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The Influence of Smoking Behavior on Cognitive Functioning Approaching Midlife

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The journey to becoming a doctor is laborious, lengthy, and fraught with uncertainty and long nights. Mine is no different. Before following the path, you must find a program. There are many online resources about getting into graduate school and navigating the application process. Across all the wise words and shared tricks, one adage was repeated, “find a good mentor”. I’m happy to say I did. Not only was I lucky enough to find a mentor who was expert in many things including quantitative methodology, behavior genetics, and development, so much so that others in the department from graduate students to faculty members deferred to her, but I found a mentor that had all those capabilities who was also kind and patient. The first person I would like to thank is my advisor, Dr. Chandra Reynolds. Thank you for all the guidance and mentorship throughout the years. My skills as a researcher have grown because of your leadership and expertise. I am indebted to you for all your support that has enabled me to reach this stage.

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Dedication

This dissertation is dedicated to the strongest woman I have ever known, my grandma, Ellen Karpas. Ellen, you were with me at the beginning of this journey and in spirit with me at the end.

We will forever miss you.

ABSTRACT OF THE DISSERTATION

The Influence of Smoking Behavior on Cognitive Functioning Approaching Midlife

by

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This dissertation's primary aim was to clarify the emergence of smoking-cognitive associations within the first half of the lifespan. In Study 1, using data from the first assessment of the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife1), smoking behaviors were examined cross-sectionally to assess their association with cognition before midlife. In Study 2 we explored how smoking behavior influences cognitive development. Prospective data were available for CATSLife1 participants from two archival longitudinal projects of twins, siblings and adoptees to track cognitive development from early adolescence to midlife. Associations between smoking and cognition were assessed using mixed effects growth models fitted to the cognitive data, with (a) smoking consumption at year 16 and (b) the smoking consumption difference score.

Study 1 showed that current smoking was associated with lower cognitive performance across most domains, including episodic memory, processing speed, spatial,

and verbal, apart from working memory/attention indexed by Digit Span. Associations remained after adjusting for cardiovascular health, educational attainment, and a state-level tobacco control score (TCS). TCS was not related to cognitive performance and did not moderate associations with smoking behaviors. Sensitivity analyses with year 12 IQ suggested that smoking-cognition findings were not due to differences in early life intellectual ability.

Study 2 results indicated adolescent smoking, and to a lesser extent adulthood smoking, have a small negative effect on cognitive performance and change from adolescence up to midlife. Higher year 16 smoking consumption was associated with lower average performance for nearly all tasks. When examining differential cognitive growth rates, results indicated that a more rapid decline in adulthood was associated with greater levels of adolescent smoking for the episodic memory task Names and Faces. For processing speed, reduced growth at greater levels of adolescent smoking at age 16 and gains in smoking into adulthood were observed for Digit Symbol. Moreover, the smoking difference score was associated with average cognitive performance at age 16 for Colorado Perceptual Speed and Block Design, indexing processing speed, and spatial domains, respectively, whereby lower age 16 performance was associated with smoking gains after age 16.

Overall, results from Study 1 and Study 2 suggest that the influence of smoking behavior on cognition emerges early in the lifespan. This dissertation's collective findings help elucidate the developmental windows of risk on cognitive development, but further work remains.

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Chapter One:

GENERAL INTRODUCTION

There is a rich history of research inquiry into the development and progression of smoking behavior across many disciplines of science (Centers for Disease Control and Prevention, 2017; Do & Maes, 2016; Erzurumluoglu et al., 2019; Liu et al., 2019; Mayhew et al., 2000; U.S. Department of Health and Human Services, 2014), most notably due to the known and accepted public health impacts and economic consequences due to tobacco use (Centers for Disease Control and Prevention, 2018; Royal College of Physicians of London: Tobacco Advisory Group, 2000; Surgeon General's Advisory Committee on Smoking, 1964; U.S. Department of Health and Human Services, 2014). Indeed, smoking behavior represents one of the most well-studied modifiable health behaviors, and there have been great gains in understanding the developmental course, individual differences and contextual factors that influence liability and development, and later consequences individuals and society suffer in the presence of tobacco use.

Although smoking behavior is well represented in the health and aging literature, more work is needed to explore the relationship with cognitive functioning, another important area of health. Worse cognitive health, as characterized by lower performance, greater decline, and greater risk for dementia, have all been linked to smoking behavior (Anstey et al., 2007; Swan & Lessov-Schlaggar, 2007). The specific influence of smoking on cognitive function does vary by task, with differences ranging from acute benefits to long-term consequences (Durazzo et al., 2010). Notably, susceptible pathways

to smoking exposure include cardiovascular health, all of which may contribute to later cognitive functioning (Lahousse et al., 2015). Although potential biological mechanisms have been suggested to explain the negative effect of smoking on cognition, there is a paucity of research examining when smoking effects may emerge, especially before midlife. Moreover, no study has evaluated how smoking may impact cognitive development from preadolescence to the cusp of midlife.

This dissertation's primary purpose was to address this gap in the literature. We tested if smoking-cognitive associations emerge earlier in the lifespan while controlling for individual differences that are common to both smoking and cognition. In addition, we evaluated if tobacco control policies, a US-based measure specifically created for this dissertation may further influence associations. The smoking-cognitive relationship was examined cross-sectionally and longitudinally using data from the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife1) sample, which leverages rich archival assessments from longitudinal studies of twins, adoptees, and siblings. Elucidating the timing of smoking-related consequences on cognitive function has important implications for research and could inform policy relevant for healthy aging.

Cognitive Development from Adolescence to Midlife

Since antiquity, philosophers have questioned and introspected aspects of the human mind and cognition (Cassel et al., 2012). To this day, interest in the measurement and conceptualization of intelligence and how cognition changes over time has remained of profound interest. Early work from Jean Piaget, who would later be known as father of

cognitive development, outlined a series of successive stages individuals progress through from childhood to young adulthood (Piaget, 1972; Piaget & Cook, 1952). As individuals exit childhood and approach adolescence, more sophisticated processes emerge to resolve problems, aid in learning new knowledge or skills, and plan for the future. The formal operational stage is the fourth and final stage in Piaget's theory of cognitive development and is reached during adolescence. In this stage, more complex processes include thinking abstractly and reasoning using hypothetical thought. Indeed, past work has supported the notion that individuals become more efficacious in tackling complex problems during adolescence (Eccles et al., 2003; Kail & Salthouse, 1994). Piaget's cognitive theory outlined an organized and segmented progression of development. However, this theory is an incomplete picture of how cognitive functioning changes over time, particularly after adolescence.

Cognitive development is not a smooth, linear pattern of growth and maturation. Further, cognition can be characterized at different levels of specificity. Early pioneering work from Charles Spearman captured the intercorrelated structure among cognitive abilities (Spearman, 1904). Based on this observation, Spearman proposed the two-factor theory, which states intelligence comprises a general domain and specific abilities. Although covariation exists among abilities, individual differences in amplitude emerge between specific abilities. Indeed, cognition represents a variety of abilities that can vary between individuals as well as over time (Hartshorne & Germine, 2015; McArdle et al., 2002; Reynolds et al., 2005; Ricker et al., 2018; Salthouse, 2009; St Clair-Thompson, 2010; Thaler et al., 2013; Troyer et al., 2011; Tucker-Drob, 2019).

During early adolescence, many cognitive abilities demonstrate rapid growth (Hartshorne & Germine, 2015; Mechie et al., 2021; Ricker et al., 2018; St Clair-Thompson, 2010; Thaler et al., 2013; Tucker-Drob, 2009, 2019). Adolescent cognitive trajectories can differ across abilities. For example, when comparing working memory to episodic memory, both domains had a fast growth rate. However, working memory demonstrated a slower linear growth, while curvilinear patterns best captured age trends for episodic memory (Thaler et al., 2013). Nonetheless, a steep growth rate best articulates cognitive development for various abilities during adolescence (Tucker-Drob, 2009).

Changes in adolescent cognition also coincide with neurological maturation, especially in cortical regions salient for learning and memory, such as the prefrontal cortex (PFC) and the medial temporal lobe (Fuster, 2002; Romine & Reynolds, 2005; Wierenga et al., 2014). Simultaneous developmental changes in the white and grey matter include gains in myelination and synaptic pruning, which alters the morphology of the maturing brain (Fuster, 2002; Paus, 2005; Romine & Reynolds, 2005; Wierenga et al., 2014). White matter density increases across childhood and plateaus around early adulthood (Fuster, 2002; Paus, 2005). Grey matter density changes regionally across ages (Fuster, 2002; Paus, 2005). First, prefrontal growth occurs from birth to age 12, then dorsal and parietal lobes reduction occurs from childhood to adolescence, and losses in the frontal cortex from adolescence to adulthood. As brain structures approach maturation in young adulthood, cognitive functioning also tends to reach peaks in performance.

