). Due to evidence that a variety of enriching experiences relate to reduced risks of dementia, the CR accrues diverse life experiences into one latent construct. It is hypothesized that these enriching life experiences build flexible cognitive networks that will compensate for the effect of pathology on the functional connectivity of the brain as individuals age (Stern, 2009). The CR theory makes the following predictions: individuals with higher CR (i.e., more enriching life experiences) maintain normal cognitive performance for longer whereas their peers with low CR (i.e., fewer enriching life experiences) present cognitive impairment sooner.

Opdebeeck et al. (2016) reviewed six cross-sectional studies examining the association between CR and late-life cognition. As expected, four studies reported that higher CR, as a composite measured by the Lifetime of Experiences Questionnaire (LEQ) or the Cognitive Reserve index questionnaire, predicted better cognition in adults 60 years and older (Opdebeeck et al., 2016). The remaining two studies found similar results and measured CR by combining education and occupation (Opdebeeck et al., 2016). Likewise, in a longitudinal design, Valenzuela and Sachdev (2006) tested the association between CR, as measured by the LEQ, and cognitive decline over 18 months. Higher CR predicted less cognitive decline in adults over 60 (Valenzuela & Sachdev, 2006). Therefore, adults with high CR are cognitively unimpaired for longer; however, the theory also predicts that when the accumulation of neuropathology eventually takes its toll, clinical symptoms emerge quickly and cognition declines precipitously (Hall et al., 2007; Stern, 2009).

The Cognitive Reserve Theory and ADHD. Although the brain reserve theory could apply to the case of ADHD (Gehricke et al., 2017), the current study will focus on how the

cognitive reserve theory applies to ADHD. By definition, a diagnosis of adult ADHD is made if the symptoms endorsed by the individual are accompanied by impairment in educational, occupational and social settings (APA, 2013). In terms of education, individuals with ADHD tend to have significantly lower educational and academic achievement than those without ADHD (Able et al., 2007; Barkley & Fischer, 2019; Biederman et al., 1993; Loe and Feldman, 2007). Across study designs and operational definitions of education, individuals with ADHD are more likely to repeat grades, spend fewer cumulative years in school, require auxiliary educational services, and achieve lower scores in literacy (Barkley & Fischer, 2019; Biederman et al., 1993; Loe and Feldman, 2007).

The struggle to learn and apply knowledge persists throughout the educational careers of individuals with ADHD and translates into their occupational outcomes (Cherkasova et al., 2022; Loe and Feldman, 2007). Across many methodological techniques investigating the impacts of ADHD on occupation, there is consensus that, in comparisons to neurotypical adults, adults with ADHD are more likely to be unemployed, have a chaotic employment history, earn lower incomes than their peers, and attain a lower socioeconomic status than their family of origin (Able et al., 2007; Barkley & Fischer, 2019; Biederman et al., 1993; Cherkasova et al., 2022; Michielsen et al., 2015).

Individuals with ADHD are more likely to also struggle across the lifespan in the domain of social participation. Michielsen et al. (2015) investigated the association between ADHD and social functioning or participation in a population-based cohort of adults over the age of 55. Using data collected from the Longitudinal Aging Study Amsterdam, Michielsen et al. (2015) found that adults with ADHD had three times higher rates of divorce or separation than those without ADHD. Furthermore, adults with ADHD had significantly fewer members in their social

networks and saw those in their networks far less frequently than neurotypical adults (Michielsen et al., 2015). Moreover, adults with ADHD reported significantly more emotional loneliness than controls (Michielsen et al., 2015). Similar results were found by Able et al. (2007) in a sample of 1104 middle-aged adults with diagnosed (and subthreshold) ADHD; participants with ADHD were more likely to report higher levels of interpersonal conflicts in dyadic relationships and negative social relationships with others (Able et al., 2007). Finally, reflecting the types of impairment related to ADHD (Zoromski et al., 2015), a review by Nijmeijer et al. (2008) found that conflicts are common in dyadic relationships for children with ADHD, often leading to social exclusion and isolation. Therefore, impairments in social functioning are observed across the lifespan for those with ADHD.

Finally, children with ADHD are more likely to experience ACEs, which could hinder the development of their cognitive reserve due to the negative relationship between ACEs and subsequent life experiences (Richards & Sacker, 2003; Swedo et al., 2023). In a large cross-sectional sample of children between 4 and 17, Brown et al. (2017) found that children with ADHD were 50% more likely to experience any type of ACE and were almost 4 times more likely to experience more than four ACEs compared to children without ADHD, after controlling for sex, age and ethnicity. The severity of ADHD was also positively associated with ACEs, and the ACEs that were most strongly associated with ADHD were socio-economic hardship and parental mental illness (Brown et al., 2017).

In addition to ACEs being more common in ADHD, ADHD may also perpetuate ACEs. In their longitudinal design, Lugo-Candelas et al. (2021) found that at baseline, children with ADHD were more likely to have experienced an ACE than children without ADHD. After controlling for ACEs at baseline, Lugo-Candelas et al. (2021) observed that ADHD at baseline

predicted new ACEs in each subsequent year. Furthermore, they found that the inattentive presentation of ADHD was most likely to experience subsequent ACEs in their sample of children 5-15. In their results, parental maladjustments were the most likely type of ACE in the subsequent time points for children with ADHD. Given that the authors were able to control for other DSM defined behavioural disorders, their results suggest that ADHD may perpetuate adversities against the child with the disorder in a context in which ACEs are already common.

According to the CR theory, the impairments related to ADHD symptoms reviewed above may result in a lower CR for adults with ADHD, which would offer less cognitive resilience against the effects of neuropathology. Therefore, the theory predicts that adults with ADHD are likely to present clinically significant cognitive impairment sooner than their neurotypical peers. Critically, although Dobrosavljevic et al. (2022) found that the risk of dementia in adults with ADHD was three times higher compared to neurotypical adults after adjusting for educational attainment, their analysis did not consider the cumulative effect of life experiences across the lifespan on the risk for dementia.

Other Explanations for Dementia in ADHD

Fewer educational, occupational and social life experiences are not the only explanations for the increased risk for dementia in adults with ADHD. ADHD also shares an important relationship with a host of health conditions, all of which relate to an increased risk for dementia. For instance, depression, obesity, diabetes mellitus and autoimmune disorders are more prevalent in ADHD populations, and these factors are independently and cumulatively significant risks for dementia (Faraone et al., 2021; see Appendix B). Unfortunately, health factors are not currently included in the definition of the CR; however, they do belong to the Scaffolding Theory of

Aging and Cognition - Revised (STAC-R), a meta-theory to which the CR theory belongs (Reuter-Lorenz & Park, 2014).

According to the STAC theory, life experiences, states, events, genetics and environments, from birth to death, enrich or deplete brain structure and function, thereby influencing the trajectory of cognitive ageing (Reuter-Lorenz & Park, 2014). Enrichments contribute positively to neural compensatory mechanisms when biological ageing begins causing an accumulation of pathology in the brain. The theory proposed by the CR fits the enrichments afforded by life experiences but excludes the other sources of enrichment such as genetics and states. Furthermore, STAC-R includes the influence of the depletion on compensatory mechanisms (Reuter-Lorenz & Park, 2014). States and diseases such as depression, obesity, diabetes and autoimmune disorders, deplete the ability for brain structure and function to compensate for the age-related accumulation of neuropathology. Given the higher occurrence of such depleting states in ADHD populations (see Appendix B), STAC-R theory proposes that these factors might also explain why adults with ADHD have higher risks for dementia.

Higher CR Despite ADHD

Although previous research suggests that individuals with ADHD are more likely to accrue fewer enriching life experiences due to the impairment associated with their symptoms, there is variability in these outcomes. For instance, a longitudinal study that followed 207 participants with ADHD from early childhood until mid-adulthood described important environmental, behavioural and cognitive factors that influenced educational attainment, occupational rank and social functioning (Ramos-Olazagasti et al., 2018). Ramos-Olazagasti et al. (2018) found that environmental, behavioural and cognitive factors measured in childhood

and adolescence had important protective effects on occupational, educational and social outcomes of individuals with ADHD in middle adulthood.

Specifically, higher parental SES in childhood positively predicted higher educational and occupational attainment at age 40 years (Ramos-Olazagasti et al., 2018). Furthermore, lower scores on a measure of behavioural difficulties (i.e., conduct problems) measured in childhood predicted better educational and occupational attainment in adulthood (Ramos-Olazagasti et al., 2018). Finally, higher childhood IQ positively predicted occupational functioning, social functioning and educational attainment in adulthood (Ramos-Olazagasti et al., 2018).

Ramos-Olazagasti et al. (2018) also examined the cascading effect of adolescent functional outcomes on subsequent adulthood functional outcomes. In their multilevel model, Ramos-Olazagasti et al. (2018) observed that children with ADHD who had higher social functioning in adolescence also had better occupational attainment and functioning in adulthood. In addition, declining symptom severity related to inattention in adolescence was associated with better occupation and education outcomes in adulthood (Ramos-Olazagasti et al., 2018). Finally, better job functioning in adolescence also predicted better social functioning in adulthood (Ramos-Olazagasti et al., 2018).

The effect of protective factors in childhood and adolescence on adulthood outcomes for individuals with ADHD has been observed in other studies (Glass et al., 2012; Hoza, 2007; Mitchell et al., 2021), and in addition to environmental, behavioural and cognitive factors that contribute to better functional outcomes in adulthood for individuals with ADHD, pharmaceutical interventions have a strong protective effect on improving functional outcomes (Cherkasova et al., 2022; Harpin et al., 2013). For these reasons, although ADHD is associated with poorer functional outcomes in the domains of education, occupation and social participation

when compared to neurotypical peers, there is variability attributable to environmental, behavioural, cognitive and treatment-related factors. Therefore, it is likely that some individuals with ADHD may still accrue enriching life experiences that might delay the onset of cognitive impairment in older adulthood.

Current Research

The relationship between neurodevelopmental disorders and dementia is scarcely reported in the literature. The purpose of this research is to explore the association between ADHD and dementia through the lens of the CR theory of ageing. Although there are health-related (see Appendix B) and other (e.g., STAC-R) explanations for the relationship between ADHD and dementia, the current research explores the relationship through the lens of CR. Furthermore, given the available sample size, the influence of other factors relevant to CR, such as premorbid IQ and physical activity, will be excluded from the current study. This exploration could inform future research on the impact of how life experiences associated with having a neurodevelopmental disorder relate to one's respective risk for dementia. Future research with more participants should also consider health-related factors in explaining the association between ADHD and dementia.

The CR literature documents significant associations between education, occupation and social engagement, and dementia (Opdebeeck et al., 2016; Stern et al., 1994; Valenzuela & Sachdev, 2006). Since previous research suggests that, although symptoms fall below threshold, the majority of adults with childhood onset ADHD continue to experience impairment related to their symptoms in adulthood (Faraone et al., 2006; Fischer & Nilsen, 2024; Kooij et al., 2016; Semeijn et al., 2016; Song et al., 2021), the current research focuses on adults with persistent ADHD symptoms. As reported in the literature, these adults more likely to have fewer experiences that build reserve (Able et al., 2007; Barkley & Fischer, 2019; Biederman et al., 1993; Cherkasova et al., 2022; Loe & Feldman, 2007; Michielsen et al., 2015), and are also at a higher risk for dementia (Dobrosavljevic et al., 2022; Fluegge & Fluegge, 2018; Golimstok et al., 2011; Zhang et al., 2022). Longitudinal data are used here to investigate whether adults with

ADHD symptoms have an earlier onset of dementia compared to neurotypical adults and, if so, whether the cumulative effect of life experiences (i.e., CR) influences this association.

Accordingly, the first objective of this research was to test whether older adults with ADHD symptoms had lower CR on average than adults without ADHD symptoms. Based on literature in samples of children, adolescents and young adults with persistent and symptomatic ADHD that reports fewer reserve building experiences in the domains of education, occupation and social participation, and on the assumption that ADHD symptoms contribute to these observed differences, it is predicted that older adults reporting symptoms of ADHD will also be characterized by lower attainment in these domains. The results from this first objective will be novel, as describing these attainments as a cumulative CR index in older adults with ADHD symptoms has yet to be contributed to the literature. Furthermore, comparing the CR of older adults with ADHD symptoms to the CR of older adults without ADHD symptoms has also yet to be contributed to the literature.

Furthermore, given previous observations regarding the higher risk for dementia in adults with ADHD (Dobrosavljevic et al., 2022; Fluegge & Fluegge, 2018; Zhang et al., 2022), the second objective of this research was to test whether dementia occurred earlier for individuals with ADHD symptoms (i.e., who may not experience enough symptoms to receive a diagnosis) than for neurotypical adults. Comparing the risk of dementia between participants with ADHD *symptoms* and non-ADHD participants is novel, as previous research has only examined the risk in adults with *diagnosed* ADHD (see Dobrosavljevic et al., 2022; Fluegge & Fluegge, 2018; Zhang et al., 2022). Therefore, this prediction aimed to replicate and extend previous results.

Finally, the third objective of this research was to test whether the risk for dementia associated with ADHD symptoms depends on the CR of participants. This prediction was made

due to previous research demonstrating that, although ADHD is associated with impairment in reserve building life experiences, factors such as higher childhood IQ, parental SES, adolescent social functioning and lower ADHD severity can positively affect the accrual of educational, occupational and social life experiences, thereby contributing to a higher CR. Considering the effect of the CR on the risk for dementia associated with ADHD is another novel contribution to the literature.

In the context of an ageing society, identifying groups that may be at a greater risk for dementia is imperative. Life experiences such as education, occupation and social engagement can be modified, therefore, exploring whether the CR of individuals with ADHD symptoms modifies their risk for dementia could provide evidence to develop intervention strategies aimed at decreasing the incidence rate of dementia for these individuals. According to *The Landmark Study* (2022), eliminating risk factors, including educational underachievement, might reduce the prevalence of dementia in Canada by up to 40% in the next 10 years. Even a delay of 1 year could reduce the incidence rate in Canada by 500,000 in 2050 (*The Landmark Study*, 2022). Therefore, the results from this research could make a meaningful difference to the incidence rate of dementia in adults with ADHD in the coming decades.

Method

Data and Study Population

Data for this research were collected by the Longitudinal Aging Study Amsterdam (LASA). LASA began in 1992 and is an ongoing cross-sequential longitudinal study in the Netherlands designed to collect data on the trajectories and consequences of physical, cognitive, emotional and social functioning as it relates to ageing. The initial sample, collected in 1992/1993 (wave B), consisted of 3107 older adults between 55-85 years, randomly selected from population registries in three regions of the Netherlands (Huisman et al., 2011). To represent the diversity of the population, LASA sampled from the rural and urbanized areas of the protestant north, catholic south and secular regions of the Netherlands (Huisman et al., 2011). To maintain representativeness of the sample over time, LASA oversampled older people and males.

Since the first wave, interviews have been conducted every three years and the sample has been refreshed three times (cohort 1: 1992-1993, n = 3107; cohort 2: 2002-2003, n = 1002; cohort 3: 2012-2013, n = 1023). A new cohort is expected to be added to LASA within the next year. The primary cause of attrition before the addition of the second cohort was death (76%), followed by refusal (14%) and frailty or loss of contact (10%) (Huisman et al., 2011). Attrition due to mortality was attributable to the following sample characteristics: being part of the oldest cohort, having four or more chronic diseases, attaining the lowest level of education (primary), having MMSE scores less than 24, experiencing more than 16 symptoms of depression (according to the CES-D) and being divorced. The data from LASA analyzed in the current study was collected from waves G (2008/2009), H (2011/2011) and I (2015/2016).

Study Population

Interviews with participants consisted of a main interview and a medical interview. The main interview, conducted in the participant's home by a trained interviewer, took 1 hour and 45 minutes to complete. Medical interviews were conducted during a separate visit in which clinical measurements and additional questions were administered. Informed consent was obtained from all participants and approval of the Ethical Review Board of the VU University Medical Centre was obtained.

In 2008/2009 (wave G), 1494 participants were assessed for symptoms of ADHD during the medical interview using an ADHD screener developed by Barkley et al. (2007). The scale was originally validated among young adults (Barkley et al., 2007) and since then, the validity of the scale has been assessed in older adults (*M*age = 71.6) using the current sample from LASA (Semeijn et al., 2013). Screener items were based on the most common complaints in adults with ADHD: seven assessed inattention, one assessed impulsivity and one assessed hyperactivity, for a score range of 0-9. In addition to the screener, LASA asked participants to report whether any of the symptoms were present before the age of 16 (based on Kieling et al., 2010; Kooji et al., 2019), a somewhat older "age of onset" than in the DSM. Therefore, evidence of a developmental origin was available alongside the symptom sum from the screener.

Although LASA evaluated the prevalence of DSM-IV defined ADHD using the DIVA 2.0 (Kooji & Francken, 2010), the diagnosis of ADHD in adults has been contentious (Faraone et al., 2006; Kooji et al., 2005; Sharma et al., 2021). As previously reviewed, research in children, adolescents and young adults finds that although symptoms decline over time, impairment persists (Faraone et al., 2006; Gordon et al., 2006). The most recent edition of the DSM changed the diagnostic criteria for adults to reflect this normative trend, however, there is evidence to

suggest the current diagnostic criteria may still not be appropriate for adults over 50 (Dobrosavljevic et al., 2023).

Given the criticisms for the diagnosis of ADHD in older adults, the current research defined ADHD using only the symptoms from the screener. If participants endorsed any symptom (1-9) AND reported a childhood onset of that symptom, they were assigned to the ADHD symptoms (ADHD-sx) group (n = 155). Participants who did not currently endorse symptoms AND did not report childhood symptoms were assigned to the group without ADHD (n = 1071). Two-hundred and twenty-four participants endorsed symptoms currently but did not report symptoms prior to age 16. Finally, 44 participants did not answer the screener.

At wave G, participants global cognitive functioning was assessed using the Mini-mental Status Exam (MMSE)[2]. Participants with ADHD-sx were not more likely to be excluded from the sample based on having an MMSE score below 24 than participants without ADHD, $\chi^2(1) = 2.06$, $p = .15$. Furthermore, participants with ADHD-sx did not have lower MMSE scores (M = 27.90) than participants without ADHD (M = 27.55), $t(217.35) = 1.81$, $p = .07$. All participants whose MMSE scores were less than 24 points were excluded from the sample (n = 162). The sample was further reduced to all participants who were considered dementia free at wave G. A Fisher's exact test revealed that participants with MMSE scores less than 24 points were not more likely to have dementia at wave G ($p = .35$), wave H ($p = .27$), or wave I ($p = .42$). At wave G, 10 participants were excluded from the sample due to evidence of dementia at present (n = 5), dementia diagnosed at a previous wave (n = 4) or due to inconclusive evidence (n = 1). A further

[2] The Mini-Mental Status Exam (MMSE) is a brief test used measure of cognitive functioning in older adults (Folstein et al., 1975). Although there is much contention with respect to appropriate cut-off scores based on sample characteristics (Anderson et al., 2007), 24 points is commonly used to separate individuals with cognitive impairment related to dementia from those with normal cognitive abilities. The MMSE is not meant to replace thorough cognitive assessments and is not intended for making clinical decisions relating to diagnosis.

21 participants were excluded due to missing values. Participants with ADHD-sx were not more likely to be excluded from the sample than those without ADHD, $\chi^2(1) = .03$, $p = .87$. These exclusionary criteria reduced the sample to 1110 participants: 147 participants ADHD-sx and 963 participants with no evidence of ADHD.

At wave G, participants with ADHD-sx were significantly younger (*M*age = 69.78, SD = 6.08) than participants without ADHD (*M*age = 72.31, SD = 8.04), $W = 82266$, $p = .002$. Since risk for dementia is significantly related to age (Wolters et al., 2020), the age distributions of the groups were matched. To match the distributions, the age of all participants was rounded down to the nearest year (e.g., 69.75 was rounded down to 69). Following the rounding process, participants without ADHD were selected if their age at wave G matched the age of any participant with ADHD-sx. Matching the distributions resulted in homogenous variance between the groups and reduced the sample size of participants without ADHD to 839. Participants without ADHD were no longer significantly older (*M*age = 70.07, SD = 6.68) than participants with ADHD-sx (*M*age = 69.30, SD = 6.11), $t(211.82) = 1.38$, $p = .17$. The final sample consisted of 986 participants who were followed from wave G until a diagnosis of dementia, loss to follow-up, or wave I, whichever came first. Figure 1 presents the selection process at wave G and the study design across waves G, H and I.

Variables

Dementia Diagnosis

Dementia was ascertained at waves H (2011/2012) and I (2015/2016) of the study using an algorithm developed by van den Kommer et al. (2018). The algorithm used evidence of persistent cognitive change in the Mini-Mental State Examination (MMSE; Folstein et al., 1975)

and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm, 2004) to determine the probability of dementia among participants. Persistent change was defined by a change in MMSE scores greater than 2 SD over the last two assessments and greater than 1 SD between the current and subsequent assessment (van den Kommer et al., 2018). Using the IQCODE, clinically significant cognitive decline was defined by a minimum score of 28 and persistent change was defined by a score greater than or equal to 28 on the IQCODE in the previous, current and subsequent waves (van den Kommer et al., 2018). If information from the MMSE and the IQCODE were not available, the algorithm used other sources of data to determine the presence of dementia such as a diagnosis from a doctor/specialist, information provided by interviewers, housing in a psycho/geriatric nursing home, or dementia as cause of death.

At each wave of the study, the algorithm reported the presence of dementia according to six categories: 0) No dementia, 1) Dementia at wave x, 2) dementia at the previous wave (x-1), 3) undetermined due to missing data at subsequent waves, 4) undetermined due to no persistent decline despite low MMSE score (less than or equal to 18) and, 5) undetermined due to inconsistent or contradictory data (see Supplementary Table 1). For this research, categories 1 and 2 were used to determine the presence of dementia. If participants did not have evidence of dementia (category 0) or their status was undetermined (category 3 & 5), their subsequent data was included until dementia was observed, or until their most recent observation.

Brain Status

Controlling for neuropathology was not possible in the LASA data. Although blood samples and isolated proteins related to Alzheimer's disease (i.e., serum amyloid P component and A1-antichymotrypsin; Dik et al., 2005; Lieberman et al., 1995; Pepys et al., 1994) were

collected, these proteins are not conclusive evidence of neuropathology (Lieberman et al., 1995; Pepys et al., 1994). Furthermore, the blood samples from which these proteins were isolated were collected in between cohort refreshment (1995/1996). Due to attrition, not all participants of cohort 1 (1992/1993) and no participants in cohort 2 (2002/2003) had data on these proteins. Therefore, although essential to testing the CR theory, it was not possible to control for neuropathology in this sample.

Cognitive Reserve Index

Life experiences in the domains of education, occupation and social participation were used to construct an index of CR. These life experiences were selected as they closely resemble the items used to construct the Lifetime of Experiences Questionnaire (LEQ), a lifespan assessment of experiences in education, occupation and social engagement developed by Valenzuela and Sachdev (2007). According to a recent systematic analysis by Howard et al. (2023), operationalizations of the CR are most robust when the CR is composed of multiple experiences across the lifespan. Therefore, although LEQ is not available in LASA, this research constructed the CR using variables that resembled those used in the LEQ.

Education was measured in LASA using a 9-point ordinal scale: elementary not completed (1; n = 40), elementary education (2; n = 163), lower vocational education (3; n = 228), general intermediate education (4; n = 140), intermediate vocation education (5; n = 163), general secondary education (6; n = 31), higher vocational education (7; n = 154), college education (8; n = 9), and university education (9; n = 58). No data were missing. Due to low frequency count in categories six, eight and nine, participants with educational attainment equal to seven were combined with participants in category six, and participants with educational

attainment equal to eight or nine were recoded to category seven. Therefore, the educational attainment scale ranged from 1 to 7.

Occupation was assessed in LASA using questions about employment, occupational class, prestige and retirement. To best capture the effect of occupation on toxic exposure and lifestyle (Moore & Hayward, 1990), this research examined the participants' longest occupation. Longest held occupation was only collected during the first wave of LASA (n = 270). To overcome missing data, a similar procedure as that described by Martin-Bassols (2023) was used: if longest held occupational data was not available, last held occupation was selected from the cohort refreshment in 2002/2003. If last held was not available, the most recent held occupation (i.e., in wave I) was used to represent occupation. Using this procedure, only 184 participants had missing data on their occupational class. A missing data analysis revealed that 65 participants were missing occupational data due to their retirement status and nine participants were missing data due to their disability status. Males were significantly more likely to be retired by wave I (n = 44) compared to females (n = 22), $\chi^2(1) = 11.25$, $p < .001$. Likewise, a Fisher's exact test revealed that males were significantly more likely to be disabled (n = 8) than females (n = 1), $p < .001$.

Most of the remaining participants with missing occupational data were female (70%, n = 77). Of these females, 19.48% also had missing income data whereas only 6% of males with missing occupational data had missing income data. 48.05% of females who reported income reported either their partner's income or their combined household income. Of those who reported their own income data, 80% of females reported low to medium level income according to the income tertiles based on the entire sample. In contrast, males with missing occupational status were most likely to report combined household income (66%) and 54.5% of males

reported low to medium level of income according to the income tertiles derived from the entire sample.

Jobs were classified by LASA according to the standard classification of occupation (SCO) from Statistics Netherlands (Statistiek, 1992). The variable on occupational class rank-ordered occupations into 43 categories based on domain (e.g., agricultural, care, teaching), required skill level (i.e., elementary through scientific, based on required education, training period, and work experience), and tasks (e.g., cattle breeding, nursing, instructing). Occupational classes were reduced into a 5-level ordinal variable based on the rank ordering used by LASA (elementary, low, medium, high and science).

Finally, LASA assessed social participation in two categories: productive and recreational. Productive activities were measured using 13 activities in which participants contributed their resources to the community through participation in political organizations or volunteer work. To capture participation in productive activities, participants were presented with a list of organizations or associations and asked to indicate whether they were members of the given organization/association and if so, report the frequency at which they attended any of the activities reported. Frequency was recorded on an 8-point scale which ranged from never (0) to every day (7).

Recreational activities included seven activities for well-being, such as visiting a cultural institution or going on an excursion (to the forest, heath, dunes, nature or entertainment park, recreation area, zoological garden or monuments). Unlike productive activities, the activities for well-being reported by participants were not summarized into one variable. Instead, participants reported their frequency of engaging in each endorsed well-being activity on an 8-point scale, ranging from never (0) to every day (7). These scores were summated across the seven types of

leisure activities and divided by seven. If participants respond “no” to any item on the list, they were assigned a score of 0 for that activity. A composite social participation score was created by adding together the reported frequency measures for productive activities and activities for well-being. There was no missing data for social participation.

Education, occupation and the social participation composite score were combined into a CR index by calculating the Euclidian distance from the origin on a combination of each axis. To give each component of the CR equal weight, education and occupation were transformed into an 8-point scale by multiplying education by 8/7 and occupation by 8/5. This index had low internal consistency, Cronbach’s alpha .41, indicating that the three scores represented relatively distinct characteristics. Despite low internal consistency, the index had evidence of good convergent validity with income such that the correlation between CR index and income was significant, $r = .42$, $p < .001$. There were 184 missing observations for the CR index. The CR index was dichotomized at its median (8.91) into high (CR = 1) or low CR (CR = 0). Although dichotomizing the CR index reduces the variance available to model, given the sample size of the ADHD-sx group, dichotomizing the index was necessary for maintaining power.

Covariates

The demographic variables considered as covariates in the analysis were age at wave G and sex. Sex and age are important covariates to take into account given the risk for dementia in older adults and in females (Wolters et al., 2020; Rasmussen et al., 2018). Age was measured in years and sex was a binary variable taking a value of “1” if female and “0” if male.

Confounding Factors

Pharmaceutical treatment translates into significant improvements with respect to the impairments in education, occupation and social relationships related to ADHD symptoms (Cherkasova et al., 2022; Harpin et al., 2013). Treatment is also associated with lower incidence of accidents and/or injuries and a lower risk for depression, substance abuse and/or other psychiatric or behavioral comorbidities (Cheraskova et al., 2021; Faraone et al., 2021). Critically, treatment is associated with a significantly lower risk for mortality (Chen et al., 2022). This effect is especially strong when diagnosis is made early, treatment follows soon after diagnosis and treatment is adhered to for longer (Chen et al., 2022).

Given the importance of treatment and the co-occurrence of depression, obesity, diabetes mellitus and autoimmune disorders with ADHD, it would be ideal to take into account these factors when explaining the influence of life experiences on the relationship between ADHD and dementia. However, due to the small sample size of adults with ADHD symptoms in LASA, and the absence of variables to measure significant risk factors such as treatment for ADHD and autoimmune disorders, the proposed research will not be able to consider the influence of these factors.

Descriptive Statistics

Socioeconomic status (SES), depression, anxiety, loneliness, medications and chronic health conditions were used to describe the sample. Socioeconomic status was created by combining education, occupation and income into a single index. Each scale was corrected to have the same range. The Euclidian distance from the origin along each scale was calculated and the product was taken to represent the index score for each participant. The internal consistency of the SES index was Cronbach's alpha .61. SES was dichotomized at its median (5.14) to simply its interpretation. There were 242 missing observations for SES index.

Depression was measured at wave G using the Centre for Epidemiological Studies – Depression (CES-D) scale which consists of 20 questions (Lewinsohn et al., 1997; Radloff, 1977). Responses are rated on a 4-point scale from 0 to 3; therefore, scores can range from 0 – 60. A sum score was computed across the 20 items. A score greater than 16 indicates clinically significant depression. If participants had missing data in any of the questions from 1 – 20, their sum score was NA. Data on depression was missing for 170 participants.

Anxiety was measured using the Hospital Anxiety and Depression scale – anxiety subscale which consist of 7 ordinal items that range from 0 to 3 (Zigmond & Snaith, 1983). Scores across the 7 items were summated to create a symptom sum score. Therefore, scores could range from 0 – 21. A score of 8-10 suggests clinically significant anxiety. If data was missing on any item, the symptom sum was NA. Clinically significant anxiety was defined if participants reported a symptom sum greater than or equal to 8 points. Data on anxiety was available for all participants.

Data on loneliness was measured at wave G using 11 items from the de Jon Gierveld scale (de Jon Gierveld & van Tilburg, 1999). Items 2, 3, 4, 6, 9, 10 were negatively worded and items 1, 4, 7, 8, and 11 were positively worded. To compute a total loneliness score, positively worded questions were reverse coded and then summated with the negatively worded items. An emotional loneliness score was created by summating across items 2, 3, 5, 6, 9 and 10. If data was missing, the score was invalid. Likewise, a social loneliness score was created by summating across items 1, 4, 7, 8 and 11. If data was missing, the score was invalid. The total loneliness score was computed by adding the score for emotional loneliness to the social loneliness score. Data on loneliness was available for all participants.

Medications were described based on whether participants reported taking medications, and the number of medications taken at wave G. Likewise, chronic health conditions were described based whether participants reported a chronic health condition, and the number of conditions reported at wave G. Data on medications and chronic health conditions were available for all participants. Finally, adverse childhood experiences (ACEs) were assessed using sixty-seven life events from the life event inventory created by Tennant and Andrews (1976). Participants reported whether the event had occurred to them, and if so, the effect the event had on their lives (i.e., positive, negative or unclear). Data on ACEs were only collected in the LASA pilot project (LSN, 1990). There were only 130 observations for ACEs.

Statistical Analysis

Descriptive Statistics

The characteristics of the sample were described based on the ADHD-sx of participants and sex. Differences between groups were compared using standard t-tests for continuously distributed variables with homogenous variance. A Mann-Whitney U was used to compare groups when variance was heterogeneous and data was not distributed normally. Finally, categorical variables were analyzed using χ^2-statistics or Fisher's exact test where appropriate.

Survival Analysis

The time to an initial diagnosis of dementia was calculated by the age of the participants at the date of either their dementia diagnosis, loss to follow-up, or the end of the study period (i.e., wave I). The initial starting point for the analysis was at wave G in 2008/2009, when all participants were assessed for ADHD and were dementia-free (n = 986). Thirty-one participants were left-censored due to dementia at wave G (n = 10) or missing dementia data (n = 21). Apart

from participants who were dementia free at the last assessment point (n = 726), death (n = 165) or loss to follow (n = 64) were sources of right censored cases. These sources of missing data were attributable to being part of the oldest cohort, higher loneliness, fewer years of education, more chronic health conditions, more reported medications, lower social participation or lower MMSE scores at wave G (see Supplementary Table 4).

Hazard ratios (HRs) for the risk of dementia were calculated using Cox-proportional hazards analyses and were adjusted for age at wave G and sex. Survival functions, which are the complement to hazard, represent the cumulative risk of the target event and estimate the probability that an individual has not experienced the target event by a certain interval (Willet & Singer, 2003). Finally, median lifetime represents the interval at which 50% of the sample has not yet experienced the target event. To quantify the importance of variation in hazard from period to period, standard error for hazard was calculated. The standard error for survival was calculated using Greenwood's approximation (Singer & Willett, 2003).

To create a statistical model of the observed data, the hazard function was transformed into the *logit* function. This is necessary for stabilizing hazard estimates and comparing hazard functions between groups (Singer & Willett, 2003). Maximum likelihood was used to estimate the parameters in each of the models, and a likelihood ratio test was used to evaluate each model fit relative to the null hypothesis which is the model where coefficients equal zero. Finally, the Wald Chi-squared statistic was used to compare model fits.