Cognitive trajectories do not continue to grow indefinitely; performance peaks at some point that varies between domains (Hartshorne & Germine, 2015; Salthouse, 2009). Episodic memory represents one cognitive ability that reaches plateaus the earliest, at around mid-adolescence (Hartshorne & Germine, 2015; Thaler et al., 2013). In contrast, abilities representing acquired knowledge, such as verbal ability, peak the latest, with some finding maximum performance reached around age 50 (Hartshorne & Germine, 2015) up to the 7th decade of life (Li et al., 2004; Pahlen et al., 2018; Reynolds et al., 2005; Salthouse, 2009). After peak performance is reached, cognitive abilities will either start to decline or establish stability, only to decline after some time. For example, processing speed peaks before age 30 and then demonstrates steady declines across adulthood (Hartshorne & Germine, 2015; Salthouse, 2009). Working memory peaks around age 30 (Hartshorne & Germine, 2015) and is relatively stable up into later adulthood, with shallower declines into the oldest ages (Hartshorne & Germine, 2015; Reynolds et al., 2005).

The differences in growth patterns lead to the two component theory of intelligence, which categorizes adulthood cognitive development by aging-sensitive/fluid abilities or aging-resilient/crystallized abilities (Baltes, 1997; Cattell, 1971; Horn & Cattell, 1967; Lindenberger et al., 2001). Fluid and crystallized intelligence are distinguished not only by the time when cognitive abilities begin to decline but the cognitive processes involved. Fluid abilities include skills to think flexibly and logically resolve new and unfamiliar problems. Cognitive abilities captured by this component include spatial ability and processing speed. Crystalized intelligence represents acquired

knowledge gained through experience. Verbal comprehension would be an example of crystallized intelligence. The two component theory is not immune to cohort effects which can influence the average cognitive performance and cognitive trajectories (Flynn, 1987; Schaie & Strother, 1968; Schaie et al., 2005). Further, individual differences and heterogeneity between abilities can also impact age trends (Hartshorne & Germine, 2015; McArdle et al., 2002; Mella et al., 2018; Wilson et al., 2002). Although trajectories of intelligence can be broadly categorized under the two component theory, the process of developmental change across abilities and time is far more complex than the two component theory allows (Horn & Blankson, 2005). Indeed, intelligence consists of multiple interconnected specific abilities that vary within person (Horn & Blankson, 2005; Spearman, 1904). The underlying mechanism leading to change across abilities and within person is still under investigation (Alain et al., 2022; Baltes, 1997; Cattell, 1971; Horn & Blankson, 2005; Horn & Cattell, 1967; Lindenberger & Baltes, 1994; Salthouse, 1996; Tucker-Drob et al., 2019). Thus, to explore cognitive development, this dissertation examined cognition across several abilities and included methods to account for individual differences to better capture the unique trajectories by ability across time.

Even though age differences for cognitive abilities have been known empirically for close to 100 years (Anderson & Craik, 2017), research examining earlier life cognitive trajectories covering the middle adulthood expanse is sparse (Tucker-Drob & Briley, 2014). More specifically, research within cognitive development tends to examine changes over a limited age range and is concentrated at the poles of the lifespan at childhood and later life. Thus, studies need to include the middle adulthood period to

better understand the factors that influence cognitive growth, maintenance, and decline. This dissertation attempts to narrow such a gap in the literature, especially concerning smoking-cognitive associations.

Smoking Development: From First Light to Persistence Use

Adolescence marks a period for "storm and stress" as characterized by G. Stanley Hall, the eminent psychologist who first coined the term adolescence and, thus, galvanized research interest surrounding earlier life development (Arnett, 1999, 2006; Hall, 1905). Although several of Hall's assertations about adolescence have gone by the wayside, his ideas surrounding risk and experimentation still hold (Arnett, 2006). Indeed, adolescence is when individuals commonly dabble with substance use, particularly for legal substances such as tobacco (Dutra et al., 2017; Fuemmeler et al., 2013; Huggett et al., 2019). There are numerous tobacco products that individuals could use, such as cigarettes, chew, pipe, cigarillos, and e-cigs. Cigarettes are the most common tobacco product (Cornelius et al., 2022; Rose et al., 2009; U.S. Department of Health and Human Services, 2014), however higher prevalence for noncombustible cigarettes or e-cigarettes has been seen in middle and high school students (Wang et al., 2019). There is a growing body of research dedicated to examining e-cigarettes, but work remains somewhat limited, given the novelty of the product. Thus, in this dissertation, smoking behavior development will refer to cigarette use.

Smoking behaviors often develop in a sequence of stages, from initiation to experimentation, regular smoking, then finally persistent or daily smoking (Mayhew et al., 2000; White et al., 2003). Earlier stages not noted here relate to attitudes and

preparatory behavior as individuals begin to approach use (Mayhew et al., 2000). Although these stages are important to understand the cultural context surrounding tobacco use and motivations to smoke, this dissertation focused on behaviors related to extant smoking. Individuals do not progress across all stages, but development starts with smoking initiation. Smoking initiation refers to the first attempts with cigarettes, often occurring during adolescence (Dutra et al., 2017; Fuemmeler et al., 2013; Huggett et al., 2019). Smoking initiation differs from smoking experimentation as smoking experimentation includes individuals who have increased the frequency of tobacco use but do not smoke at regular intervals (Mayhew et al., 2000; White et al., 2003). Smoking experimentation starts around a similar time after initiation, but experimenters tend to quit using by young adulthood (Dutra et al., 2017).

Regular smoking is defined by individuals who continue to smoke at an increased frequency and captures more consistent use patterns, but individuals have yet to progress to daily smoking (Mayhew et al., 2000). There is a moderate risk of transition to daily consumption once individuals reach this stage. For example, once individuals started smoking weekly, more than half transitioned to daily smoking within a year (Dierker et al., 2012). The last stage is daily smoking, and individuals are persistent users by then. Age at smoking initiation predicts whether an individual is more likely to reach daily smoking before adulthood, where the younger an individual starts, the more likely they will become smokers at an earlier age (Dierker et al., 2012; Huggett et al., 2019; Rose et al., 2009). Although adolescence is a common time to adopt smoking behaviors, some individuals do start later in their college years (Dutra et al., 2017; Johnson et al., 2009).

Late starters or late escalators are a small proportion of smokers, with only 8% of ever smokers falling within this smoking class trajectory (Dutra et al., 2017). An important end period for many, but unfortunately not for all, is cessation. Smoking cessation refers to the complete withdrawal from continued use of any tobacco products. Successfully quitting is difficult as relapses are common and successful cessation at one time doesn't necessarily guarantee continued abstinence (Belsky et al., 2013; Rose et al., 2009).

Smoking behavior development encompasses various stages to capture the progression of one behavior that then, in turn, influences the transition to the next. Thus, smoking behavior stages represents an interconnected structure of liability (Belsky et al., 2013; Huggett et al., 2019; Rose et al., 2009). Although this dissertation work did not examine smoking trajectories, it is important to acknowledge the course and shape of development. Smoking represents a modifiable health behavior with onset originating at a salient developmental window for cognitive growth and neurological maturation. Therefore, it is imperative to know the lineage of smoking behavior to better understand how this health risk may affect cognitive development and aging processes.

Research into the Empirical Links between Smoking and Cognition

Smoking exposure is not a ubiquitous force on cognition. Rather the smoking effect on cognition will vary by cognitive domain and time. Some domains show improved effects for acute exposures via smoking or nicotine administrations, with enhanced performance seen in attention and working memory tasks (Heishman et al., 2010; Swan & Lessov-Schlaggar, 2007). A meta-analysis (Sutherland et al., 2015) examining neural activity after acute smoking exposure found nicotine led to

acetylcholine receptor activation and was associated with increased activity in the lateral prefrontal regions and decreased activity in the ventromedial PFC and posterior cingulate cortex. These specific activation patterns are particularly relevant because of their link to improved performance on attention and working memory tasks and may implicate neurobiological mechanisms of nicotine on cognitive enhancement (Herman & Sofuoglu, 2010; Sutherland et al., 2015).