After dichotomizing age at its median (*Mdn* = 69), age and sex were added into Model 1. A significant, positive estimate for age indicates that adults over 69 had a higher risk for dementia compared to adults under 70. A significant, positive estimate for sex indicates that females had a higher risk for dementia than males. In model 2, ADHD was added as a covariate.

Significant ADHD-sx predictor indicates that adults with ADHD-sx, regardless of age or sex, have a higher risk to dement than their non-ADHD peers. Finally, in model 3, a covariate for CR and an interaction term between ADHD-sx and CR was added. A significant, negative estimate for CR indicates that adults with higher CR, regardless of ADHD status, age or sex, have a lower risk to dement than their high CR peers. A significant, negative estimate for the interaction between ADHD and CR indicates that the risk for dementia associated with ADHD is modified by CR such that individuals with higher CR have a lower risk for dementia than those with lower CR.

With respect to the nested models, model fit was evaluated based on the likelihood ratio test. Likelihood ratio test generated for each model was compared. Fit was evaluated using Chi-squared distribution, where alpha was set to .05. Results were summarized using graphs and tables. All analyses were performed using RStudio with version 4.3.1 of R.

Results

Of the 986 participants followed over the course of the study period, 726 participants remained dementia free, 30 participants were diagnosed with dementia, 165 were right censored due to death and 64 were lost to follow-up (see Table 1). Fisher's exact tests did not reveal a significant association between ADHD-sx and dementia (see Table 1).

Missing Data Analysis

Table 1 describes the following missing data analysis. Accordingly, cohort 1 (1992/1993) participants were more likely lost to follow up ($\chi^2(1) = 3.94$, p = .04) or censored due to death ($\chi^2(1) = 70.68$, $p < .001$). Similarly, censored due to death was more likely for older participants (OR = 1.14, 95%CI [.12, .16], $p < .001$). Furthermore, missing data was more likely in participants who reported higher loneliness (OR = 1.07, 95%CI [.02, .11], $p = .002$), fewer years of education (OR = .90, 95%CI [-.16, -.05], $p < .001$), more chronic health conditions (OR = 1.62, 95%CI [.36, .61], $p < .001$), more number of medications (OR = 1.26, 95%CI [.17, .28], $p < .001$), less social participation (OR = .79, 95%CI [-.31, -.18], $p < .001$), or lower MMSE scores at wave G (OR = .82, 95%CI [-.30, -.09], $p < .001$). Therefore, censorship was generally attributable to being older and having poorer mental and physical health at wave G. Although missing dementia data was not more common overall among participants with ADHD-sx, ($\chi^2(1) = 2.71$, p = .10), participants with ADHD-sx were significantly more likely to have missing dementia data by wave I than participants without ADHD, ($\chi^2(1) = 3.99$, $p = .04$).

Between Group Demographics

Most participants (46.94%) with ADHD-sx reported one symptom at wave G (n = 69; see Figure 2). As shown in Table 2, ADHD-sx was significantly associated with meeting the clinical

thresholds for depression and anxiety when compared to the group with no symptoms of ADHD in childhood or adulthood. Furthermore, the group with ADHD-sx was composed of significantly more females and, although there were no statistical differences in terms of number of medications, ADHD-sx were significantly more likely to report taking medications (see Table 2). In addition, ADHD-sx reported significantly more chronic health conditions, symptoms of depression and anxiety, and loneliness (see Table 2). Significant differences were not observed between groups on education, social participation, number of reported medications, ACEs, income, occupational class or SES (see Table 2). Critically, contrary to the first hypothesis, participants with ADHD-sx did not have significantly lower CR than participants without ADHD, $\chi^2(1) = .14$, $p = .71$.

Survival Analysis

The hazard ratios (HR) for dementia diagnosis related to ADHD-sx are presented in Table 3. In the baseline model, females were at significantly higher risk for dementia than males (HR: 2.94; 95% CI: [1.08, 8.00], $p = .03$) (see Model 1, Table 3). Over the study period, the adjusted HR for participants with ADHD-sx compared to those without ADHD was 1.29 (95% CI: .43, 3.88, $p = .65$) (see Model 2, Table 3). Importantly, contrary to hypothesis two, ADHD-sx were not associated with a higher risk for dementia in this sample. The interaction between ADHD-sx and CR was examined in Model 3; however, due to insufficient data, it was not possible to estimate the risk for dementia associated with ADHD-sx in older adults with higher CR. Therefore, hypothesis three was not testable. Figure 3 displays the results from estimating the covariate-adjusted Cox-proportional hazard model. Table 3 presents the model comparison statistics for each Cox-proportional hazard model. In comparison to models 2, model 1 fit the data best.

Discussion

The three goals of this research were: to describe and compare the CR of adults with ADHD symptoms to adults without ADHD symptoms, to extend previous research by examining the association between ADHD symptoms and risk for dementia, and to investigate whether CR affected the risk for dementia in older adults with ADHD symptoms. Critically, in light of the growing population over 65, describing the risk for dementia among older adults with ADHD is important as individuals with neurodevelopmental disorders may represent a higher risk group (Siguier et al., 2024). A description of the CR of adults with ADHD symptoms, the risk for dementia associated with ADHD symptoms, and the potential modifying effect of CR on this risk has yet to be contributed to the literature.

Among individuals with post-mortem evidence of neuropathology consistent with processes related to dementia, 25% demonstrate cognitive performance within normal limits prior to death (Ince, 2001). The paradoxical absence of cognitive impairment in the presence of neuropathology is at least partially explained by the cognitive reserve (CR) theory of aging. Accordingly, individual differences in cognitive decline are attributable to neural enrichments over the lifespan (Stern et al., 2020). In light of the extensive literature that reports significantly reduced risk for dementia among individuals with extensive educational, occupational and social life experiences (see Opdebeeck et al., 2016 for a review), the CR theory proposes that exposure to these experiences contributes to the formation of CR which in turn, delays the onset of cognitive impairment in spite of accumulating neuropathology (Stern et al., 2020).

Although the neural basis for the CR has yet to be elucidated, enriching experiences are purported to contribute to the development of neural capacity, efficiency and flexibility (Steffener & Stern, 2012). When neuropathology begins to place challenge on the brain in older

adulthood, the cognitive resilience developed by the accrual of enriching life experiences is recruited to meet task demands and maintain cognitive performance (Steffener & Stern, 2012). Although not all older adults will develop neuropathology, among those who do, the CR theory of aging predicts that cognition remains unaffected for longer in individuals with more exposure to enrichments (Stern et al., 2020).

Despite extensive literature describing the resilience against cognitive decline afforded to individuals with higher CR, the influence of the CR on risk for dementia in populations with neurodevelopmental disorders is understudied. Due to the impairment in social, educational and occupational settings caused by symptoms, it is likely that neurodevelopmental disorders, such as ADHD, may limit an individual's exposure to enriching life experiences[3] (for a review, see Cherkasova et al., 2022). Hypothesis one leads to the first prediction of this research which was to test whether individuals with ADHD-sx had lower CR than their neurotypical peers.

Objective One

Contrary to the first prediction, CR in those with ADHD-sx was not statistically different from the CR of participants without ADHD-sx. In fact, although not statistically significant, the ADHD-sx group had higher observed mean CR than the no-ADHD group (see Table 2). Dichotomizing CR at the median (n = 802) also did not result in significant differences with respect to the proportion of participants in each category of CR between groups ($\chi^2(1) = .14$, $p = .71$). These results suggest that, compared to participants with no ADHD symptoms,

[3] It is also possible that limiting exposure to enriching life experiences may increase the risk of negative life experiences (Brown et al., 2017; Lugo-Candelas et al., 2021; Reuter-Lorenz & Park, 2014). The effect of negative life experiences (referred to as neural resource depletion by Reuter-Lorenz & Park, 2014) on compensatory mechanisms during cognitive aging are explained in the Scaffolding Theory of Cognitive Aging (Reuter-Lorenz & Park, 2014).

participants with ADHD-sx had similar exposure to enriching experiences across their lifespan. The discrepancy between the first prediction and the results could be explained by the operational definition of ADHD used by this study; however, the effect of selection or survival bias on sample characteristics may better explain the results.

ADHD Operationalization

In the current study, participants were assigned to the ADHD-sx group if they currently reported at least one ADHD-sx and that the symptom(s) onset occurred prior to the age of 16. A primary concern related to using the symptom screener instead of the ADHD diagnostic assessment is the possibility of misclassification. Unlike the diagnostic criteria for ADHD, the screener used by LASA did not evaluate whether symptoms could be better explained by other mental conditions. In the context of older adulthood, symptoms related to mild cognitive impairment (MCI), such as forgetfulness, trouble doing things in order, and sustaining attention during tasks, overlap with ADHD symptoms (Callahan et al., 2017). Furthermore, although literature is scarce, ADHD symptoms resemble symptoms experienced during the peri- and post-menopause (Camara et al., 2022; Pines, 2016). Given the that ADHD is expected to be more prevalent in adult males than in females (1.6:1, adult male to female; APA, 2013), the higher-than-expected prevalence of adult females with ADHD-sx in the current sample (1:1.49, adult male to female; χ^2 (1) = 5.72, p = .02) could partly reflect that symptoms endorsed by females that are better explained by peri- or post-menopause. In summary, selecting participants based on their diagnostic results, rather than their scores on the screener, could have offered more certainty that the etiology of their symptoms was not attributable to MCI or menopause.

However, even if the diagnostic criteria were used to select participants with ADHD, issues related to memory impairment are not overcome. The primary complication for assessing

ADHD in late life is the retrospective assessment of symptoms. In older adults, reliance on memory to recall symptom onset compromises the validity of the diagnosis, due to memory impairment, recall bias, and self-knowledge, each of which are demonstrably more impaired in individuals with ADHD and in older adults (Sharma et al., 2021). Since current symptom severity influences retrospective assessment of symptom burden in childhood (Miller et al., 2010), the effect of recall bias is especially problematic for adults whose childhood predates the diagnostic era for ADHD, as they, and their circles of care, were not aware of a diagnostic label to explain their behavioural differences. Furthermore, symptom recall is also biased by a normative phenomenon called the reminiscence bump, which describes the observation that individuals have a bias for recalling events that occurred between the ages of 10-30 years (Munawar et al., 2018; Sharma et al., 2021). Given that criterion B requires participants to recall symptom onset before the age of 12, it is possible that the reminiscence bump could also impair their recollection of symptoms, and, therefore, exclude them from diagnosis.

In addition to the issues for diagnosis presented by memory impairment and recall bias, the symptom threshold of criterion A may be inaccurate for older adults. Currently, criterion A requires at least 5 symptoms in either dimension of ADHD to meet the threshold for diagnosis in adulthood (APA, 2013). This symptom threshold was introduced in the fifth edition of the DSM due to mounting evidence that symptoms wane from childhood to young adulthood (Biederman et al., 2000; Döpfner et al., 2015). However, symptoms continue to wane after young adulthood, suggesting that the symptom threshold should be further adjusted for older adults (Fischer & Nilsen, 2024; Kooij et al., 2016). Therefore, diagnostic issues with criterion A and B have called into question the validity of the diagnosis for ADHD in older adults.

If diagnostic criteria had been used instead to define participants in the current sample, it is unlikely that significant differences between the diagnosed ADHD and the no-ADHD group would have been found on their CR. Although diagnosed ADHD is expected to relate to more severe dysfunction in educational, occupational and social settings (APA, 2013), previous research with the LASA sample suggested that participants with diagnosed ADHD were not statistically different from those with ADHD-sx on the three sociobehavioural proxies of the CR (Michielsen et al., 2012). Using a stricter definition for subthreshold ADHD than the current study (i.e., participants whose symptom count was greater than 3), Michielsen et al. (2012) found no significant differences between LASA participants with diagnosed ADHD and those with subthreshold ADHD on education or income. Although the subthreshold definition of ADHD used by Michielsen et al. (2012) was more conservative than the definition used by the current study, Michielsen et al. (2015) also did not find an association between number of ADHD symptoms and educational or occupational attainment. Likewise, Michielsen et al. (2015) observed that number of ADHD symptoms did not relate to less social participation among LASA participants. Critically, an exploratory sensitivity analysis, conducted as part of the current project, between participants with two or more symptoms and those with one or more symptoms also revealed no significant differences between groups on any sociobehavioural proxies of CR (see Supplementary Table 2).

Since the diagnostic criteria have yet to be validated in older adults, using the screener seemed a more appropriate choice. In the sample selected by LASA for the ADHD side-study, Semeijn et al. (2013a) examined the criterion validity of the ADHD screener developed by Barkley et al. (2007) for detecting ADHD in adults over 60. Although the operational definition of ADHD of the current research used a cut-off score of one or more symptoms, Semeijn et al.

(2013a) found that a cut-off score at two points offered the best balance between sensitivity and specificity, and correctly identified 13% of true cases and 99% of false cases. The one symptom cut-off score was chosen instead of the two-point cut-off score due to careful consideration of the appropriate contexts for sensitivity and specificity, and issues related to sample size.

The value offered by sensitivity, specificity and their complements (i.e., positive and negative predictive power) depend on the contexts in which they are assessed (Trevethan, 2017). In the cases of sensitivity and specificity, these values are determined among those who are diagnosed; they assess the proportion of individuals with the diagnosis and who are screened positively for the diagnosis by the screening tool's cut-off scores. Semeijn et al. (2013a) used the DIVA 2.0 diagnostic assessment, however, and as mentioned previously, given that the DIVA 2.0 has not yet been validated in adults over 60 (Pettersson et al., 2018; Ramos-Quiroga et al., 2019), using sensitivity or specificity to assess the validity of symptom screeners may be inappropriate because the reference standard has yet to be validated (Trevethan, 2017). In this context, sensitivity and specificity underestimate the prevalence of type I and II errors (Trevethan, 2017). Therefore, according to Treventhan (2017), predictive values are more useful than sensitivity or specificity during the screening process. Based on this recommendation, the cut-point analysis by Semeijn et al. (2013a) suggests a minimal difference between one point and two-point cut-off scores. Given the sample size associated with a two-point cut-off (n = 78), and evidence that suggests self-report underestimates symptom burden compared to informant report (Barkley et al., 2002), a one-point cut-off score was selected as the operational definition for ADHD in this study.

Taken together, although using diagnostic status could reduce the possibility of misclassification, the diagnostic criteria for ADHD have not yet been validated for adults over

60. Due to diagnostic issues with respect to criterion A and B, using the screener to identify participants with ADHD was more appropriate. Moreover, although diagnostic criteria are expected to relate to more severe impairments in educational, occupational and social participation, previous research using the LASA ADHD-side study suggest that the sociobehavioural proxies of the CR were not different between those diagnosed with ADHD and those with symptomatic ADHD. Therefore, it is unlikely that the operational definition for ADHD used by this study accounts for the discrepancy between the prediction made by hypothesis one and the results.

Selection and Survival Bias

Negligible group differences on the CR may be better explained by selection and survival bias. Specifically, it is likely that participants with ADHD-sx were not representative of the childhood cohorts from which they originated. Selection bias refers to sampling biases which make the distributional characteristics of a sample different from the cohort they intend to represent. Selection bias in ageing research is driven by health disparities and socio-economic differences which favour healthier, wealthier and more educated study participants, relative to the population from which they are sampled (Enzenbach et al., 2019; Zajacova & Burgard, 2013). For instance, in a sample of 14,466 older adults from the Healthy Retirement Study conducted in the United States, Zajacova and Burgard (2013) describe that the characteristics of a sample shift towards healthier, wealthier and more educated participants over time. Although LASA oversampled older people and males to make up for their higher rates of mortality, it is likely that LASA, and other ageing studies, unintentionally over-sample healthier, wealthier and more educated adults (Mody et al., 2008; Zajacova & Burgard, 2013).

Previous studies based on samples of children or adolescents followed into adulthood suggest that individuals with ADHD are at higher risk for various adverse functional outcomes. Studies previously conducted in samples of children and adolescents with ADHD demonstrate that, in comparison to their neurotypical peers, these individuals attain fewer years of education, lower occupational prestige, lower incomes and smaller social networks (Cherkasova et al., 2022). In stark contrast to the studies conducted in children and adolescents, the current study found no significant differences between groups in educational attainment, occupational class, income or social participation.

Further, evidence of survival bias is observed in an exploratory analysis which did not find a significant difference between groups with respect to their risk for death (see Supplementary Table 3 and Supplementary Figure 1). This is in stark contrast to the results by Barkley and Fischer (2019) which found that, in a sample of young adults with ADHD followed since early childhood, children with ADHD had 8.4-year reduced life expectancy compared to controls. Their shorter life expectancy was partly explained by the occurrence of chronic health conditions, engagement in risky behaviours, and higher risk for injury or accidents[4] (Barkley & Fischer, 2019). Indeed, individuals with ADHD are at greater risk for a range of adverse health outcomes such as obesity, diabetes and autoimmune disorders (see Appendix B).

Consistent with this observation, participants with ADHD-sx were significantly more likely to report taking medications and, although ADHD-sx was not more likely to report a

[4] These adverse outcomes could be explained by delayed treatment seeking among individuals with ADHD. According to a nationally representative epidemiological survey conducted in the United States (n = 34,653), individuals with ADHD were less likely to seek treatment than individuals with other psychiatric disorders (Dakwar et al., 2014). In fact, among the youngest cohort (18-29) in the study by Dakwar et al. (2014), the median delay for treatment seeking after symptom onset was 10.5 years. For individuals over 44, the median delay was 28 years (Dakwar et al., 2014).

chronic health condition, the number of chronic health conditions were not equally distributed between the groups; the proportion of one or more chronic health conditions was higher in the ADHD-sx group (see Table 2). However, in contrast to the observation that children with ADHD are at higher risk for engaging in risky behaviours (Cherkasova et al., 2022), Semeijn et al. (2013b) described that number of ADHD symptoms of participants in the LASA ADHD-side study were not associated with either smoking or alcohol consumption. Engagement in fewer health compromising behaviours may at least partly explain the result from an exploratory survival analysis with death as the outcome. Moreover, since the group differences with respect to chronic health conditions are cross-sectional, it is possible that a longitudinal investigation could better elaborate differences with respect to healthy life expectancy between groups.

Given the stark differences in life expectancy and health associated with ADHD, it is possible that a selection and survival bias may be influencing the sample characteristics of the adults with ADHD-sx. The results of hypothesis one suggests that participants with ADHD-sx sampled in this study may have been the least disadvantaged by their symptoms over their lifespan and therefore, became the healthiest, wealthiest and most educated members of their childhood cohorts. As previously mentioned, the selection bias observed in this sample is often observed in other community samples of older adults (Enzenbach et al., 2019; Zajacova & Burgard, 2013). The demographic characteristics of this sample may explain how adults with ADHD-sx were able to gain exposure to the same enriching lifespan experiences, and therefore, were no different from their peers without ADHD.

Future Directions

Although a diagnosis of ADHD would have improved certainty that those in the ADHD-sx group were not misclassified, the diagnosis was not used due to issues with the validity of the

assessment for adults over 60. In addition to making the necessary adjustments to criterion A and B, the reliability of ADHD assessment in older adults can be improved if future research considers collecting informant reports. Given impairments in memory which are more common in ADHD and a normative aspect of cognitive aging, informant report from family members or friends could improve confidence that a developmental origin of the symptoms existed.

Furthermore, repeated assessment should be considered necessary for establishing diagnosis. As demonstrated in Sibley et al. (2017), repeated assessments uncover whether symptoms are better explained by another mental disorder. In older adults, ensuring that symptoms are not due to a major neurocognitive disorder or (peri-) menopause is essential to accurate case identification. Finally, establishing a family history may be important to identifying ADHD in older adults. Starck et al (2016) reported that clinically relevant ADHD symptoms were prevalent in 50% of parents whose children were diagnosed with ADHD. Therefore, interviewing participants about the prevalence of ADHD in their children may confirm that observed symptoms in older adults are consistent with ADHD.

If a diagnostic assessment cannot be performed, the limitation related to using the screener to identify individuals with ADHD can be overcome if future research considers sampling participants with diagnosed ADHD from a clinical population. Similar to Dobrosavljevic et al. (2022), collecting data from population health registries could increase the sample size of individuals with diagnosed ADHD and overcome the issue of retrospective assessment since diagnostic status is recorded in the health registry at the time of diagnosis.

Finally, given the unexpected health, wealth and educational attainment of the ADHD-sx sample, future research should consider collecting qualitative data on the life experiences of older adults with ADHD to better understand the factors that may have protected them from

adverse health outcomes frequently observed in children and young adults. A qualitative study by Michielsen et al. (2018) explored the burden of ADHD on quality of life in the sample of LASA participants with diagnosed ADHD. They reported participant strategies to adapt and compensate despite the impairment caused by their symptoms in social, occupational and educational domains (Michielsen et al., 2018). Future research might explore adaptation and compensation as a theme across the lifespan of older adults with diagnosed ADHD. Previous research in a sample of young adults suggests that strategies to compensate for impairment may mask symptoms and improve functional outcomes for individuals with ADHD (Mitchell et al., 2021). Therefore, it is possible that compensation may protect individuals with ADHD from the deleterious consequences of their symptoms to health and well-being.

Objective Two

The second objective of this research was replication of previous observations that individuals with ADHD have a higher risk for dementia than their neurotypical peers. In a population-based study, Dobrosavljevic et al. (2022) found a significantly higher risk for dementia in adults diagnosed with ADHD, which did not attenuate after adjustments for age, sex, other comorbid health conditions, educational attainment and other developmental disorders. Other studies, such as a case control study by Gomlistok et al. (2011), and a hospitalization discharge study by Fluegge and Fluegge (2018), described a similar increased risk for dementia in adults with ADHD compared to neurotypical controls. Critically, using the Wilcoxon two-sample test, Dobrosavljevic et al. (2022) found that adults with ADHD were significantly younger than adults without ADHD at the age of their dementia diagnosis.

Although these results suggest a shorter median survival time for adults with ADHD, comparing group differences does not address group differences in risk for dementia. Describing

when 50% of the sample with ADHD-sx are at risk for dementia and whether they reach the median survival time sooner than participants without ADHD is an important contribution to the literature. Therefore, to replicate and extend previous observations, the second objective of this study was to use survival analysis to test the prediction that participants with ADHD-sx would have a higher risk for dementia and dement earlier than participants without ADHD.

Model two indicated significant group differences based on age and sex; however, the hazard estimate for ADHD-sx revealed no significant difference between groups with respect to risk for dementia (see Model 2, Table 3). Therefore, contrary to prediction, adults with ADHD-sx did not have a higher risk for dementia than adults without ADHD after adjusting for age and sex. Critically, when comparing model fits, model two was not a significant improvement over model one, $\chi^2(1) = .20$, $p = .65$.

Although the Likelihood ratio test indicated that model 2 was significantly different from a zero-coefficient model, the hazard estimates reported in Table 3 should be interpreted with caution, due to the low number of events observed in the data set. According to Kocak and Onar-Thomas (2012), at least 67 events must be observed per binary covariate to reliably estimate a hazard ratio of two. In model one, although a hazard ratio of 2.94 was estimated for sex, the confidence interval suggests uncertainty in the estimate. This is likely due to the observation of only 22 events (8 events removed due to missing data on age). When ADHD was added to model two, the power to detect group differences in the outcome was further compromised because of the limited number of events observed per covariate. Therefore, failing to reject the null hypothesis was attributable to the limited number of dementia events observed in the sample. Reasons for the limited number of events include: the severity of ADHD captured in the sample;

the age of participants; and most importantly, informative censoring, each of which are discussed next.

ADHD Severity and Risk for Dementia

In contrast to the studies by Dobrosavljevic et al. (2022), Gomlistok et al. (2011) and Fluegge and Fluegge (2018), ADHD was not defined by the diagnostic criteria of the DSM V/IV in the current study. Since a DSM V diagnosis requires that an adult endorses at least 5 symptoms in either dimension of ADHD (APA, 2013), the symptom burden of most participants in the current study was not as high as in the previous research. Although not perfectly associated, symptoms and impairment are positively related and share a significant amount of variance (Gordon et al., 2006). Since the symptom burden of participants in previous studies was higher than in the current study, it is possible that participants of previous studies were more impaired by their symptoms, which may have resulted in significant group differences with respect to the incidence of dementia observed in the sample. Therefore, if there is a true effect of ADHD on the risk for dementia, the discrepancy between the results previously reported and those of the current study could be explained by the severity of ADHD characterized by the operational definition of this study.

Age and Incidence of Dementia

Furthermore, the limited number of events observed in the data could be attributable to the age of participants at the analysis baseline (i.e., wave G). Contrary to previous literature, model one suggested that age was not significantly associated with risk (HR = .19, 95% CI [.03, 1.13], p = .07). This unexpected result might be explained by selection bias related to an assumption imposed by the survival analysis: all participants had to be at risk for the event at

baseline (Willet & Singer, 2003). In other words, all participants had to be dementia free at baseline to conduct the survival analysis. Although excluding participants from the sample due to their dementia status at baseline did not favour younger participants, t (2247.8) = .46, p = .64, participants with ADHD-sx were significantly younger (*Mage* = 69.78, SD = 6.08) than participants without ADHD (*Mage* = 72.31, SD = 8.04), W = 82266, p = .002. To reduce the confound of age on the risk for dementia between groups, the age distribution of the participants without ADHD was matched to the age distribution of ADHD-sx. Matching the distributions reduced the number of participants over 69 from 594 to 424, and the number of events observed in participants over 69 from 34 to 27. Therefore, the analytic strategy used to match age distributions reduced the proportion of participants over 69, and, by extension, the incidence of dementia in the sample was also reduced, especially among the older individuals, who are at greatest risk for dementia.

Interestingly, the significant differences between ADHD-sx groups with respect to depression, anxiety and loneliness suggest that a longer window of time might have revealed more cases of dementia in the ADHD-sx group (see Table 2). According to previous literature, anxiety and depression may indicate prodromal neuropsychiatric symptoms of dementia (Stella et al., 2014). Critically, using the LASA ADHD-side study, Michielsen et al. (2013) observed that symptoms of depression and anxiety increased over the three waves preceding wave G in both participants with diagnosed and syndromatic ADHD. The comorbidity of anxiety or depression with ADHD in older adults has also been observed in other samples (Fischer & Nielsen, 2024). Therefore, it is possible that the higher anxiety and depression symptoms observed in the participants with ADHD-sx were harbingers of dementia. Given the younger age of the sample currently observed with ADHD-sx, and the 6-year window of time in which they

were observed, the incidence of dementia for the ADHD-sx group may have eventually increased had the window of observation extended into the subsequent waves of the LASA study.

Informative Censoring

Finally, given the prospective nature of the study design, missing data was highly prevalent. In contrast, Dobrosavljevic et al. (2022) selected their participants from national population patient and death registries. The advantage of participant selection from registries is that data is available from birth to death. In this way, missing data are minimized. Likewise, Gomlistok et al. (2011) and Fluegge and Fluegge (2018) used a case-control design to select their participants. Selecting participants based on their outcomes also minimized the effect of missing observations, thereby improving their statistical power.

Unfortunately, the reason for missing data was related to the occurrence of dementia which posed a serious threat to the validity of the survival analysis. Informative censoring occurs when missing data, after the baseline assessment, are related to the risk of the outcome (Willet & Singer, 2003). In contrast, non-informative censoring occurs when data are censored randomly or due to the design of the study (Willet & Singer, 2003). When data are censored because the collection period ends, it can be assumed that those who were censored would have remained in the study had the collection period not ended. Importantly, the validity of a survival analysis depends on non-informative censoring (Willet & Singer, 2003).

A missing data analysis suggests that censored cases were not missing at random and were related to the risk for dementia. For instance, censored cases were significantly related to being deceased, $\chi^2(1) = 238.38$, $p < .001$. Death is an important semi-competing risk for adults at risk for dementia since the risk for death is significantly higher for adults with dementia than

non-demented adults (Østbye et al., 1999). Critically, due to the 3-year interval between assessments, it is possible that participants who were dementia-free at a previous assessment point and censored due to death at their final assessment point reached a status of dementia in between assessments. Although participants could have transitioned from a healthy state to death and avoided dementia, unobserved dementia between intervals may have underestimated the incidence of dementia and ultimately affected the power of the current analysis (Joly et al., 2002). Interestingly, when examining the frequency of missing dementia data per wave, participants with ADHD-sx were more likely to have missing dementia data at wave I, ($\chi^2(1) = 3.99$, $p = .04$). Furthermore, ADHD-sx group was more likely to report taking medications at wave G and reported significantly more chronic health conditions than the no-ADHD group. Given that previous research reports higher risk for dementia and/or mortality related to multimorbidity and polypharmacy (Park et al., 2017; Valletta et al., 2023), the observation of more missing dementia data for ADHD-sx participants at wave I and poorer physical health at wave G might suggest that ADHD-sx participants were more affected by processes related to transitioning from a healthy state to either dementia or death.

Moreover, cases censored due to death were significantly more likely for individuals who were older at baseline assessment, and for individuals with higher baseline loneliness, fewer years of education, higher number of medications reported, higher number of chronic health conditions, lower social participation and lower MMSE scores (see Supplementary Table 4). Each of these characteristics are independently and collectively related to a higher risk for dementia (Chen et al., 2023; Livingston et al., 2017), and multimorbidity is a significant risk factor, not only for death, but also for dementia (Valletta et al., 2023).

In summary, censored cases were related to mortality, and to poorer mental and physical health. These explanations for missing data are strongly related to the risk for dementia, as observed by previous studies, and suggest that the mechanism for missing data was related to the outcome under investigation. Missing not at random is a major methodological issue and likely explains why the results failed to replicate previous observations.

Future Directions

If ADHD is related to a higher risk for dementia, the low symptom burden in the current study may have missed the effect of ADHD on the risk for dementia observed by previous research. Future iterations of this research should consider using data from population health registries to reduce the issue related to ADHD severity and sample size. Furthermore, the use of health registries could also improve the bias introduced by matching distributions to control for the confounding effect of age.

To overcome the limitations of informative censoring, future research should consider statistical models that are less vulnerable to the effect of informative censoring. As proposed by Joly et al. (2002), a multi-state, illness-death transition model can account for the competing risk of death by modelling the risk for transitioning from health to dementia, death, or dementia to death, thereby minimizing the effect of censorship on the parameter estimates for dementia. Unfortunately, the current research could not explore the possibility of an illness-death transition model due to sample size.

Alternatively, a multilevel model could also overcome the issue introduced by missing data. Critically, the use of a multilevel model would allow a reconceptualization of the outcome from a binary (i.e., dementia status) to a continuous outcome (i.e., cognitive performance). A

major advantage of reconceptualizing the outcome is that variability in the dependent variable would increase. Since dementia is a binary outcome which represents cognitive decline beyond a specific threshold (i.e., as defined by van den Kommer et al., 2018), the number of individuals who were declining cognitively but who had not yet reached threshold were observed as non-demented in the current study. This may be a major limitation since it has been previously observed that a large proportion of the population with meaningfully compromised cognitive function score under diagnostic threshold for dementia (Low et al., 2004). According to a population survey conducted by Low et al. (2004), 33.3% of participants met their criteria for cognitive impairment without dementia (CIND) whereas only 2.4% met the criteria for possible dementia. The higher prevalence of CIND compared to dementia is consistently reported in the literature (Pais et al., 2020) and is also observed in other mental disorders of the DSM, such as ADHD (Kotov et al., 2022). Therefore, in the context of the current research, operationalizing the outcome as a binary variable likely reduced the number of observed events and limited the ability of the model to estimate risk.

A shift from classification-based to continuum-based assessments is gaining popularity in the field of Psychology due to the large proportion of individuals with sub-threshold symptom burden and the important effect subthreshold symptom burden has on impairment in social, educational and occupational settings (Kotov et al., 2022). Therefore, to increase the variability in the dependent variable, and ultimately the power to detect an effect, future research should consider operationalizing cognition on a continuum rather than as a binary classification. This paradigm shift suggests that human cognition and behaviour exists on a continuum; such a reconceptualization would facilitate the use of a multilevel model which might be more appropriate in future iterations of the current research.

Objective Three

As previously explained, the CR theory of aging proposes that enriching experiences over the lifespan contribute to forming resilience against cognitive impairment despite accumulating neuropathology by challenging the brain to develop cognitive flexibility, capacity and efficiency to meet task demands (Stern et al., 2020). Previously, research has provided evidence that enriching experiences in education, occupation and social participation, independently and in combination, reduce the risk for dementia (Opdebeeck et al., 2016). Although previous research reports that individuals with diagnosed or symptomatic ADHD experience impairments in occupational, educational and social settings in childhood, adolescence and young adulthood (for a review, see Cherkasova et al., 2022), literature on CR considering the effect neurodevelopmental disorders may have on the risk for dementia is sparse (Dobrosavljevic et al., 2022; Siguier et al., 2024).