Even though nicotine is a major compound within tobacco products, there are many other hundreds or thousands of other constituents (Heishman et al., 2010). Moreover, nicotine's independent benefits to cognition will be obscured if administered through smoking a cigarette (Herman & Sofuoglu, 2010). In other words, smoking is not an advisable delivery mechanism for nicotine, given the other hazardous materials found in cigarette products. For example, important compounds that could negatively impact cognitive health include formaldehyde, acetaldehyde, and cadmium, which have been associated with the degradation of the respiratory system (Swan & Lessov-Schlaggar, 2007). Overall, nicotine may be beneficial, but long-term smoking could lead to consequential impacts on other mechanisms of health related to cognitive functioning. For example, cardiovascular health is at risk given the smoking-related risk of increased inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol (Ambrose & Barua, 2004).

Although there may be cognitive benefits for acute use, the hard reality is that smokers are not infrequent users, and many smokers will spend years daily smoking. The benefits smokers may have experienced for cognitive enhancement or mood regulation

comes with a cost, as persistent use shifts to consequential impacts on neurological and cognitive health (DeBry & Tiffany, 2008; DiFranza, 2020; Dwyer et al., 2009; Thorpe et al., 2020). Indeed, persistent use is associated with lower performance and greater risk for cognitive decline and impairment (Anstey et al., 2007; Conti et al., 2019; Durazzo et al., 2010; Peters et al., 2008; Swan & Lessov-Schlaggar, 2007). Specific cognitive abilities susceptible to hams of with persistent smoking include processing speed, working memory, executive functioning, and episodic memory (Conti et al., 2019; Durazzo et al., 2010, 2012). In particular, processing speed appears to be most vulnerable to the negative effects of chronic smoking, as many studies have evidenced associations across international samples, across different ages, and cohorts (Bahorik et al., 2021; Corley et al., 2012; Dai et al., 2022; Durazzo et al., 2010; Hotta et al., 2015; Kasl-Godley, 1996; Lo et al., 2014; Meier et al., 2022; Nooyens et al., 2008; Vermeulen et al., 2018).

Most of our knowledge about the effects of smoking on cognitive functioning has been gained through the studies of older adults (Anstey et al., 2007; Conti et al., 2019; Durazzo et al., 2010). Few studies of adolescents and young adults exist, and findings are mixed (Castellanos-Ryan et al., 2017; Fried et al., 2006; Jacobsen et al., 2005; Mahedy et al., 2018; Mahedy et al., 2021). Research has acknowledged the vulnerability of substance use during adolescence on neurological maturing processes (Dwyer et al., 2009; Goriounova & Mansvelder, 2012; Mooney-Leber & Gould, 2018; Thorpe et al., 2020). As outlined by Morin et al., (2019) for adolescent substance use with cannabis and alcohol, several proposed models may follow across time. First, the neuroplasticity model proposes that substance use imposes harm with concurrent use, but the brain can rebound

through neuroplasticity, reduction in consumption, or cessation. In contrast, the neurotoxicity model presumes impairments gained through substance use persist across time. Lastly, the developmental sensitivity hypothesis refers to the neuroplasticity and neurotoxicity processes most pronounced during salient developmental ages.

More evidence has emerged of the neurotoxicity effects of tobacco, with neurological differences emerging in the PFC and medial temporal lobe regions (Akkermans et al., 2017; Chaarani et al., 2019; Zeid et al., 2018), fundamental regions responsible for learning, memory, and compensatory processes related to aging (Reuter-Lorenz & Park, 2014). Indeed, even the lightest amount of smoking is associated with brain differences as early as childhood for those that report ever trying a cigarette (Dai et al., 2022) and adolescence for those that have only smoked a few cigarettes (Chaarani et al., 2019). A robust literature exists on the effects of smoking on brain age, where smokers have older brains and their brain ages faster than nonsmokers (Franz et al., 2021; Linli et al., 2022; Ning et al., 2020; Whitsel et al., 2022). Smoking may impact other health pathways, such as cardiovascular functioning which could lead to changes in the brain and cognitive functioning. For example, oxidative stress due to elevated carbon monoxide within cigarette smoke can exacerbate cerebrovascular disease and cerebral hypoxia (Durazzo et al., 2010; Lahousse et al., 2015). Most research has focused more on the neurobiological rather than the functional effects of smoking before midlife, however.

More work is needed to explore the earlier life associations between smoking and cognition, especially tracking the influence of smoking on cognitive change across time. Past prospective work has thus far been limited, with many studies only typically

evaluating the association via a single follow-up (Nooyens et al., 2008; Richards et al., 2003; Whalley et al., 2005), most notably in research examining early use starting in childhood or adolescence (Castellanos-Ryan et al., 2017; Dai et al., 2022; Meier et al., 2012; Weiser et al., 2010). Indeed, some of the mixed findings within the literature may reflect study design differences based on the number of measurement occasions. For example, studies that only examined cognitive decline between two assessments based on a difference score (Chen et al., 2003; Deal et al., 2020) failed to find associations with smoking behavior which was less common in studies tracking growth over time (Amini et al., 2021; Collins et al., 2009; Olaya et al., 2017; Sabia et al., 2012; Vermeulen et al., 2018). Moreover, the time metric, such as using age rather years between measurement occasions, is important to consider for modeling cognitive trajectories given the distinct patterns across age (Hartshorne & Germine, 2015; McArdle et al., 2002; Reynolds et al., 2005; Ricker et al., 2018; Salthouse, 2009; St Clair-Thompson, 2010; Thaler et al., 2013; Troyer et al., 2011; Tucker-Drob, 2019). Thus, this dissertation work expanded on past literature by examining smoking-cognitive associations before midlife and how smoking behavior may influence age-curves for cognition from early adolescence to midlife.

Confounding and Contextual Factors

Education and Childhood IQ

Educational attainment is an important predictor of cognitive ability (Lövdén et al., 2020; Ritchie & Tucker-Drob, 2018) and modifiable health behaviors, including tobacco use (Corley et al., 2019; Daly & Egan, 2017; Johnson et al., 2011; Kubička et al., 2001; Pampel et al., 2014; Silventoinen et al., 2022; Whalley et al., 2005). In the US,

those with less education tend to have a higher prevalence of tobacco use (Centers for Disease Control and Prevention, 2017; U.S. Department of Health and Human Services, 2014). Indeed, there seems to be a higher risk for tobacco use among disadvantaged groups (Hiscock et al., 2012), which can start earlier in life and persist over time (Corley et al., 2019; Pampel et al., 2014). Moreover, educational links with smoking behavior are fairly consistent across multiple developed countries, suggesting an effect that is not unique to the United States (Cavelaars et al., 2000; Silventoinen et al., 2022).

The effect between education and cognition, as measured by IQ, is a relatively small effect, where each additional year of education confers, on average, a 3.4-point gain in IQ (Ritchie & Tucker-Drob, 2018). Average cognitive performance is related to education but not change across time (Lövdén et al., 2020; Ritchie et al., 2016). Even though past work suggests that low education does not accelerate cognitive decline, higher education has important connections with compensatory mechanisms related to offsetting cognitive losses in later life (Reuter-Lorenz & Park, 2014; Stern, 2009; Stern et al., 2019). The importance of compensatory mechanisms can be seen in the Vietnam Era Twin Study of Aging (VETSA) study, where neurological health in later life, even in the face of unfavorable health behaviors, is more maintained for individuals with higher cognitive ability at age 20 (Franz et al., 2021). To say it another way, individuals with higher cognition at younger ages, which may be influenced by education in some part, are protected to a certain extent from the harms of smoking and other unfavorable health behaviors. Indeed, past prospective work has shown childhood intellectual ability can also be protective against later cognitive decline by midlife (Richards et al., 2004).

Moreover, lower childhood IQ is also predictive of smoking behaviors such as initiating smoking, persistent smoking, and likelihood to quit (Corley et al., 2019; Daly & Egan, 2017; Kubička et al., 2001). Since childhood intellectual ability as well as educational attainment, which is often completed by young adulthood, has connections with cognitive functioning and processes related to cognitive maintenance, and these early experiences contribute to beneficial versus inequitable health outcomes.

Lower educational attainment represents a confluence of disadvantaged conditions and systems that can persist across time for cognition (Lövdén et al., 2020; Ritchie & Tucker-Drob, 2018) and smoking (Corley et al., 2019; Pampel et al., 2014). Contextual factors restricting educational opportunities can entrap individuals into cycles of poverty and addiction. Indeed, due to a multitude of barriers in healthcare and resource access, lower-educated individuals are less likely to quit smoking (Agaku et al., 2020; Garrett et al., 2014; Hill et al., 2014; van Wijk et al., 2019). As outlined, selection differences can arise within the education gradient that influences cognitive functioning (Lövdén et al., 2020; Ritchie & Tucker-Drob, 2018) and smoking behavior (Corley et al., 2019; Daly & Egan, 2017; Kubička et al., 2001; Pampel et al., 2014; Silventoinen et al., 2022; Whalley et al., 2005). Therefore, this dissertation included measures of education and childhood IQ to test if shared common factors explain smoking-cognition associations.

Tobacco Control Policies

The United States' relationship with tobacco is complicated. Tobacco has its roots across American history, dating back to before the country was founded (Gately, 2001).

As a major colonial agricultural export, farming tobacco was a lucrative enterprise that helped establish wealthy plantations in the southern colonies, which relied on slave labor as an essential resource to cultivate the plant. Two future founding fathers and presidents, George Washington and Thomas Jefferson, were tobacco farmers. Interference with tobacco trade based on pricing and taxation fueled efforts toward the war of independence (Gately, 2001). Indeed, years later, discussions on the exploitation of labor and ethics of slavery planted seeds for future strife that would erupt in the civil war.

Today, tobacco use, specifically smoking, is recognized as a major health and economic burden (Centers for Disease Control and Prevention, 2018; Royal College of Physicians of London: Tobacco Advisory Group, 2000; U.S. Department of Health and Human Services, 2014). However, tobacco use was not always considered a public health risk (Gately, 2001). In fact, military personnel were issued government-subsidized cigarettes, and tobacco companies touted the health benefits of their cigarette brands to rival other brands. Even the eminent statistician and geneticist R.A. Fisher, an avid smoker, asserted smoking was protective against disease (Fisher, 1958). In the 1950s, smoking was popular and public attitudes were positive; however, health concerns were mounting as the first studies started linking smoking with lung cancer (Studlar, 2002; Wipfli & Samet, 2009).

The warning from the Surgeon General in 1965, highlighting the dangers of tobacco use, changed the course of public policies (Studlar, 2002). Warning labels were added to cigarette packages soon after, with mandated statements that changed over subsequent years to more direct and explicit warnings. The Federal Trade Commission

(FTC) and Federal Communication Commission (FCC) banned cigarette advertising on radio and television in 1972 (Studlar, 2002). What followed suit for the next 50 years were tobacco control initiatives and policies related to smoke-free spaces, pricing, advertising, legal tender age, and cessation support at various levels of governance (Studlar, 2002; Wipfli & Samet, 2009).

As a whole, tobacco control policies were considered effective as the prevalence of tobacco use (Farrelly et al., 2014; Farrelly et al., 2008; Hawkins et al., 2016; Wilson et al., 2012) and tobacco-related deaths declined (Bradley et al., 2016; Gebreab et al., 2015; Jemal et al., 2003; Meyers et al., 2009). However, not all states or localities demonstrated the same reduction (Boardman, 2009; Drope et al., 2018; Shmulewitz et al., 2016; Studlar, 2002). Disparities in smoking behavior exist between states that vary on tobacco control which persist to this day. Notably, there are 13 states located in the Midwest and South, which exceeds the national average for smoking prevalence and is referred to as the tobacco nation (Truth Initiative, 2019). Given the differences in tobacco control across states, where one lives can inform and shape access and affordability to tobacco.

Tobacco control varies regionally across the United States, thus, it is, therefore, important to consider how the context of tobacco-related policies may influence smoking-cognition associations. Indeed, smoking and cognitive development are embedded within larger ecological context which includes the policies surrounding tobacco access, cost, and restrictions to use. A theoretical framework to understand the ecology of human development would be Bronfenbrenner's bioecological model (Bronfenbrenner, 2005; Bronfenbrenner & Ceci, 1994). The bioecological model

postulates that development operates through the coaction of multiple systems of influence that vary in distance from proximal (i.e., family and peer influence) to more distal (state-level tobacco control). Within this model, the person is at the center of their own development between proximal processes of the immediate environment that has consistent influence (i.e., the child and parent) and context characterized by different environmental levels. Tobacco control and governance would represent an ecological context surrounding tobacco use and would be a relevant environmental factor to consider relating to the influence tobacco development. We therefore explored the level of tobacco control people experienced during CATSLife1.

To date, there is no standardized metric to gauge tobacco control at different levels of governance in the United States. To explore variation in tobacco control, at a feasible scale for this dissertation, we examined control policies at the state level. Building upon the Tobacco Control Scale (Joossens et al., 2019; Joossens & Raw, 2006), we developed a tobacco control score (TCS) to index the level of smoking policies across states. The tobacco control scale is based on the Framework of Convention on Tobacco Control (FCTC) developed by the World Health Organization, which outlined specific legislation for curbing tobacco use. The tobacco control scale has been scored in 36 European countries, and numerous studies have utilized the measure (Feliu et al., 2020; Gao et al., 2022; Palali & van Ours, 2019).

We cannot divorce ourselves from the larger ecological contexts where we reside. Contextual features of the environment include public health initiatives and given the role tobacco control has had on reducing smoking prevalence across time in the United States

and beyond, it is an important factor to consider. Moreover, tobacco control policies will vary between states, with more permissive states concentrated in the Midwest and South. Thus, to elucidate the smoking-cognitive associations and explore the broader role of public health, this dissertation examined how state-level tobacco control may influence that relationship.

Purpose and Aims of the Dissertation

This dissertation aims to test smoking-cognition associations before midlife, including evaluating whether smoking behavior impacts cognitive development. Specifically, the aims of this dissertation are to (a) assess the adulthood cross-sectional associations of smoking behavior on seven specific cognitive abilities representing five domains while considering individual differences common to both smoking and cognition, and tobacco control policy efforts and (b) using the same cognitive measures, explore the longitudinal associations of adolescent consumption and adulthood smoking consumption gains with cognitive functioning from early adolescence to midlife. Research within the smoking-cognitive literature is scant for ages in the first half of the lifespan. This dissertation work will clarify the timing of smoking effects in the lifespan thereby fortifying evidence that smoking effects emerge before midlife and bolstering the salient intervention ages earlier in the lifespan for cognitive health. Figure 0.1 illustrates the associations between smoking behaviors and cognition across time explored in this dissertation.

Dissertation aims were evaluated within two studies. In Study 1, cross-sectional smoking-cognitive associations were evaluated for adults approaching midlife in five

cognitive domains: episodic memory, working memory, processing speed, spatial ability, and verbal ability. Using data from Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife1; Wadsworth et al., 2019), smoking and cognitive associations were tested with two status smoking measures (current and ever) and a dosage-dependent measure (pack years). To account for possible confounders, we include cardiovascular health, educational attainment, tobacco control policies, and year 12 IQ into analyses. In addition, to evaluate if tobacco control policies influence the interrelation between smoking behavior and cognition we tested if smoking-cognitive associations are moderated by tobacco control score.

Although Study 1 adds to the extant literature to examine an age period often understudied in relation to cognitive development (Tucker-Drob & Briley, 2014), this study only provides support that smoking effects emerge earlier than previous studies have commonly examined. Thus, Study 2 evaluates how smoking behavior influences cognitive development and later aging by using the combined data from two archival longitudinal projects and ending just prior to midlife with the CATSLife1 assessment. The same cognitive tasks from Study 1 were used in Study 2. For most cognitive tasks, assessments are available as early as at age 12 with the latest available assessment on average at age 33 years for the CATSLife1 wave (range= 28 to 49 years). Smoking behavior was assessed via daily smoking consumption during adolescence (i.e., age 16) and change in smoking consumption by CATSLife1 (i.e., the difference in consumption from age 16 consumption and CATSLife1).

Aims & Research Questions

Elucidating the earlier life timing effects of smoking on cognitive functioning is needed to inform healthcare and public policy measures aimed at reducing smoking harms on cognitive health. Understanding how public health contexts shape the relationship between smoking and cognition as well characterizing the age-curves in relation to smoking is fundamental for informing policy. Tobacco use is one of many harmful modifiable behaviors that impact health across the lifespan. Tracking the influences of smoking behavior will help clarify the interrelationship with cognitive development and maintaining cognitive abilities. We hence propose and test the following aims and research questions.