Previous literature has reported that environmental, behavioural and cognitive factors can influence exposure to enriching life-experiences, despite ADHD status. For instance, in a sample of children with ADHD, higher parental SES predicted higher educational attainment in adulthood (Ramos-Olazagasti et al., 2018). Moreover, in the same sample, higher childhood IQ predicted higher occupational ranking and functioning in adulthood for individuals with ADHD (Ramos-Olazagasti et al., 2018). Higher childhood IQ also predicted better social functioning in adolescence and adulthood (Ramos-Olazagasti et al., 2018). Since deficits in IQ are not more likely in ADHD than in neurotypical individuals (Bridgett et al., 2006), the results by Ramos-Olazagasti et al. (2018) suggest that children with ADHD and higher IQ are more likely to attain higher educational, occupational and social outcomes in adulthood.

In addition to the effect of SES and IQ on functional outcomes, Ramos-Olazagasti et al. (2018) found that positive social functioning in adolescence, measured in terms of friendships and social participation, played an important role in positive occupational outcomes in adulthood for individuals with ADHD. This result may reflect the protective effect of friendships on adulthood outcomes for individuals with ADHD (Hoza, 2007). For instance, in the context of friendships, Glass et al. (2012) found that ADHD symptoms were not associated with negative friendship quality. Although individuals with ADHD typically report fewer friends and smaller social networks (Glass et al., 2012; Hoza et al., 2005; Michelsen et al., 2015), the quality of their friendships, as reported by both members, is not significantly more negative or less positive than the quality of friendship between neurotypical individuals (Glass et al., 2012; Hoza et al., 2003). Given that friendships are important context for developing skills relevant to occupational contexts (i.e. cooperation, negotiation, conflict resolution, communication etc.; Hoza et al., 2007), positive social functioning in the context of friendships may be protective to adolescents with ADHD and contribute to better occupational functioning in adulthood.

Finally, although the previous literature reports poorer romantic relationship outcomes (Michielsen et al., 2015; Wymbs et al., 2021), these relationships are nuanced. In a sample of 159 emerging adults, Knies et al. (2020) observed that avoidant attachment styles predicted better relationship quality in couples where one individual had ADHD. Given that insecure attachment styles are more prevalent in the ADHD population (Storebø et al., 2016), it is possible that avoidant attachment styles are not always maladaptive for individuals with ADHD in the context of romantic or intimate relationships. Taken together, a host of environmental, behavioural and cognitive factors may contribute to better educational, occupational and social outcomes for individuals with ADHD, thereby contributing to a higher CR. Therefore, the third

hypothesis for this research led to the prediction that the risk for dementia associated with ADHD-sx would depend on the CR of participants.

Unfortunately, hypothesis three was not testable because the model failed to converge, which is likely due to the methodological issues previously addressed: since too few dementia events were observed, the models could not reliably estimate hazard. With the addition of two more covariates in model 4, there were not enough events per covariate to estimate hazard. In the following section, reasons for model non-convergence are explained: in addition to introducing a new source of missing data, the results from hypothesis three may have failed to reject the null due to negative skew in the CR variable and *a priori* grouping of indicators assumed to represent the CR.

Missing Data and the Homemakers Hypothesis

The most likely explanation for the limited number of events in the data was the missing data problem, which was amplified in hypothesis three: as opposed to having 22 events and 85 observations removed due to missing data in Hypothesis Two, 246 observations were removed due to missing data for CR and only 15 dementia events were observed in Hypothesis Three. To form the CR of each participant, data on their education, occupational and social participation were collected, and a score was generated by treating each proxy as an axis and computing the participant's total distance from the origin. Importantly, if participants had missing data on any of the three proxies, a CR score could not be generated.

Although there was no missing data for education or social participation, 184 participants were missing occupational class data. Investigating the cause for missing data revealed that 65 participants were missing because they were retired. Of the participants who still had missing

data, nine were missing because of a disability. Importantly, the remaining participants who had missing data for occupational class (n = 110) were disproportionately female (n = 77), $\chi^2(1)$ = 17.6, $p < .001$.

Due to cultural norms at the time of their emerging adulthood and adulthood, it is possible that these participants with missing data did not report occupational class because they were homemakers during the 1920s-present. In support of this hypothesis, males were significantly more likely to be retired (n = 44) than females (n = 22), $\chi^2(1) = 11.25$, $p < .001$, and a Fisher's exact test revealed that males were significantly more likely to have received disability insurance (n = 8) than females (n = 1), $p < .001$. Based on the LASA data collection procedures, these statuses were contingent on previous employment, thereby suggesting that these males previously held an occupation.

To further support the "*homemakers hypothesis*", 19.48% of females with missing occupational class also had missing income whereas only 6% of males with missing occupational data had missing income, $\chi^2(1) = .2.24$, $p = .13$. Again, data on income could imply that participants had an employment that may have been missing because the occupation was unlisted, or because they were receiving disability insurance or a pension. Therefore, missing income among females could be taken as more evidence that employment was more prevalent in males than in females.

Finally, among the sample with missing occupational class, 48.05% of females who reported an income reported either their partner's income, or their combined income. Of those who reported their own income, 80% of females reported low to medium level income according to the income tertiles derived from the entire sample. In contrast, males were more likely to

report a combined income (66%) than females. Moreover, only 54.5% of males who reported their own income reported low to medium level of income. Reporting combined income and occupying the lower income tertiles might suggest that females were not financially independent from their partners, which might be related to unemployment. In summary, a large portion of data for the CR was missing because of missing occupational class, which was mainly attributable to being female and likely related to being homemakers in the 1920s-present.

These results reveal a critical gap in the ageing literature; homemaking is an overlooked occupational status. Despite proportional representation of females in samples of older adults, the occupational status of homemaking, which was an especially common occupational status for Dutch females pre- and post-World War II (de Groot, 2023; Van Poppel et al., 2009), is excluded from many longitudinal ageing studies. Failure to include homemaking as an occupational status resulted in a large loss of data, which is likely not unique to LASA. Although there is an absence of literature on how the skills and tasks related to being a homemaker affect executive functioning, a study by Bickel and Cooper (1994) found that the annual incidence of dementia was the highest among women without occupational status who reported being housewives. Therefore, it is likely that if homemaking were included in the LASA data, the missing data salvaged for CR might have increased the observed number of events and the incidence rate for dementia in the sample.

High CR Sample

Another reason for the inconclusive results of Hypothesis Three could be the distribution of CR in the sample. Based on the CR index, the midpoint of the scale (CR = 6.9) described a prototypical individual with 10-11 years of education, occupational class between non-specialized and service or care, and engagement in activities for well-being or productive

activities a few times per month. Critically, only 242 participants (30%) had scores below the midpoint of the scale. Therefore, the sample was skewed to the left, suggesting that participants with high CR may have been overrepresented.

In fact, the median level of CR was 8.91, which described a prototypical individual who had 11-12 years of education, an occupational class in services and care, and who engaged in activities for well-being or productive activities a few times per month to every week. Although the definition of education varies substantially across the literature (Opdebeeck et al., 2016), the Leipzig Longitudinal Study of the aged (LEILA75+), a previous study with an age-cohort like that sampled by LASA found that education greater than 10 years was associated with a reduced risk for dementia (Then et al., 2016). Furthermore, like the service and care occupational class, the meta-analysis by Valenzuela and Sachdev (2006) found that occupational classes related to professional or skilled employment were associated with a reduced risk for dementia compared to unskilled employment. Finally, the effect of social participation on reducing the risk for dementia has been observed for individuals who are highly or moderately engaged in social activities (Valenzuela & Sachdev, 2006; Verghese et al., 2003). Therefore, regardless of whether missing data due to occupational class had interfered with model convergence, the predictions by derived from Hypothesis Three (and Hypothesis One) may have failed to reject the null due to the skew in the distribution towards high CR.

CR Construct Validity

Until a direct measure of the CR is developed, the CR will remain an unobserved latent construct which may influence the relationship between neuropathology and cognition in older adulthood (Stern et al., 2020). Although the theory of CR proposes a latent variable model, a critical issue is that the CR construct is not consistently tested. According to a recent review by

Howard et al. (2023), 53 proxies have been used to represent the reserve since 1990. In stark contrast to evidence of convergent validity, Howard et al. (2023) found that the correlation between 28 of the most used CR proxies was weak in most cases, and negligible in a few. Therefore, there is reason to doubt whether proxies used to represent the CR are valid indicators of the construct. Further aggravating issues around CR construct validity, most studies of CR have only operationalized the CR using one proxy (Howard et al., 2023; Opdebeeck et al., 2016). Since the CR theory implies that a range of life experiences contribute to developing resilience, operationalizing the CR with only one proxy is not construct valid.

Moreover, using single proxies to operationalize the CR likely conflates the proposed moderating effect of CR with alternative paths that may also influence the relationship between neuropathology and cognitive decline. For instance, although education, the most commonly used single proxy of the CR, could influence the relationship between neuropathology and cognitive decline due to its reserve building properties, the effect of education on the relationship between neuropathology and cognitive decline could instead reflect the cohort-related increases in average education and education-related opportunities observed over the last 100 years, rather than the reserve building effect of education (Jones et al., 2011; Schaie et al., 2005).

Similarly, the effect of education on cognitive decline could also be explained by its relationship with pre-educational cognitive abilities: since previous research has observed a relationship between childhood IQ and risk for cognitive decline (Whalley et al., 2000), the effect of educational attainment on cognitive decline could also reflect individual differences in pre-educational cognition rather than CR. In this way, single proxy measures of the CR lose explanatory power due to the alternative paths by which proxies affect the relationship between neuropathology and cognitive decline.

According to Howard et al. (2023), operationalizations of the CR that include multiple indicators demonstrate the strongest associations with late-life cognition, and, therefore, are recommended instead of single proxy indicators. Per this recommendation, a major strength of the current research is that the CR was composed of multiple indicators. Although there is also speculation regarding the validity of questionnaires[5], the CR score used in this study paralleled a popular CR questionnaire, the Lifetime of Experiences Questionnaire, which operationalizes CR by equally weighted education, longest held occupational class and social participation.

Although these indicators were grouped because they correlate with each other, grouping indicators to represent the CR *a priori* may present another major methodological limitation to the current research. Specifically, the construct validity of the CR measure used in this study would ideally have been tested prior to using it in the survival analysis. According to Salthouse et al. (2003), there are four steps to testing construct validity: in model A, convergent validity is assessed by examining the shared variance across proxies of the CR (Salthouse et al., 2003). If a significant amount of variance is shared, model B tests discriminant validity by assessing the strength and significance of correlations between the CR construct and a theoretically un-related construct (i.e., personality; Salthouse et al., 2003). In model C, a more stringent test of discriminant validity is tested where the correlations between each indicator variable of the CR construct and the un-related construct are examined one at a time (Salthouse et al., 2003). Finally, model D extends the discriminant validity of model C by testing the correlations

[5] Due to their face validity, questionnaires, such as the Lifetime of Experiences Questionnaire, have gained popularity in the CR literature; however, the measurement properties of these questionnaires have also been called into question. According to a review by Kartschmit et al. (2019), assessment of measurement properties such as structural validity, internal consistency, reliability, measurement error, content and construct validity of the most common CR questionnaires has yet to be reported in the literature. Therefore, until measurement properties are properly tested, the results using these scales should also be interpreted with caution.

between each indicator variable of the CR construct and the un-related construct, simultaneously (Salthouse et al., 2003).

In the context of the CR, the results from each model could contribute to understanding whether the CR is a distinct and coherent construct. Previous research that has evaluated the construct validity of the CR has unearthed a problematic observation: although the indicators used to represent the CR generally demonstrate good convergent validity, the CR construct is indistinguishable from executive functioning constructs (Siedlecki et al., 2009). Furthermore, although the CR theory proposed by Stern et al. (2020) suggests two sources of reserve (i.e., brain reserve and cognitive reserve), the discriminant validity which separate these constructs has yet to be tested. Further, the definitional breadth of enriching life experiences is not clear or consistent (Howard et al., 2023), creating confusion as to which life experiences contribute to building CR. Given the lack of consistency and construct validity across the literature with respect to proxies of the CR, effort must be made to generate a reliable and robust model of CR.

Critical to generating a reliable CR construct is careful consideration of whether indicators are formative to or reflective of CR. Accordingly, Stern et al. (2020) proposes that life experiences *form* the CR (Stern et al., 2020). Therefore, the indicators used to measure the CR should be treated as formative. However, clarifying the theoretical, causal relationship between the latent factor, CR, and its indicators is critical to choosing a formative model. Importantly, a valid model of the CR must unravel the antecedent experiences that build CR and the consequence of CR on subsequent cognitive abilities.

Due to the stage of life at which CR proxies were measured (i.e., older adulthood), the indicators in the current study were more likely consequences of the CR rather than its antecedents. For instance, in the current study, social participation was operationalized by

participants' currently reported engagement in productive activities or activities for well-being. In older adulthood, lower, or declining, levels of social engagement could reflect a prodromal symptom of dementia, thereby implying that higher social engagement in older adulthood is a consequence of higher cognitive abilities (Saczynski et al., 2006). Furthermore, as previously mentioned, since educational attainment could also be considered a consequence of higher pre-educational cognitive abilities (Whalley et al., 2000), education could be a reflective indicator, although it might not make theoretical sense that CR causes educational attainment.

Finally, previous research has suggested that occupational attainment could be a consequence of cognitive abilities, although it has also been observed to contribute to subsequent CR (Kleineidam et al., 2022). In a sample with eight measured proxies of the CR, Ikanga et al. (2017) found that the following indicators suited a reflective model of CR better than a formative model of CR: education, occupation and intellectual functioning. Likewise, in Huang (2013), IQ measured in adolescence was related to occupational class in adulthood such that three IQ distributions (left-skewed, normal and right-skewed) were associated with high, middle and low occupational class, respectively.

The results from the studies reviewed above highlight the importance of longitudinal data to unravelling the cascading effect of life-experiences on building reserve. Given that cognition is situated in the environments which confer enriching life experiences, identifying the causal relationship is especially challenging when proxies are measured in older adulthood. Whether proxies are formative or reflective likely depends on the stage of life at which they are measured, a construct including both formative *and* reflective aspects may be more valid for operationalizing the CR.

For instance, Ikanga et al. (2017) tested a model of CR composed of both formative and reflective indicators. Their factor structure revealed that parental SES, health literacy, lifetime leisure activities, physical activity and spiritual and religious behaviours loaded onto a CR factor which in turn, caused the levels observed in intellectual functioning, education and occupation. Although the formative indicators likely reflect experiences accumulated over the lifespan, given that the data from Ikanga et al. (2017) was collected in a sample of older adults, the causal relationship between life experiences and subsequent changes in cognitive function or ability remains entangled.

A lifespan approach may be essential to clarifying which proxies form or reflect the CR. Recently, Conte et al. (2023) used a principal component analysis (PCA) to form the CR using the indicators that were theorized to reflect experiences that promoted cognitive flexibility and adaptability. Importantly, the following indicators were measured in adolescence: sport practice, musical experiences, cultural activities and relationships with peers and family. A 12-component solution summarized most of the variance in the life experiences collected by the researchers' questionnaire (Conte et al., 2023). Interestingly, the researchers followed up their PCA with a confirmatory factor analysis in a sample of young adults to test how the components generated in the PCA related to theorized reflective proxies of the CR: intelligence, education, occupation and executive functioning. The factor structure from the first study fit the data of the second study well and, although the model fit worsened, a second-order CR factor explained the common variance across the 12 first order factors and the reflective proxies of the CR were significantly associated with the second-order CR factor (Conte et al., 2023). The results from Conte et al. (2023) are like those of Ikanga et al. (2017) in implying that a coherent model of CR is likely composed of both formative and reflective indicators. Importantly, the results by Conte et al.

(2023) support the argument for measuring formative CR indicators in early life rather than in older adulthood.

In line with the Life Course Health Development framework (LCHD; Halfon & Forrest, 2018), the processes that contribute to resilience against cognitive impairment despite neuropathology likely unfold over the lifespan, are subject to complex reciprocal interactions, and are sensitive to the timing of environmental exposures or experiences. Therefore, it may be useful to identify CR indicators in the formative years of childhood and adolescence since CR measured in older adults via the typical indicators is more likely reflective of CR than formative.

Rather than representing a fixed level of CR which translates into observable effects on cognition in late life, it is more likely that the CR formed in early life is plastic and amenable to change over the lifespan. In this way, indicators measured in early life may represent a potential CR (p-CR) that sets the stage for complex reciprocal interactions between subsequent life experiences, which are a consequence of p-CR, and which simultaneously contribute to the maintenance of p-CR over the lifespan. Conte et al. (2023) offer a similar theoretical proposal.

The cumulative effect of the p-CR is observable in crystallized cognitive abilities. As previously observed, measures of crystallized abilities, such as the Peabody Picture Vocabulary test and the Wide Range Achievement Test, are thought to represent the consequence of enriching life experiences and demonstrate good convergent validity when tested as a construct of CR (Siedlecki et al., 2009). Interestingly, the Siedlecki et al. (2009) results suggest that the discriminant validity between the CR construct and executive functioning construct is weak. Therefore, it may be reasonable to collect early life experiences in a p-CR construct which then travels with the individual throughout life and, in older adulthood, translates to an observed CR

(o-CR), reflected in crystallized cognitive abilities, which serve to delay the manifestation of cognitive impairment in spite of neuropathology.