Aim 1: Uncover the Cross-sectional Associations between Cigarette Smoking Behavior and Cognitive Performance in Adults Approaching Midlife.

Research Q1: What is the association between cigarette smoking behavior (e.g., smoking status and pack years) and cognitive performance and do the associations vary by smoking measure for each cognitive domain?

Research Q2: Are the associations between smoking behavior and cognitive performance attenuated by cardiovascular health status, educational attainment, or childhood IQ?

Research Q3: Are associations between smoking behavior and cognitive performance attenuated by state-level tobacco control policy? Do state-level tobacco control policy measures moderate smoking and cognition associations?

Aim 2: Evaluate Longitudinal Associations of Smoking Behavior with Cognitive Functioning from Adolescence to Midlife.

Research Q1: Does smoking consumption at age 16 influence cognitive development up to mid-life? That is, do individuals who smoke more cigarettes at age 16 show worse cognitive developmental trends by the cusp of midlife (i.e., either dampened growth or cognitive decline)?

Research Q2: Do changes in smoking consumption influence cognitive development and change up to midlife? Moreover, do individuals who start regularly smoking after age 16, as captured by smoking consumption gains by the cusp of midlife, show differential adolescent cognitive functioning that may not be captured by extant adolescent smoking?

Hypotheses

Hypothesis 1.1

As past research has found variations in the smoking-cognitive associations attributable to specific ability (Anstey et al., 2007; Conti et al., 2019; Durazzo et al., 2010; Swan & Lessov-Schlaggar, 2007), it is likely we will also observe this differential pattern, notably by whether the ability is age-sensitive or not. Based on prior work, we therefore expect smoking behavior will be significantly associated with the four age-sensitive cognitive abilities (i.e., episodic memory, working memory, processing speed, and spatial ability) but not the crystallized ability (i.e., verbal ability).

Hypothesis 1.2

Smoking behavior and cognition share common influential factors such as cardiovascular health (Sabia et al., 2009; Samieri et al., 2018; Yaffe et al., 2020) and educational attainment (Lövdén et al., 2020; Ritchie & Tucker-Drob, 2018). We expect partial attenuation on the smoking effects once these factors are entered into the analysis for all age-sensitive tasks. Further education should be more robust compared to cardiovascular indictors as attenuation patterns with education has been observed previously (Batty et al., 2007; Corley et al., 2019; Sabia et al., 2008). Moreover, given the age of the sample, cardiovascular health may not be strongly related to cognitive performance (Eagan et al., 2002; Gao et al., 2017) or tobacco use (Ross et al., 2022).

Hypothesis 1.3

Study 1 aims to disentangle whether effects found between smoking and cognition are impacted based on region as defined at the state level. Based on the cross-sectional approach of this study, there are various patterns we might observe. First, we expect state-level policy will be unrelated to cognitive performance because it is unlikely that tobacco policies implemented would directly benefit cognitive functioning. In other words, it is unlikely policies related to smoke-free spaces and tax increases on cigarettes have any systematic consequence to cognitive functioning. Another pattern we may observe is that policy scores may weaken associations between smoking and cognition. If control scores attenuate the effects, this might signal bias based on state residence.

Next, we tested if control score moderates smoking effects. If smoking behavior is moderated by policy score, then greater state engagement in policies that reduce smoking

behavior such as delaying initiation, smoking less frequently, or earlier and more successful quitters may reduce associations between smoking and cognition in states with higher control. In contrast, states with low control will magnify smoking-cognitive associations. If moderation is not observed then this might indicate the policy score does not capture the full range of policy initiatives that target smoking, or differences in smoking behavior influenced by control efforts have not taken place yet, that a larger lag time is needed to observe the associations. It is possible no moderation may mean the contemporary policy scores are unsuccessful in changing smoking behavior, but this is less likely the case given the established literature on the impact tobacco control has had on smoking prevalence, smoking frequency, and cessation rates (Apollonio et al., 2021; Dinno & Glantz, 2009; Farrelly et al., 2008; Hopkins et al., 2010; Shmulewitz et al., 2016).

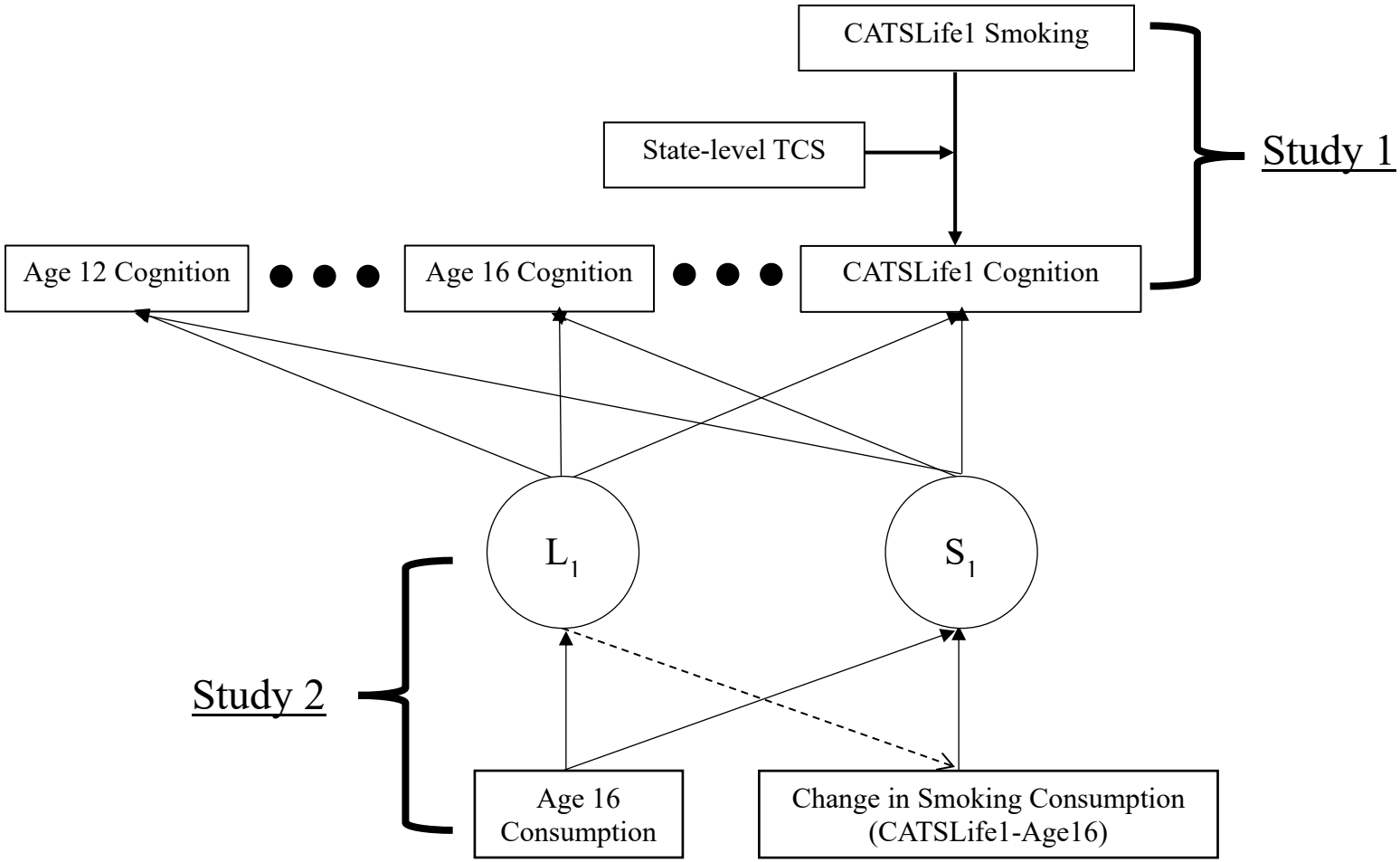
Hypothesis 2.1

Relative to studies examining smoking and cognition in the second half of the lifespan, few observational (Fried et al., 2006; Jacobsen et al., 2005; Mahedy et al., 2018; Mahedy et al., 2021) and prospective studies (Castellanos-Ryan et al., 2017; Meier et al., 2012; Weiser et al., 2010) have examined the impact of adolescent tobacco smoking on cognitive function prior to mid-adulthood. We hypothesize that smoking differences (e.g., smoking gains) will be a more robust influence on cognitive trajectories than adolescent smoking as noted by the proximal smoking-cognition associations observed in prior research (Amini et al., 2021; Collins et al., 2009; Lo et al., 2014; Nooyens et al., 2008; Sabia et al., 2012; Vermeulen et al., 2018; Weiser et al., 2010; Whalley et al., 2005).

Hypothesis 2.2

We expect to find associations with a smoking difference score on cognitive longitudinal trends because prior research has evidenced the consistent effect of current smoking on cognitive performance compared to ever or former smokers (Amini et al., 2021; Collins et al., 2009; Lo et al., 2014; Nooyens et al., 2008; Sabia et al., 2012; Vermeulen et al., 2018; Weiser et al., 2010; Whalley et al., 2005). We are uncertain if the associations will only be associated with average cognitive performance across time or if smoking gains will also modify cognitive trajectories by dampened growth or more rapid decline. Based on prior work evaluating the ‘‘Use It or Lose It’’ hypothesis, there are two hypothesized patterns for growth models: preserved differentiation and differential preservation (Salthouse, 2006). Preserved differentiation is the expectation that only individual differences in predictor such as smoking consumption influence level or average cognitive performance but not rate. In contrast, with respect to differential preservation smoking consumption would influence rate of change (slope) in cognitive performance but not level. If we find smoking consumption moderates the slope for cognitive performance, then this would be suggestive of differential preservation or the widening of differences in cognitive performance deficits across age for individuals with greater gains in smoking consumption.

Figure 0.1. Conceptual model showing examined associations between smoking behavior, state-level tobacco control score (TCS), and cognitive performance and change.



Note. The dashed arrow reflects the expected temporal direction of the association.

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Chapter Two:

Uncover the cross-sectional associations between cigarette smoking behavior and cognitive performance in adults approaching midlife.

Cigarette smoking is a known risk to physical health (Centers for Disease Control and Prevention, 2017; Do & Maes, 2016; Erzurumluoglu et al., 2019; Finch, 2018; Liu et al., 2019; Mayhew et al., 2000; U.S. Department of Health and Human Services, 2014). Notable pathways susceptible to smoking exposure include cardiovascular, pulmonary functioning, and neurobiological health (Bahorik et al., 2021; Elliott et al., 2021; Lahousse et al., 2015; Whitsel et al., 2022). Given the direct impact smoking behavior may have on health pathways, research has examined the later consequences of behavior arising from poor health, such as cognitive performance. Indeed, past research has shown smoking-associated outcomes of lower cognitive performance, cognitive decline, and increased risk for Alzheimer's disease and dementia (Anstey et al., 2007; Livingston et al., 2020; Orgeta et al., 2019; Swan & Lessov-Schlaggar, 2007). The smoking-cognitive relationship between midlife and late-life has been explored, largely given the mechanisms linking smoking with physical health (Anstey et al., 2007; Conti et al., 2019; Durazzo et al., 2010), although earlier associations may emerge.

While smoking-related consequences to health are more prevalent in later life, the potential harm smoking may impose on cognitive performance might emerge before individuals become symptomatic. Morbidity associated with aging presents after midlife

(Rockwood et al., 2011), with increased morbidity and accelerated aging among smokers (Bourassa et al., 2022; Corley et al., 2019; Dugué et al., 2018; Elliott et al., 2021; Linli et al., 2022; Lu et al., 2019; Ning et al., 2020; O'Shea et al., 2022; Wendell et al., 2014; Whitsel et al., 2022). Moreover, cardiovascular or pulmonary damage as a consequence of smoking may take decades to develop (Eagan et al., 2002; Gao et al., 2017). Emerging effects of tobacco use on physical health indices can be seen in early adulthood using the twin subsample from the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife1) (Ross et al., 2022). After controlling for other substance use behavior, associations with adult weight problems and rapid heart rate emerged when examining adolescent tobacco frequency (Ross et al., 2022). Moreover, Ross and colleagues (2022) observed that the number of physical health associations increased when considering concurrent associations CATSLife1, where smoking frequency was associated with a higher resting heart rate along with self-reported rapid heart rate, chronic pain, and breathing problems when participants were on average age 29.3 years (SD=1.2). In addition, smoking was negatively associated with other lifestyle factors such as a healthy diet, e.g., eating fewer fruits and vegetables. Interestingly, tobacco frequency and average lifetime use were unrelated to biomarkers of pulmonary and cardiovascular health such as forced expiratory volume (FEV), forced vital capacity (FVC), and diastolic and systolic blood pressure.

Smoking behavior may represent a multidimensional impact on health that accumulates over time but is not solely captured by one physical health index. Earlier influences of smoking have been found in research examining neurological differences or

brain age that were evident by early midlife (Bahorik et al., 2021; Franz et al., 2021; Lane et al., 2019; Livingston et al., 2020; Ning et al., 2020; Whitsel et al., 2022). Aggregating health indices have also shown associations with smoking and accelerated biological age (Dugué et al., 2018; Elliott et al., 2021; Lu et al., 2019; O'Shea et al., 2022). Biological age intends to capture the biochemical and physiological processes implicated in aging that contribute to individual differences separate from chronological age (Elliott et al., 2021; Kirkwood, 2005). Moreover, GrimAge (Lu et al., 2019), a measure of epigenetic aging and a specific component of biological aging, includes smoking pack years within the DNA methylation profile.

The impact of smoking on health across the lifespan is relatively known, but the smoking-cognition relationship for individuals at the cusp of midlife is less clear. Examinations of cognitive performance covering the middle-adulthood period are salient, given that this period marks the transition from peak performance to age-associated normative cognitive performance declines, with more pronounced effects seen for domains covering perceptual speed, memory (working and episodic memory), reasoning, and spatial ability (Hartshorne & Germine, 2015; Li et al., 2004; McArdle et al., 2002; Salthouse, 2009; Tucker-Drob, 2019). Verbal ability, alternatively, demonstrates gains across the middle adulthood period into late life (Li et al., 2004; Pahlen et al., 2018; Reynolds et al., 2005; Salthouse, 2009). Smoking behaviors also tend to develop before the occurrence of cognitive aging. Smoking initiation often occurs during adolescence, with later adolescence and early adulthood marking the transition to persistent use (Huggett et al., 2019; Rose et al., 2009). Several cognitive domains that are age-sensitive

tend to also show associations with smoking behavior, with worse performance seen for episodic and working memory, visual search speeds, processing speed, cognitive flexibility, attention and executive functions (Bahorik et al., 2021; Conti et al., 2019; Durazzo et al., 2010; Nadar et al., 2021; Nooyens et al., 2008; Sabia et al., 2012; Swan & Lessov-Schlaggar, 2007). Given the timing of smoking behavior development and the incremental impact smoking may impose on health and aging, cognitive health may be susceptible at earlier ages than originally presumed.

Smoking predicts worse physical health but mechanisms responsible for the smoking-cognitive associations are obscured by other social determinants of health. Social determinants of health include individual, sociological, and environmental factors and structures that contribute to health disparities (World Health Organization, 2019). In particular, socioeconomic status (SES) is of interest because measures such as education influences both cognitive (Lövdén et al., 2020; Ritchie & Tucker-Drob, 2018) and smoking development (Corley et al., 2019; Daly & Egan, 2017; Kubička et al., 2001; Pampel et al., 2014; Silventoinen et al., 2022; Whalley et al., 2005). However not all SES measures are as robustly related to smoking behavior. Past work has shown the inclusion of SES indicators weakens the effect of smoking on cognition (Sabia et al., 2008) with education attenuating the associations more than adulthood occupation or social status (Batty et al., 2007; Corley et al., 2019). When considering different SES indictors, earlier life measures tend to perform better than concurrent measures, thus suggesting that the interrelation between education and smoking behavior emerges before adulthood.

Moreover, early life indictors such as childhood IQ is also predictive of educational attainment and smoking behavior (Corley et al., 2019; Daly & Egan, 2017; Kubička et al., 2001). Thus, we must account for individual factors such as childhood IQ and educational attainment given selection differences can arise within the SES gradient that influence the likelihood of starting smoking, transitioning to persistence use, and successfully quitting. Therefore, our study will include measures of education and earlier life IQ to test whether the associations may be explained by shared factors common to both smoking and cognition.