Among those who build a high p-CR and maintain it throughout their lifespan, a high o-CR is observed in older adulthood and predicts delayed cognitive impairment in spite of neuropathology. On the other hand, for those who may have built a high p-CR but who experience adverse events across their lifespan, their o-CR in older adulthood might be lower than expected and consequently, the effect of the p-CR on delaying cognitive impairment might be compromised.

Critically, a model that considers how experiences measured in early life build a p-CR that is amenable to change over the lifespan and affects the o-CR in older adulthood overcomes major limitations of the current CR theory by: disentangling the causal relationship between indicators and the CR; building a model that is both formative and reflective; and, most importantly, allowing for individual differences in the effect of formative life experiences on o-CR in older adulthood.

This last point is an important consideration in explaining the effect of formative life experiences on cognitive resilience in older adults with neurodevelopmental disorders because it considers the principle of thriving proposed by the LCHD framework (Halfon & Forrest, 2018). For instance, despite negligible group differences in educational attainment, adults with childhood ADHD demonstrated significantly lower reading and arithmetic achievement than neurotypical adults in a prospective study by Voigt et al. (2017). This observation was partly explained by the higher rates of learning disabilities in the sample with ADHD (Voigt et al., 2017). Therefore, due to the cognitive, behavioural or emotional difficulties, life experiences that are typically thought of as enriching may not confer the same neural enrichments for

neurodiverse individuals. The distinction between p-CR and o-CR allows for the possibility that favourable matches between individual abilities and environmental settings build a higher p-CR which translates into to higher o-CR whereas unfavourable matches, which still build a higher p-CR, result in a lower o-CR due to the adverse effect of the experiences in the environmental settings on o-CR over the lifespan.

Future Directions

The ability to model group differences based on CR was constrained due to substantial missing data. Furthermore, the model was limited by the skew in the distribution of CR observed in this sample. Although the sample was divided into low and high CR based on the sample median, more than 50% of the sample had levels of education, occupation and social participation consistent with higher CR (Then et al., 2016; Valenzuela & Sachdev, 2006; Verghese et al., 2003). The over representation of high CR may be related to selection bias previously described (Enzenbach et al., 2019; Zajacova & Burgard, 2013).

Future research should consider using longitudinal cohort designs to overcome the bias introduced by sampling in older adulthood. If data collection begins in childhood or adolescence, the survival bias typically observed in ageing research could be incorporated into the model and therefore, the observed CR may be less biased towards individuals with higher CR. Critically, the missing data associated with occupational class may have contributed to the left skew observed for CR in this sample. Since the source of this missing data was likely attributable to being a homemaker, future research should consider including and examining the characteristics of homemakers when collecting data on occupational class. Not only would the inclusion of this category reduce the bias towards individuals with higher CR, but it could elaborate on the types

of enriching exposures related to homemaking which are not currently addressed by literature on cognitive ageing.

Importantly, the construct validity of the CR must be tested instead of grouping variables *a priori*. As previously explained, the construct validity of the CR could be tested using the four-model solution offered by Salthouse (2003). To guide the selection of CR indicators, future research should take a Life Course Health Development perspective to studying the construct validity of the CR. Since the life experiences that form CR likely begin in early childhood, future research could consider beginning the investigation of CR in early life. Furthermore, since the CR is likely both a formative and reflective construct, observing how the construct may develop in early childhood and unfold over the lifespan would likely improve the construct validity of the CR, overcoming conflations of causal relationships between life experiences and CR.

Critically, as previous research has suggested, the reflective indicators of the CR in older adulthood are likely indistinguishable from crystallized cognitive abilities which afford resilience against cognitive impairment in spite of accumulating neuropathology. Therefore, considering the complex reciprocal interactions between life experiences that form the CR and in turn, affect observed cognition may lead theory towards the idea of a potential CR (p-CR). Given that cognition unfolds over the lifespan, a revised theory of the CR might test the hypothesis that p-CR travels with the individual across the lifespan, is formed by enriching experiences and is reflected in cognitive abilities.

In older adulthood, this revised theory might permit testing the hypothesis that the accumulated reserve is finally expressed as an observed CR (o-CR) in the individual's crystallized cognitive abilities which protect them against cognitive impairment despite neuropathology. To this point, future research must also consider collecting a measure of

neuropathology to test the moderating role of CR on the relationship between neuropathology and cognitive decline. Finally, due to measurement inconsistencies observed across scales used to evaluate the life experiences which form the CR, future research might consider using time as a unifying metric. Since the proposed effect of life experiences on reserve is the exposure to enrichments afforded by experiences, using time to quantify the length of exposure may offer consistency across different types of exposures.

Despite the limitations of the current research, there are strengths worth mentioning. This research attempted to address and elaborate on a critical issue in the current aging population: older adults with neurodevelopmental disorders may be at higher risk for dementia than neurotypical adults (Siguier et al., 2024). Given the contention around the diagnostic criteria for ADHD in older adults, this research considered a more relaxed definition of ADHD to capture those who may have previously met criteria but, due to the developmental course of ADHD, no longer met the symptom threshold for the diagnosis. The reconceptualization of ADHD in the current study, from diagnosis to symptoms, is a strength as it reflects a continuum-based taxonomic system which is gaining favour in the field of psychopathology (Kotov et al., 2022).

To that end, the operationalization of dementia in this study (i.e., persistent cognitive decline, see van den Kommer et al., 2018) likely included individuals below the threshold for a dementia diagnosis. Including participants with changing cognitive performance 2 SD below the sample's mean cognitive change also supports a continuum-based approach to dementia and, given the implications of the CR with respect to delaying the onset on dementia, operationalizing dementia in this way likely identified the manifestation of cognitive decline in participants with higher CR. According to Hall et al. (2007), although participants with higher educational attainment demonstrated a slower decline in the years prior to dementia diagnosis, they were

more likely to present an accelerated cognitive decline in the years following diagnosis than participants with lower educational attainment. Given the interval between repeated assessments (i.e., 3 years on average), this operationalization of dementia may have allowed the current research to identify participants with higher CR who were likely to meet diagnostic criteria in the interval between assessments.

Finally, the longitudinal, cross-sequential design of LASA was a strength of the current research. In comparison to purely longitudinal designs, longitudinal cross-sequential designs permit partial inroads to the statistical disentanglement of age-related change from cohort related idiosyncrasies (Schaie & Hertzog, 1982, though also see Donaldson & Horn, 1992). Separating these effects is essential to considering the influences of age and socio-historical context on the risk for dementia in older adults. Especially given the developmental course of ADHD and its diagnostic history, the longitudinal cross-sequential design was essential to describing the presentation of ADHD symptoms with respect to age and the socio-historical attitudes towards the disorder.

Conclusions

This research sought to investigate the CR theory of aging in the context of neurodevelopmental disorders. In a sample of older adults with ADHD symptoms, the current study explored whether adults with ADHD-sx had fewer enriching life experiences in the domains of education, occupation and social participation than adults without ADHD. The results addressing the first objective did not reveal significant differences between the groups on their CR. The null result based on the test of hypothesis one could have been attributable to the operational definition of ADHD; however, the null result was more likely attributable to selection biases which select healthier, wealthier and more educated participants in ageing research.

The second objective of this research was to replicate previous observations that adults with ADHD are at higher risk for dementia than their neurotypical peers. Unfortunately, due to substantial missing data, the model constructed for survival analysis could not reliably estimate hazard. Critically, the validity of the analysis was brought into question due to the role of informative censoring. Missing data were significantly related to death, as well as poorer physical and mental health. Given the relevance of these factors to dementia, the data were not missing at random and therefore, the validity of the analysis was compromised.

The final objective of this research was to investigate whether the risk for dementia associated with ADHD status was modified by CR. Due to the limitations associated with the results from Hypothesis One and Two, the model constructed to test Hypothesis Three failed to converge. Failure of the model to converge was attributable to the missing data problem which was amplified in Hypothesis Three due to missing data associated with occupational class. In

summary, the null hypothesis related to each objective was not rejected, at least in part due to issues related to group construction, group differences and power.

Future research exploring the role of the CR theory of aging in the context of ADHD should first consider collecting data from population health registries so that issues related to diagnostic misclassification and retrospective symptom assessment can be overcome. Sample selection from population health registries may also reduce issues related to selection bias and missing data. Future iterations of this research should also consider using statistical models that are robust to missing data and that can account for the semi-competing risk of death. For instance, multi-state models are well suited for modelling the semi-competing risk of death in the context of dementia research. Moreover, in comparison to the proportion of the ageing population meeting the diagnostic threshold for dementia, a larger proportion experiences symptoms of cognitive decline below the diagnostic threshold for dementia (Low et al., 2004). Therefore, better suited for examining change in a continuous outcome over time and in between groups, longitudinal multilevel models should be considered for testing future iterations of the hypotheses in the current research.

Reconceptualizing the outcome of the current research as a continuous rather than a binary variable aligns with the paradigm shift in Psychology represented by taxonomies such as the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2022). Critically, the reconceptualization from category to continuum may be more construct valid when describing and explaining human behaviour and cognition. Importantly, this reconceptualization increases the variability in the dependent variable, which is essential to testing models such as transition models or multilevel models.

Finally, future research should carefully consider the validity of the CR construct. As previously described, proxies thought to form the CR should be rigorously tested using multivariate methods. Moreover, disentangling formative from reflective indicators of the CR is an important task for future research informed by the CR theory of ageing. The Life Course Health Development (LCHD) framework (Halfon & Forrest, 2018) should inform future research testing the construct validity of the CR. As suggested by LCHD, a coherent theory of the CR should consider the unfolding nature of CR and disentangle the complex reciprocal interactions between formative proxies and reflective indicators by taking a longitudinal approach to its measurement. A unifying theory of CR should reflect the plasticity of development and the timing of environmental exposures theorized to form CR. Ultimately, a CR theory of aging which also includes the principle of thriving will be best suited to appropriately investigate the effect of enriching life experiences on resilience against cognitive decline, in spite of neuropathology, among older adults with a neurodevelopmental disorder.

Despite the theoretical and methodological challenges that arise with the CR construct, literature is consistent in its observation that life experiences in education, occupation and social participation contribute to a reduced risk for dementia, or slower cognitive decline, in older adults (Opdebeeck et al., 2016). Therefore, designing interventions to enhance life experiences for individuals with ADHD symptoms is still warranted.

Critically, interventions designed to target young children at risk for developing ADHD may be the most effective at reducing the sequalae related the development of the disorder (Halperin et al., 2012). Interestingly, considered as a proxy of CR, Hoza et al. (2015) demonstrated the effect of aerobic physical activity on reducing ADHD symptoms in young children in the context of school and at home. Confirming the signal detected by Hoza et al.

(2015), Xie et al. (2021) published a meta-analysis reviewing the effectiveness of physical activity interventions for children and adolescents with ADHD. The authors reported that physical activity demonstrated a consistent and significant reduction in symptoms, especially in young children (Xie et al., 2021). Therefore, physical activity in early childhood may be an effective intervention strategy for altering the developmental course of ADHD, thereby reducing the functional impairment that follows symptoms.

The context of peer-relationships may be another important target for intervention in individuals with ADHD. Given the increasing importance of friendships from childhood into adolescence (Youniss & Haynie, 1992) and the relevance of social functioning in predicting occupational outcomes for individuals with ADHD (Ramos-Olazagasti et al., 2018), the period of adolescence may be an optimal time for implementing interventions to improve social functioning in ADHD. For instance, Hoza et al. (2003) demonstrated that a friendship intervention delivered through a coached buddy system at a summer camp improved friendship quality and teacher-reported symptoms in children between 5-12 with ADHD. Further, the Program for the Education and Enrichment of Relational Skills (PEERS; Laugeson & Frankel, 2010), an evidence-based social skills training program, has demonstrated effectiveness in improving social functioning for adolescents with ADHD (Cordier et al., 2023; Geannopoulos et al., 2024). Therefore, interventions such as these show promise for increasing exposure to the reserve building experiences found in social settings for individuals with ADHD.

In the context of adulthood, in addition to the interventions previously mentioned, some research suggests that workplace support, in the form of accommodations or group therapy, can contribute to improving impairment related to symptoms (Lauder et al., 2022). However, most of the research on interventions for adults focuses on pharmaceuticals, which are effective at

reducing the impairment related to symptoms and improving workplace, social and educational outcomes (Cherkasova et al., 2022; Harpin et al., 2013). Therefore, it would be remiss to overlook the importance of pharmaceutical interventions in improving exposure to enriching life experiences. Finally, it may be that the context in which research examines functional outcomes for adults with ADHD overlooks the person-environment match that may manifest for adults with ADHD (Turgay et al., 2012). Future research should consider the possibility that non-traditional life experiences may be contexts in which adults with ADHD thrive.

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Table 1

Group Associations with Dementia, Death, Lost at Follow-Up or Right Censorship

Status	Test	value	*p*-value	no-ADHD (n = 839)	ADHD-sx (n = 147)
Dementia, *n*(%)	Fisher's exact test		.79	25 (2.98%)	5 (3.40%)
Deceased by wave I, *n*(%)	χ^2	2.89	.09	148 (17.64%)	17 (11.56%)
Lost to follow-up, *n*(%)	χ^2	<.001	.99	56 (6.67%)	9 (6.12%)
Right censored, *n*(%)	Fisher's exact test		.80	610 (72.71%)	116 (78.91%)

Note. ADHD-sx = participants who report with one or more ADHD symptoms currently, and who report a childhood onset of their symptom(s); no-ADHD = participants without ADHD symptoms; Fisher's exact test was used instead of Chi-squared when number of observations in any cell was less than 6.

* $p < .05$; ** $p < .01$; *** $p < .001$

Table 2

Demographic Characteristics of the ADHD-sx and no-ADHD groups

Characteristic	Whole sample (*n* = 986)	ADHD-sx (*n* = 147)	no-ADHD (*n* = 839)	*p*-value
Age at wave G, mean (SD)	69.95 (6.60)	69.30 (6.11)	70.07 (6.68)	.17
Sex, % female	53.14%	59.86%	51.97%	.09
Nationality, Dutch	99.49%	99.32%	99.52%	-
Educational attainment, median (IQR)	4 (3)	4 (2.5)	4 (3)	.97
Occupational attainment, median (IQR)	3 (1)	3 (1)	3 (1)	.94
Social participation (total score), mean (SD)	5.13 (2.62)	5.23 (2.69)	5.11 (2.61)	.63
Medications				
% taking medications	56.59%	65.31%	55.07%	.02*
Number of medications, median (IQR)	2 (3)	2 (3)	2 (3)	.88
Chronic Health Conditions				
% with at least one CHC	85.60%	87.76%	85.22%	.50
Number of CHC, median (IQR)	2 (2)	2 (2)	2 (2)	< .001***
Depression, mean (SD)				
Score >=16, count	146	33	113	.009**
Symptom sum, mean (SD)	12.81 (3.38)	13.58 (3.78)	12.67 (3.28)	.008**
Anxiety				
Score >= 8, count	41	13	28	.004**
Symptom sum, mean (SD)	3.80 (1.77)	4.32 (2.03)	3.71 (1.7)	< .001***
ACEs, % with at least one	13.49%	14.97%	13.23%	.09
Loneliness, median (IQR)	12 (3)	12 (3)	12 (3)	.002**
Income, median (IQR)	2 (2)	2 (2)	2 (2)	.49
SES, mean (SD)	5.40 (1.64)	5.48 (1.52)	5.41 (1.66)	.65
CR, mean (SD)	8.73 (2.42)	8.77 (2.43)	8.73 (2.41)	.87

Note. ADHD-sx = participants who report with one or more ADHD symptoms currently, and who report a childhood onset of their symptom(s); no-ADHD = participants without ADHD symptoms; CHC = chronic health conditions; ACEs = Adverse childhood experiences; SES =

socio-economic status index score; CR = cognitive reserve index score; In the case where variances were not equal between groups and distributions were non-normal, Mann-Whitney U tests were used to evaluate group differences and median (IQR) were reported.

* $p < .05$; ** $p < .01$; *** $p < .001$

Table 3

Estimated Hazard Ratios from Cox-Proportional Hazard Analysis

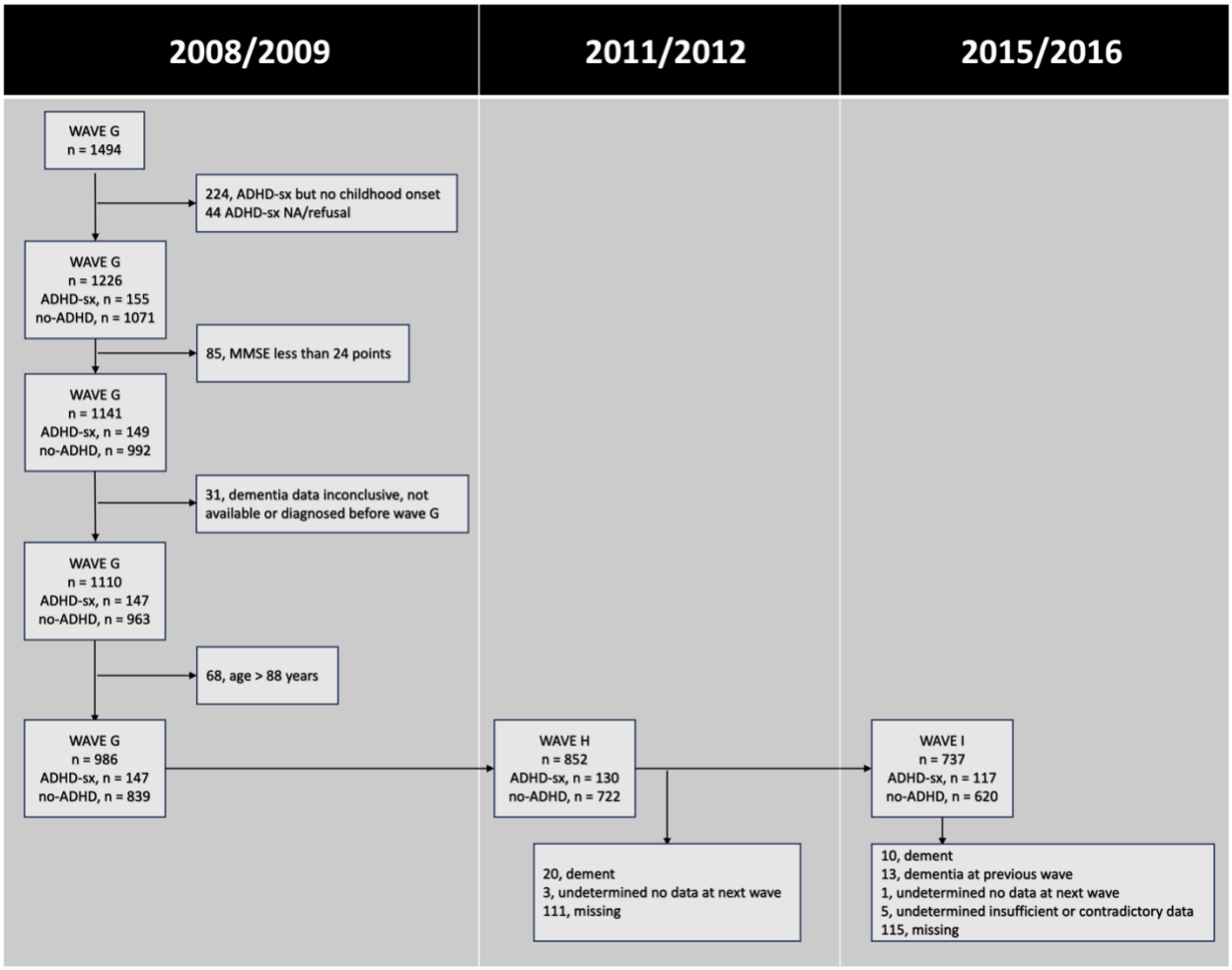
Terms	HR	95% CI	L^2	*df*	*p*-value
Model 1			8.51	2	.01
Sex	2.94*	(1.08, 8.00)			
Age	.18	(.03, 1.10)			
Model 2			8.71	3	.03
Sex	2.91*	(1.07, 7.92)			
Age	.19	(.03, 1.13)			
ADHD-sx	1.29	(.43, 3.88)			
Model 3			13.65	5	.02
Sex	4.65*	(1.24, 17.39)			
Age	2.22	(.02, 2.53)			
CR	1.14	(.35, 3.76)			
ADHD-sx	4.12	(.94, 18.07)			
CR*ADHD-sx	<.001	(0, Inf)			
Model comparisons					
Model 2 vs. Model 1			.20	1	.65
Model 1 vs. Model 3			5.14	3	.16
Model 2 vs. Model 3			4.94	2	.08

Note. L^2= the Likelihood ratio test statistic; ADHD-sx = participants who report one or more ADHD symptoms currently, along with a childhood onset of their symptom(s);The estimates reported are exponentiated log hazard ratios (i.e., hazard ratios); Sex is relative to males; Age is divided into two groups based on the median, 61-69 = 0, 70-88 = 1; ADHD-sx is relative to participants without ADHD; CR is relative to low CR (i.e., CR <= 8.91); Based on $\chi^2(3) = 5.14$, $p = .16$, Model 1 fits the data better than Model 3.

* $p < .05$; ** $p < .01$; *** $p < .001$

Figure 1

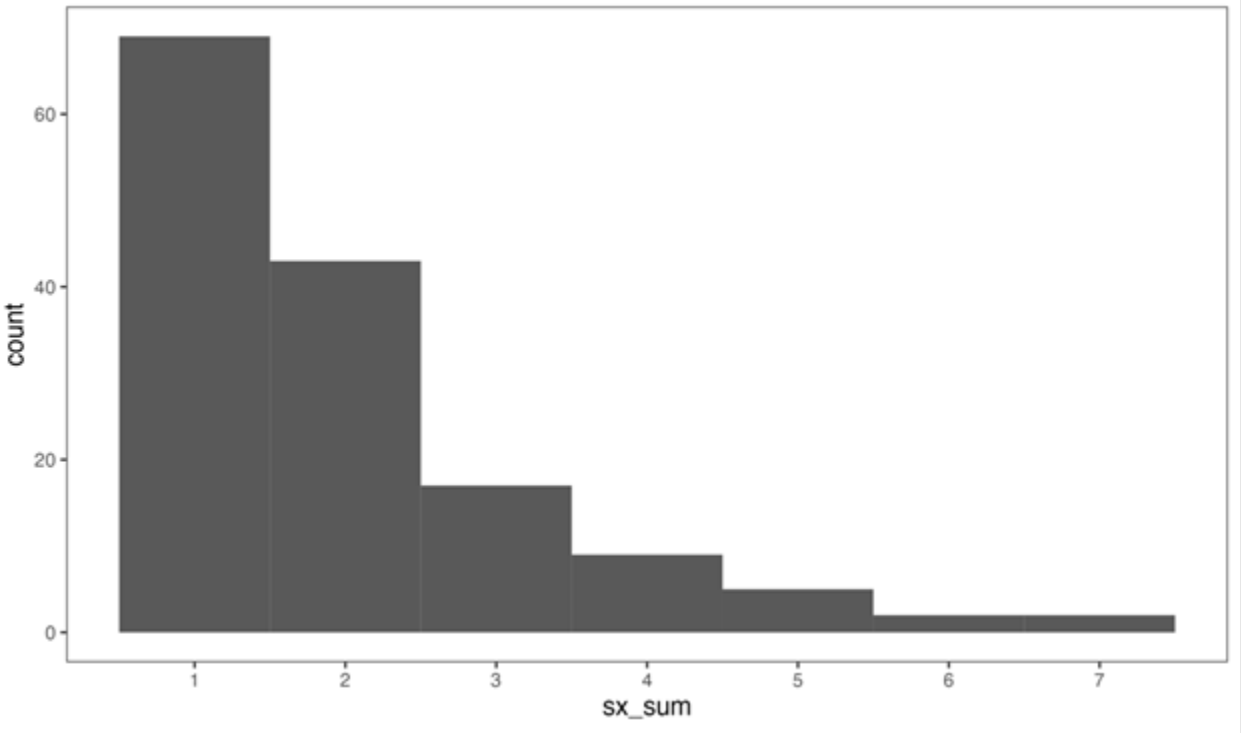
Participant Selection Process at Wave G and Design Across Wave G, H, and I



Note. Wave G was measured in 2008/2009, wave H was measured in 2011/2012, and wave I was measured in 2015/2016.

Figure 2

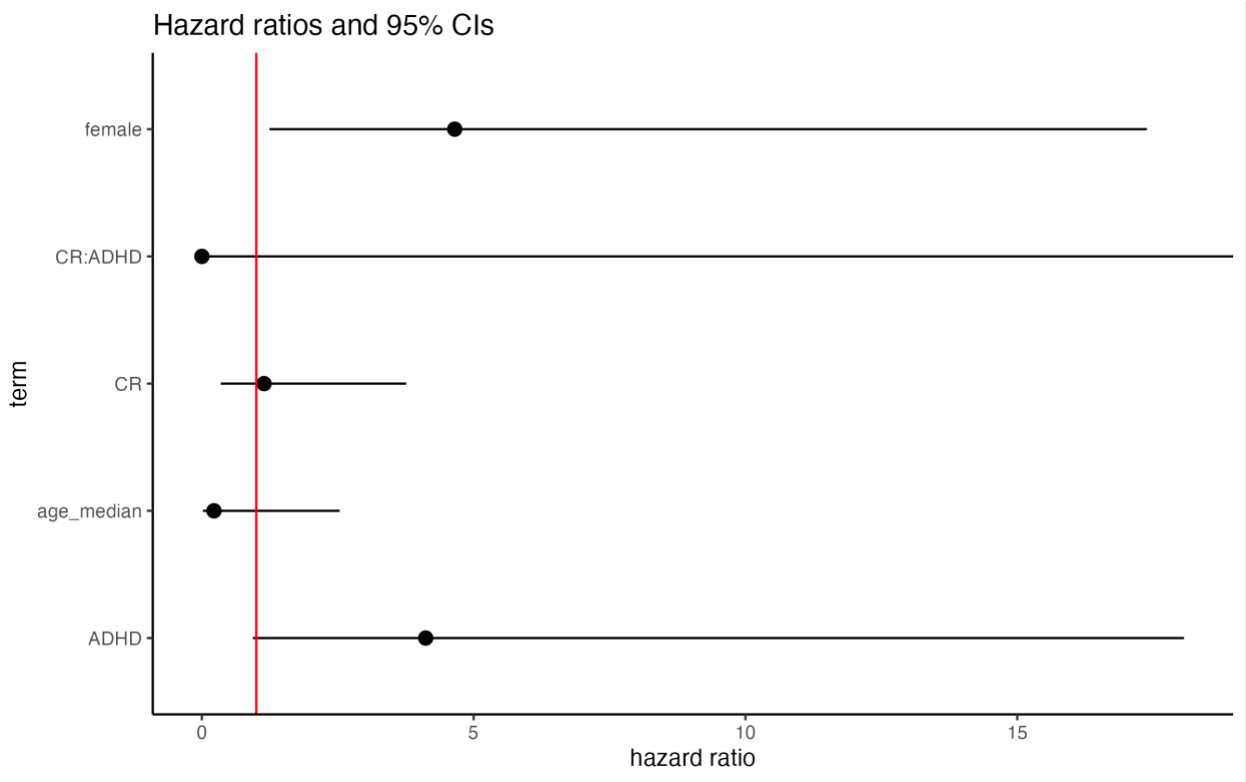
Frequency of ADHD Symptoms Reported by Participants with ADHD-sx (n = 147)



Note. 147 participants had evidence of childhood ADHD symptoms and reported one or more symptoms at the time of assessment in 2008/2009 (wave G). Sixty-nine participants reported one symptom. Seventy-eight participants reported two or more symptoms.

Figure 3

Hazard Ratios and 95% CIs for Estimates in Model 3



Note. Forest plot for hazard ratio estimates of each term in Model 3. The red vertical bar represents a HR = 1; Female = sex is relative to males; Age is divided into two groups based on the median, 61-69 = 0, 70-88 = 1; ADHD = ADHD-sx group hazard estimate relative to participants without ADHD symptoms. CR = cognitive reserve, hazard estimate for high CR relative to low CR (i.e., CR <= 8.91). CR:ADHD represents the hazard estimate for the interaction between ADHD-sx and high CR.

Supplementary Table 1

Dementia Statuses from Wave G to Wave I Between Groups

Wave	No dementia (0)	Dementia at current wave (1)	Dementia at previous wave (2)	Undetermined, no data at the next wave (3)	Undetermined, insufficient data or contradictory data (5)
G (2008/2009)	986				
ADHD-sx	147				
no-ADHD	839				
H (2011/2012)	852	20 (2.35%)		3 (.35%)	
ADHD-sx, %	130	2 (1.54%)		0	
no-ADHD	722	18 (2.49%)		3 (.42%)	
I (2015/2016)	737	10 (1.36%)	13 (1.76%)	1 (.14%)	5 (.68%)
ADHD-sx	117	3 (2.56%)	2 (1.71%)	0	2 (1.71%)
no-ADHD	620	7 (1.13%)	11 (1.77%)	1 (.16%)	3 (.50%)

Note. Dementia statuses were formed using the algorithm by van den Kommer et al. (2018). Category 4 (i.e., undetermined, no persistent change but MMSE <=18) is missing since all participants with MMSE scores less than 24 were removed from the analysis. ADHD-sx = participants who report one or more ADHD symptoms currently, along with a childhood onset of their symptom(s).

Supplementary Table 2

Demographic Characteristics of ADHD-2+ sx and no-ADHD

Characteristic	Whole sample (n = 917)	ADHD-2+ (n = 78)	no-ADHD (n = 839)	*p*-value
Age at wave G, mean (SD)	69.99 (6.63)	69.13 (6.03)	70.07 (6.68)	.20
Sex, female	53.00%	64.10%	51.97%	.05
Nationality, Dutch	99.45%	98.72%	99.52%	-
Educational attainment, median (IQR)	4 (3)	4 (2)	4 (3)	.63
Occupational attainment, median (IQR)	3 (1)	3 (1)	3 (1)	.92
Social participation (total score), mean (SD)	5.10 (2.62)	4.92 (2.69)	5.11 (2.61)	.55
Medications				
% taking at least one medication	76.99%	85.90%	76.16%	.07
# medications, median (IQR)	2 (4)	3 (4)	2 (3)	.05
Chronic Health Conditions				
% with at least one CHC	85.39%	87.18%	85.22%	.76
# CHC, median (IQR)	2 (2)	2 (2)	2 (2)	< .001**
Depression, mean (SD)				
Score >=16, count	146	17	113	.08
Symptom sum, mean (SD)	12.78 (3.38)	13.97 (4.13)	12.67 (3.28)	.008*
Anxiety				
Score >= 8, count	41	10	28	<.001**
Symptom sum, mean (SD)	3.80 (1.76)	4.74 (2.08)	3.71 (1.7)	< .001*
ACEs, % with at least one	13.30%	14.10%	13.23%	.23
Loneliness, median (IQR)	12 (3)	13 (4)	12 (3)	< .001*
Income, median (IQR)	2 (2)	2 (2)	2 (2)	.56
SES, mean (SD)	5.15 (1.66)	5.10 (1.54)	5.15 (1.67)	.83
CR, mean (SD)	8.29 (2.45)	7.99 (2.49)	8.32 (2.44)	.32

Note. ADHD-2+ = participants who report two or more ADHD symptoms currently, along with report a childhood onset of their symptom(s); no-ADHD = participants without ADHD symptoms; CHC = chronic health conditions; ACEs = Adverse childhood experiences; SES = socio-economic status index score; CR = cognitive reserve index score; In the case where

variances were not equal between groups and distributions were non-normal, Mann-Whitney U tests were used to evaluate group differences and median (IQR) were reported.

* $p < .05$; ** $p < .01$; *** $p < .001$

Supplementary Table 3

Estimated Hazard Ratios from Cox-Proportional Hazard Analysis with Death as Outcome

Terms	HR	95% CI	L^2	*df*	*p*-value
Model 1			.13	1	.70
ADHD-sx	.94	(.66, 1.34)			
Model 2			54.23	3	<.001
Sex	.72**	(.57, .93)			
Age	.23***	(.14, .36)			
ADHD-sx	.90	(.63, 1.29)			
Model comparisons					
Model 2 vs. Model 1			54.10	2	<.001

Note. L^2= the Likelihood ratio test statistic; ADHD-sx = participants who report with one or more ADHD symptoms currently, and who report a childhood onset of their symptom(s);The estimates reported are exponentiated log hazard ratios (i.e., hazard ratios); Sex is relative to males; Age is divided into two groups based on the median, 61-69 = 0, 70-88 = 1; ADHD-sx is relative to participants without ADHD; Model two is a significantly better fit for the data then model one.