Other social determinates of health include features about the environment where an individual resides, including in the USA. Notably, health and mortality disparities exist between states (Lochner et al., 2001; Mensah et al., 2005) to geographic regions that vary based on rurality (Couillard et al., 2021; Harris et al., 2016; Singh et al., 2017). Where one lives can speak volumes about the different experiences and exposures individuals have which in turn may shape health expectancies. Given the governance and legislative structure of the United States, public health policies can vary from the federal to city level thereby inducing variation surrounding access and affordability of tobacco products. Public health policies are relevant to our work to explore if political contexts surrounding tobacco use also influences cognitive performance. Smoking behavior inequalities exist across the United States (Boardman, 2009; Drope et al., 2018; Shmulewitz et al., 2016; Studlar, 2002). In particular, the Tobacco Nation represents a constellation of 13 states starting at Michigan and stretching down to Mississippi and representing Midwest and much of the South (Truth Initiative, 2019). These states have

the highest smoking prevalence, above the national average and are on par with nations that report the highest smoking rates in the world.

Public health policies have been successful in reducing smoking behaviors including smoking prevalence, delaying initiation age, and smoking frequency (Farrelly et al., 2014; Farrelly et al., 2008; Hawkins et al., 2016; Wilson et al., 2012). Moreover, reductions in the prevalence of several smoking-linked health conditions including cardiovascular health and lung cancer have followed (Bradley et al., 2016; Gebreab et al., 2015; Jemal et al., 2003; Meyers et al., 2009). In other words, the more public health investments that are made, such as developing initiatives aimed at reducing unfavorable behaviors (e.g., tax increases on cigarettes) the better state constituents tend to fare in health and functioning outcomes. Public health policies are certainly important to understand as it relates to the contextual factors that shape smoking behavior, however there is no current standard metric in the United States to gauge and evaluate policies aimed at tobacco use. Advocacy organizations such as the American Nonsmokers' Rights Foundation has helped to usher in legislation aimed at curbing environmental tobacco exposure and created the only national repository for state and local regulation on smoke-free initiatives (American Nonsmokers' Rights Foundation, 2021). Outside the United States, efforts have been made to create a national Tobacco Control Scale that harmonizes policies that target curbing tobacco use across countries (Joossens & Raw, 2006). The Tobacco Control Scale is scored across 36 European countries and covers several policy domains such as price, advertising, warning labels, and treatment. Using

the framework from the Tobacco Control Scale this study will create a similar measure to capture the variation of control scores across states.

Considering state-level policy control can inform the current investigation on whether current tobacco control impacts the relationship between smoking and cognition. To date, no study has investigated whether the policy environments surrounding cigarette use influences cognitive functioning. We expect it is unlikely concurrent state-level policies alone will have a systematic influence on cognitive performance given policies address tobacco use and would not include general health or education initiatives that also benefits cognitive development. Rather, including control policies will allow us to evaluate if bias exists for participants based on geographic location. Hence, we expect policy scores to moderate the associations between smoking and cognition. More specifically we expect smokers in states with low to minimal tobacco regulations will demonstrate greater deficits on cognitive performance while smokers in states with higher tobacco control score will minimizes the impact of the smoking-cognitive effects. This moderation pattern would be indicative of the policies effectiveness by delaying smoking initiation, reducing cigarette consumption, or increasing quitting at earlier ages thereby reducing the amount of time smoking may impose as a burden to cognitive functioning before midlife.

The current study will examine whether smoking-cognitive associations are observable for adults approaching midlife, an important period when health interventions aimed at smoking cessation may avoid or reduce later health risks (Pirie et al., 2013) and later cognitive functioning and health (Baumgart et al., 2015; Deal et al., 2020;

Livingston et al., 2020; Mons et al., 2013). Past research has generally found chronic smoking to impact cognition negatively, but whether worse cognitive performance is observable before midlife is less clear. Indeed, later life investigations between smoking and cognition cannot determine when smoking might begin to impact cognitive health. Given the age accelerated influences due to smoking behavior, it's important to explore the impacts on cognitive health as normative cognitive declines emerge during middle adulthood. Thus, smoking behavior may be identified as a modifiable health behavior that interventions should target before midlife (Franz et al., 2021; Livingston et al., 2020). The current study will explore the cross-sectional smoking-cognition relationship using CATSLife1 data which represents a sample at the cusp of midlife. We expect to see cognitive-smoking associations with cognitive performance based on prior work. Beyond examining the interrelationship, we will also compare different smoking behavior measures, potentially revealing dosage-dependent (pack years) or timing influences (i.e., smoking status). In other words, if ever smokers tend to show cognitive deficits compared to non-smokers this may suggest the timing for deficits could have emerged prior to the cognitive assessment and indicate the long reach of smoking impacts even for individuals who have quit. Alternatively, suppose cognitive deficits are better captured by proximal use (i.e., current users). In that case, this may indicate that persistent smoking might have an enduring impact on cognitive performance, whereas a recovery period may be evident for former smokers. We will also evaluate the extent to which cardiovascular health, educational attainment, tobacco control policies, and early-life cognitive ability may potentially weaken the associations seen between smoking and cognitive

performance. Thus, we will test whether the smoking-cognitive associations persist even after including other explanatory associations. Moreover, we will test if tobacco control policies modify the interrelation between smoking behavior and cognition potentially revealing broader contextual influences on associations.

Method

Participants

Data were derived from the CATSLife1 study (Wadsworth et al., 2019) which completed data collection efforts between the years of 2018 to 2021. CATSLife1 is the combined follow-up of the Colorado Adoption Project (CAP; Plomin & DeFries, 1983) begun in 1976, and Longitudinal Twin Study (LTS; Rhea et al., 2013) begun in 1984. The complete CAP sample consists of 490 families balanced between adoptive and control families, including 982 probands and their siblings (53 % male; 468 adopted vs. 514 control). The sample of the LTS was drawn both from the Twin Infant Project sample and independent registry recruitment, with a total N in LTS of 483 pairs (male twin pairs: 240; female twin pairs: 243).

The combined CAP and LTS samples include adopted and nonadopted pairs of siblings and same-sex twin pairs. Data collection for both studies started in infancy with follow-ups about every year up to age 16 and with follow-ups approximately every five years through early adulthood, with the current CATSLife1 assessment targeting ages 28-49 years old and an N of 1,323 (M_{age}=33.3, Female=53.1%, 219 adopted individuals, 343 complete twin pairs). Overall, nearly all CATSLife1 participants (N=1,257 or 95.0%) completed at least one cognitive assessment examined in this study. Of the participants

with cognitive data, the analytic sample only included individuals with smoking behavior, cardiovascular health, educational attainment, tobacco control score, and noted covariates (N=1,175, M_{age}=33.2 years, Female=52.9%).

Demographics on race and ethnicity were captured primarily by self-report and refined by parent reports and GWAS genotyping for some adopted individuals. The analysis sample is primarily White (92.1%), with about 7.9% of the sample coded as non-white for American Indian/Alaska, Asian, Black, Native Hawaiian, Pacific Islander, multiracial, and unknown/not reported. About 92.3% of the analysis sample are Non-Hispanic.

Measures

Cognitive Functioning

Seven cognitive tests were used in this study. Three tasks were adopted from the Hawaii Family Study of Cognition protocol (DeFries et al., 1981; Wadsworth et al., 2019): 1) Names and Faces [sum score of total correct across immediate and delayed], 2) Picture Memory [sum score of total correct across immediate and delayed], and 3) Colorado Perceptual Speed [sum score of total correct across, adjusting for errors]. Additionally, an IQ battery was given from the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III; Wechsler, 1993) and we make use of four subtests, e.g., Vocabulary, Digit Span, Block Design, and Digit Symbol. All WAIS-III cognitive scores used were the original point scores for the given subtest rather than the scale scores. Across the seven cognitive tasks, 5 specific cognitive ability domains are represented: 1) Episodic Memory: Picture Memory (PM) and Names and Faces (NF), 2) Working

Memory/Attention: Digit Span (Dspa), 3) Perceptual Speed: Colorado Perceptual Speed (CPS) and Digit Symbol (DSy), 4) Spatial Reasoning: Block Design (BD) and 5) Verbal: Vocabulary (V). All cognitive test scores were standardized to a t-score scale (*M*=50, *SD*=10).

Smoking Behavior

Smoking Status. Smoking behavior was self-reported and followed the PhenX protocol (Hamilton et al., 2011). Smoking status included three categories: non-smokers, former smokers, and current smokers. Non-smokers was defined as those that did not smoke at least 100 cigarettes. Former and current smokers were those who smoked at least 100 cigarettes but either do not currently smoke (former) or do smoke at least some days (current). To allow for further examination of smoking status, an additional category was created for ever smoker by combining former and current smokers.