* $p < .05$; ** $p < .01$; *** $p < .001$

Supplementary Table 4

Missing Data Analysis of Cases Censored Due to Death or Lost at Follow-up

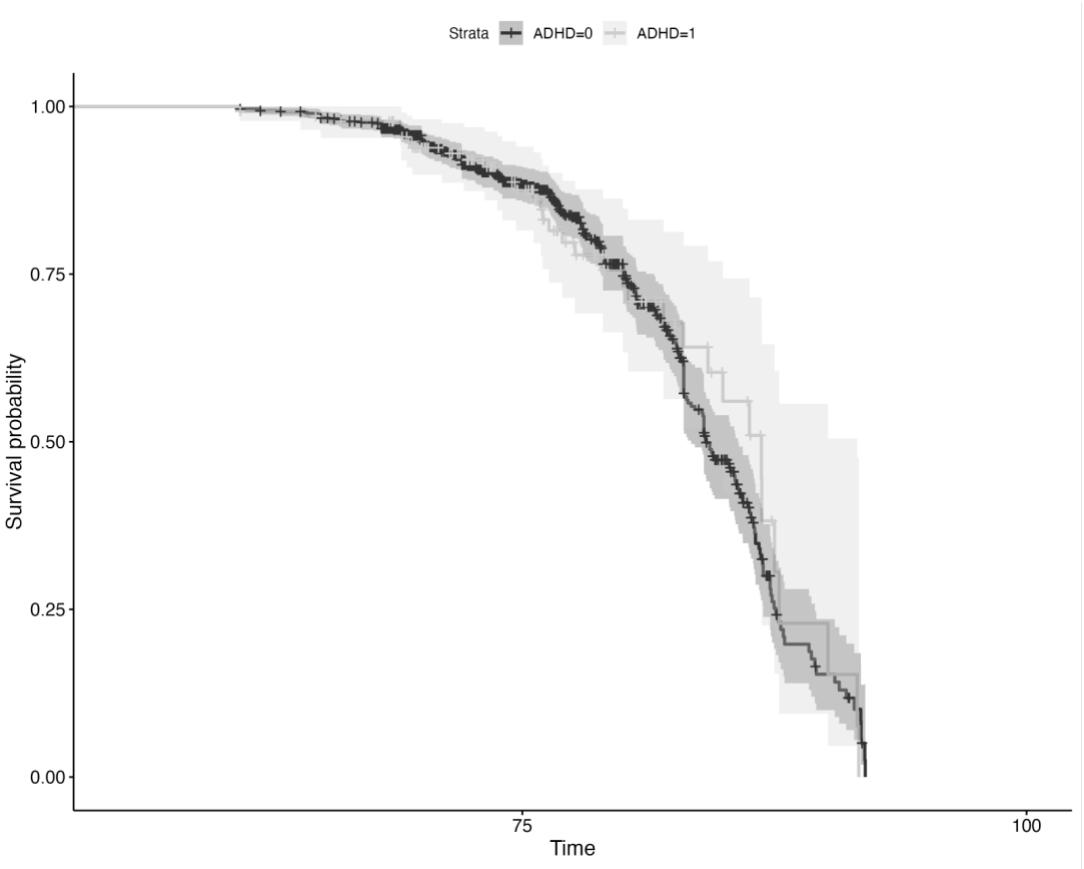
Explanatory variable	OR	95% CI	*p*-value
Death			
Age	1.15***	(.11, .16)	<.001
Loneliness	1.07**	(.03, .11)	.002
Education	.90***	(-.16, -.05)	<.001
Number of chronic health conditions	1.62***	(.36, .61)	<.001
Number of medications	1.23***	(.17, .28)	<.001
Social participation	.79***	(-.31, -.18)	<.001
MMSE	.82***	(-.30, -.09)	<.001
Lost at follow-up			
Age	.95*	(-.09, -.01)	.02
Social participation	.90*	(-.21, -.02)	.02

Note. MMSE = Mini-mental status exam; Each explanatory variable was measured at baseline assessment (i.e., wave G).

* $p < .05$; ** $p < .01$; *** $p < .001$

Supplementary Figure 1

Kaplan Meier Survival Curve Between ADHD-sx Groups with Death as Outcome



Note. Time is indexed as age at wave G. ADHD = 0, no-ADHD group; ADHD = 1, ADHD-sx group. Median survival time for no ADHD group was 84.1 years whereas the median survival time for ADHD-sx group was 86.6 years.

Appendix A

The cognitive reserve theory could explain part of the risk for dementia in neurodevelopmental disorders; however, evidence of the risk for dementia among neurodevelopmental disorders has only been explored for ASD and ID without Down's Syndrome. The relationship to dementia shared with other NDDs such as communication disorders, learning disorders and motor disorders has yet to be contributed to the literature.

In the case of ASD, criterion D of the DSM requires that impairment is apparent in social, occupational or other important areas of functioning (American Psychological Association, 2013). Indeed, previous research has found that outcomes in terms of occupation, relationships, independent living and mental health are poorer for adults with ASD than their same aged peers (Howlin et al., 2017). However, outcomes depend on a variety of factors such as intellectual ability, family environment and ASD severity (Howlin et al., 2017). For those whose disorder impairs functional outcomes across the lifespan, it is likely that their life experiences have built a lower cognitive reserve and therefore, could relate to a higher incidence of dementia. This hypothesis has yet to be explored in the literature.

In the case of ID without Down's Syndrome, criterion B of the DSM states that the intellectual disability must limit functioning in social participation and independence across multiple environments, such as home, work, school and community (American Psychological Association, 2013). Therefore, due to the impairments caused by ID, it is likely that life experiences build a lower cognitive reserve and therefore, could relate to a higher incidence of dementia. It is also possible that the relationship between ID and dementia can be explained by the brain reserve hypothesis since it has been observed that individuals with ID have lower gray and white matter volume than neurotypical controls (Ma et al., 2021). Less quantitative volume

in the brain is also hypothesized to afford less resilience to neuropathology (Stern, 2009). Therefore, the cognitive and brain reserve hypothesis could explain the association between the prevalence and incidence of dementia in ID. However, this hypothesis has yet to be tested.

Appendix B

Depression, ADHD and Dementia

In adults over 60, the relationship between depression and dementia is complicated by their common symptom presentations. For instance, according to the DSM-V, both disorders require a change in cognition from previous functioning, and dementia can be specified by behavioral disturbances such as mood disturbances, agitation or apathy, each of which are listed as symptoms of major depressive disorder (American Psychological Association, 2013). Due to overlaps in their definition and the significant risk for dementia in older adults with depression (Byers & Yaffe, 2012), it has been proposed that depression may be a prodromal phase of dementia in older adults (Enache et al., 2011). In young adults, studies reviewed by Byers and Yaffe (2012) reveal that early life depression related to a 2-4-fold increased risk of dementia in later life. The strength of the relationship depended on the duration of depressive episodes and their frequency through the lifespan, into older adulthood (Byers & Yaffe, 2012). Therefore, depression increases the risk for dementia.

Critically, adults with ADHD are more likely to experience depression than their neurotypical peers. According to an epidemiological study using a National Registry of over 5 million Swedish adults between 18 and 64 years, the prevalence of depression was nine times higher in the portion of the sample with a diagnosis of ADHD than in the rest of the sample (Chen et al., 2018). The higher prevalence of depression among those with ADHD remained significant when the analysis was restricted to adults between 50 and 64 years (Chen et al., 2018). Similar findings are reported in samples collected in the United States (Cherkasova et al., 2022; Di Lorenzo et al., 2021; Kessler et al., 2006) and Canada (Cherkasova et al., 2022; Di Lorenzo et al., 2021). Therefore, depression is a comorbid psychiatric disorder with ADHD in

young and old adults. Since young adults with ADHD have an elevated risk of experiencing depression during their lifespan, their risk for depression places them at a significantly higher risk for dementia. Therefore, in addition to evidence of lower CR, the relationship between ADHD and dementia may be explained by their shared risk with respect to depression.

Obesity, ADHD and Dementia

ADHD and obesity share a bidirectional relationship. In a systematic review by Cortese and Tessari (2017), 41 peer reviewed studies addressed the relationship between ADHD and obesity. According to the studies, obesity was significantly more prevalent among individuals with ADHD compared to controls. This relationship remained statistically significant after controlling for socio-economic status, depression and anxiety. In their meta-analysis, Cortese and Tessari (2017) found that the pooled risk ratio for obesity was 40% higher for children and 70% higher for adults with ADHD than for normal weight, age-matched controls. Interestingly, those who are medicated for ADHD shared the same risk for obesity as controls (Cortese & Tessari, 2017). This result emphasizes that treatment is important for mitigating obesity in ADHD.

Complementing the observed prevalence of obesity in ADHD populations, ADHD is also more prevalent in obese populations. According to Altfas (2002), 27% of patients had ADHD in a sample of adults (n = 215) undergoing treatment for their obesity. Alarmingly, 43% of the sample who was morbidly obese had a diagnosis of ADHD. Similarly, an epidemiological study of 34,653 American adults revealed that those with ADHD had significantly higher BMIs than adults without ADHD (Cortese et al., 2013). However, unlike the results of the meta-analysis by Cortese and Tesssari (2017), after controlling for socio-demographic factors and the co-occurrence of other DSM diagnoses (i.e., mood disorders, anxiety disorders and personality disorders), ADHD no longer shared a significant relationship with obesity (Cortese et al., 2013).

This result suggests the potential for a mediating mechanism to explain the relationship between ADHD and obesity. As such, ADHD may relate to obesity through comorbid disorders, such as conduct disorder, or through the lifestyle factors that are more common in ADHD such as abnormal eating patterns and sedentariness (Cortese & Tessari, 2017). There is also the possibility that ADHD and obesity share a relationship due to a common factor, which has yet to be elucidated (Cortese & Tessari, 2017).

Obesity is related to a higher risk for dementia. According to a meta-analysis by Beydoun et al. (2008), 10 prospective studies that followed participants 40 years and older over a maximum of 36 years found that obesity increased the risk for dementia in men and women when compared to normal weight participants. Specifically, the risk ratio for Alzheimer's disease was 80% higher for those with BMI greater than 30. When examining risk ratios by gender, Beydoun et al (2008) found that the risk for dementia was greater for females with BMIs over 30 (RR = 3.01), although the risk was still significantly high for males (RR = 2.32). These risk ratios remained significant after controlling for socio-demographic factors, lifestyle and most critically, health-related factors that are comorbid with obesity (i.e., hypertension, diabetes mellitus type 2 and dyslipidemia). Therefore, obesity shares an important relationship with dementia. Given the relationship shared between obesity and ADHD, the influence of obesity on the increased risk for dementia observed in adults with ADHD must be taken into consideration.

Diabetes, ADHD and Dementia

Diabetes mellitus could be another explanation for the relationship shared between ADHD and dementia. In a nationally representative sample of American adults between 20-79 years, Xu et al. (2021), found that the risk for any type of diabetes, except for diabetes related to pregnancy, in adults with ADHD was 54% higher than the risk in those without ADHD after

controlling for sociodemographic and lifestyle factors, including BMI. The consensus paper on ADHD by Faraone et al. (2021) reports similar results; according to a study analyzing the risk of diabetes in a sample of 650,000 children under 19, the risk of type 1 diabetes was 40% higher in children with ADHD than in children without ADHD (Kapellen et al., 2016). With respect to type 2 diabetes, in a sample of 5.5 million adults between 18-64 years, the prevalence of type 2 diabetes was twice (95% CI: 2.27-2.55) as high for adults with ADHD than for adults without ADHD (Chen et al., 2018). Although the analyses did not control for BMI, Chen et al. (2018) found that the prevalence of type 2 diabetes remained significantly higher in 50–64-year-olds who were diagnosed with ADHD compared to those without ADHD. Therefore, across studies, the risk of type 1 and 2 diabetes is consistently higher for individuals diagnosed with ADHD than for those without ADHD.

Critically, those with diabetes have a higher risk for dementia. In a meta-analysis of 28 studies by Gudala et al. (2013), the pooled risk ratio for any-type of dementia in participants with either type 1 or type 2 diabetes was 1.57-1.63 after controlling for heterogeneity across the studies (i.e., follow-up periods, BMI, cardiovascular disease and the prevalence of APOE e4 allele). Interestingly, when the risk ratio was analyzed separately for Alzheimer's disease (AD) and vascular dementia (VaD), the pooled risk was statistically significant for both but significantly higher for VaD, compared to AD; whereas the risk for AD was 1.54-1.57, the risk for VaD was 2.0-2.3 for study participants with diabetes type 1 and 2.

Reviews predating the meta-analysis by Gudala et al. (2013) report similar findings and suggest possible mechanisms for the relationship between diabetes and dementia. For instance, Pasquier et al. (2006) suggest that dementia could be more prevalent in those with diabetes due to: 1) the direct effect of diabetes on vascular disease (a possible explanation for the higher risk

ratio for VaD observed by Gudala et al.), which in turn affects the pathogenesis of AD; 2) insulin resistance and its relationship to tau protein phosphorylation, amyloid deposition; 3) the effect diabetes has on glycemic control in the body and by extension, the brain. Given that diabetes is more prevalent in ADHD and that it relates to a higher risk of dementia, it is possible that the observed relationship between diagnosed ADHD and dementia can be explained by the relationship they share with diabetes.

Autoimmune disorders, ADHD and Dementia

Allergic and autoimmune diseases, such as asthma and ulcerative colitis, share an important relationship with ADHD and may be another explanation for the observed risk of dementia in adults with ADHD. Neilsen et al. (2017) investigated the risk for subsequent diagnosis of ADHD in a sample of children diagnosed with any autoimmune disease. For their research, all children born in Denmark from 1990-2007 (n = 983,680) were followed for 17 years, and admission to the Danish National Hospital Registry due to an autoimmune disorder was recorded. In accordance with population prevalence estimates, 2.4% of the total population was eventually diagnosed with ADHD (Nielsen et al., 2017). Critically, the incident rate for a subsequent diagnosis of ADHD in the sample after any autoimmune disease was diagnosed was significant (OR = 1.24, 95% CI: 1.10 - 1.40). Interestingly, the authors found that any autoimmune disease in the mother, but not the father, was significantly associated with the child’s subsequent risk for ADHD diagnosis (Neilsen et al., 2017). Specifically, mothers' chronic conditions such as type 1 diabetes, autoimmune hepatitis and ankylosing spondylitis were most associated with subsequent diagnosis of ADHD in children with an initial diagnosis of any autoimmune disease (Neilsen et al., 2017).

Complementing the findings by Nielsen et al. (2017), Chen et al. (2017) collected a sample of children with ADHD and age-matched controls from a National Hospital Registry in Taiwan to investigate the association between ADHD and any autoimmune disease. Autoimmune diseases were divided into two categories: allergic diseases and autoimmune disorders. The authors found that the adjusted risk of a comorbid allergic disease, such as asthma, atopic dermatitis, and allergic rhinitis, were 1.5 times higher for children with ADHD than their age-matched controls. Likewise, the risk of a comorbid autoimmune disorder such as ulcerative colitis, autoimmune thyroid disease or ankylosing spondylitis were 2 times higher for children with ADHD than controls. Therefore, the prevalence and risk of any autoimmune disease in individuals with ADHD is higher than it is for those without ADHD.

A hypothesis proposed by Raison et al. (2006) may explain the observed association between ADHD and any autoimmune disease: accordingly, inflammatory responses to allergies or autoimmune activity weaken and eventually penetrate the blood brain barrier, leading to autoimmune activity in the brain. Raison et al. (2006) suggested that autoantibodies, such as cytokines, interact with receptors found on specific neurons in pathways involved with behavioral and emotional regulation, implicating neural mechanisms related to ADHD and other psychiatric disorders.

Critically, this explanation provides a connection between the observed relationship between ADHD and any autoimmune disease, and ADHD and dementia. According to D'Andrea et al. (2005), the Alzheimer's disease autoimmune hypothesis proposes that a weakened blood brain barrier allows antibodies into the brain which in turn, bind to neurons and trigger apoptosis (i.e., programmed cell death). For individuals with heightened immune activity due to any autoimmune disease, antibodies are more prevalent in the blood and therefore, could effect more

neuronal cell death in the brain once they pass the blood brain barrier. Therefore, it is likely that Alzheimer's related pathology is more prevalent among individuals with any autoimmune disease. Indeed, an epidemiological study conducted by Li et al. (2018) on over 780,000 adults without dementia upon admission to hospital found that patients with any autoimmune disease were at a significantly higher risk than the sample of adults without an autoimmune disease for all type dementia, Alzheimer's disease, Vascular dementia and other cause dementia later in life. Autoimmune diseases associated with the higher risk included: type 1 diabetes, celiac disease, and various forms of thyroiditis (Li et al., 2018). In conclusion, individuals with any autoimmune disease are at higher risk for dementia than those without an autoimmune disease. Critically, since autoimmune diseases are more prevalent in those with ADHD, the observed risk for dementia in adults with ADHD may be partially explained by co-occurrence of any autoimmune disease.