Pack Years (PKYRS). CATSLife1 includes measures of smoking consumption (i.e., how many cigarettes an individual report smoking on average). Smoking duration was derived from the age difference when an individual reported smoking fairly regularly and their current age for current smokers or the last age when they last used tobacco for former smokers. Pack years (PKYRS) is then calculated by first finding the number of packs a person smokes per day, i.e., the number of cigarettes a person reports smoking divided by 20, the standard cigarette pack size. The daily pack consumption total is then multiplied by the duration in years. The pack-year score indexes the maximum smoking exposure an individual has experienced and tests for a dosage-dependent effect. To adjust for skew, pack years was log-transformed.

Years of Education

Participants self-reported educational attainment in CATSLife; adopted from the CAP protocol, participants were asked, "What is the highest year of school you have completed?" and selected one of 10 different categories ranging from less than a high school diploma or GED to Advanced degree (e.g., doctorate, M.D., law degree). Year equivalents were then mapped to the International Standard Classification of Education (ISCED; UNESCO, 1997) based on the theoretical years of completion that best matched the 7 distinct levels outlined in the ISCED: "Less than high school diploma or GED" =11 yrs, "high school or GED" =12 yrs, "one year college" =13 yrs, "two years (Associate of Arts)" =14 yrs, "three years [4-year college]" =15 yrs, "four years [4-year college], no degree" =15.5 yrs, "five years or more [4-year college], no degree" =15.5 yrs, "bachelors" =16 yrs, "masters" =18 yrs, "Advanced degree (e.g., doctorate, M.D., law degree)" =20 yrs. ISCED mapping also accounted for participants who were active students at the time of collection but did not yet receive their degree: "one year college" and attending a trade school=12.5, "three years" and attending a trade school=12.5 yrs, "three years" and attending a 2-year college=13.5 yrs, "bachelors" and attending graduate school=17 yrs, "masters" and attending graduate school=19 yrs.

Lastly, archival educational attainment data for CAP participants that completed the yearly study of Nature and Nurture in Social Demography (NNSD) between ages 21 and 25 was compared with current educational attainment reported during CATSLife1 (McClelland et al., 2013). As the NNSD data included the same educational attainment question but also included the type of school the individual was actively attending or

previously attended, the school type could then be referenced to further refine years of education for those that had ambiguous duration noted (i.e., years noted but no degree). Overall, there were 22 participants whose years of education assignment were updated based on the combination of NNSD archival responses and CATSLife1 concurrent responses.

Years of education was centered on 16 years or the equivalent of a bachelor's degree.

State-Level Tobacco Control Score (TCS)

A tobacco control score (TCS) was created across states in the USA to index the level of smoking control policies within the USA by the year 2018 (see Figure 1.1). Only 3 states are not scored as no CATSLife1 participants reside in those locations: Alabama, Missouri, and Vermont. Utilizing the Framework of Convention on Tobacco Control (FCTC) developed by the World Health Organization, policy-specific legislation was scored by state according to the 2019 version of the Tobacco Control Scale (Joossens et al., 2019; Joossens & Raw, 2006) within domains of price (30 points), smoke-free (22 points), advertising bans (13 points), and warning labels (10 points) for a total (75 points); higher scores indicating greater levels of tobacco control. TCS was then scaled to 100 points to represent the percent of tobacco control coverage (i.e., a raw score of 30 would mean a 40% compliance to the TCS scale scored).

Domains not included due to lack of publicly available information across all states were health insurance coverage aimed at supporting cessation/treatment programs, interstate illicit tobacco trade, public information campaigns spreading awareness on the

hazards of tobacco use, legislation on preventing tobacco industry lobbying interference, and ratifying to the WHO FCTC future recommendations. Although these policy domains, are important when considering policies focused on decreasing initiation rates (e.g., public campaigns) or increasing cessation (e.g., insurance), would require policy experts to validate these specific measures adequately. For example, state-level insurance policies would require examining specific health insurance policies that vary by state, with coverage options also varying based on the individual's employer. For a fuller description of domain scoring see supplemental materials in Appendix 1. Additionally, supplemental Tables S1.1-3 show state-level scoring per policy domain.

Cardiovascular Function

Cardiovascular Status. Participants self-reported ever experiencing heart problems and ever having a stroke. Scores ranged from 0 to 2 maximum possible score.

Mean arterial Pressure. Systolic and diastolic blood pressure was measured three times at one-minute intervals using a digital BP monitor (Omron IntelliSense machine HEM-907XL). Mean arterial pressure was calculated by adding systolic to twice the diastolic pressure, then divided by 3.

Year 12 IQ: Sensitivity Analysis

The year 12 cognitive assessment included WISC IQ was assessed for both CAP and LTS, but studies differed in the test version administered. The CAP study administered the WISC-R (Wechsler, 1974) and LTS administrated the WISC-III (Wechsler, 1991). Version slightly differed between projects, however the IQ scale scores

were based on the same subtests. In total, the sensitivity analysis included *N*=922 (CAP=349, LTS=573).

Covariates

Several covariates were included in these analyses: age, mean centered at 33.28 years, sex (0=F, 1=M), project (0=CAP, 1=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Hispanic, 1=Non-Hispanic), and race (0=Non-White, 1=White).

Statistical Analysis

Multilevel models were fitted using PROC Mixed in SAS 9.4 (SAS Institute Inc, 2016) to evaluate the associations of smoking behavior with cognitive performance. Full-information maximum-likelihood was used. All models accounted for clustering by siblings and sibling type (i.e., adoptive family siblings, control family siblings, monozygotic and dizygotic twins) and estimated separate random effects for the between (σ^2BW) and within (σ^2WI) siblings. Intraclass correlations (ICCs) were then found to index sibling similarity. They were calculated as the proportion of between effect (σ^2BW) over the sum of the between (σ^2BW) and within effect (σ^2WI) by family type. All models accounted for covariates, including age, project, sex, adopted status, Non-Hispanic ethnicity, and race.

Overall, nine separate models were fitted to evaluate the influence of smoking behavior on cognitive performance. First, Model 1 included all covariates as predictors of the cognitive performance outcome. Next, Models 2-4 added one smoking behavior measure, i.e., (2) Ever, (3) Current, or (4) PKYRS. To assess the model fit between the

models that varied on smoking measures included, we used the chi-square difference test where the current model was compared to the nested base Model 1. A significant difference in the chi-square for the 1 df test suggested improvement in fit with the inclusion of the specific smoking variable. To compare models 2-4 with the same parameters, we used the Akaike Information Criterion (AIC), where the preferred model was the model with the lowest possible values (Beal, 2007). If Models 3 and 4 were each found to be significant, we next tested Model 5, entering both Current smoking and PKYRS to see if including both improved model fit. To evaluate the fit of Model 5, this model was compared to Model 3 or 4, whichever had the lowest AIC. If Model 5 did not show a significant improvement in fit, then the model with the lowest AIC from Models 2-4 was selected. For example, if Model 5 was a nonsignificant improvement in fit and Model 3 (i.e., Current smoking) had the lowest AIC, this smoking measure was included in Models 6-9.

Once the model with the best smoking behavior measure(s) was found, Models 6-8 further tested whether including concurrent CVD indictors (Model 6), years of education (Model 7), and state-level tobacco control policy (Model 8) mediated or attenuated the smoking effect on cognitive performance. Lastly, Model 9 tested whether there were possible disparities between smoking behavior and cognitive performance based on location. Under this model, we tested to see if state-level TCS moderated smoking behavior.

Although we included years of education in the model to review possible attenuation of smoking behavior with an SES indicator, we also included sensitivity

analyses to examine possible developmental differences in earlier IQ and later smoking. Sensitivity analysis included year 12 IQ to account for earlier cognitive differences and was added to the best fitting model with a smoking measure. That is, individuals with lower IQ may be at risk for later smoking, and the association found between smoking behavior and adult cognitive performance may represent group differences in individuals at greatest risk for smoking rather than smoking influencing cognition.

Results

Descriptive Statistics

Most of the CATSLife1 sample were non-smokers or had never smoked more than 100 cigarettes (63.2%). About 20.9% of the sample were former smokers, and 15.9% were current smokers. Ever-smokers, on average, tend to have about 7.0 (*Mdn*=5.0, *SD*=7.0, skew=1.9) PKYRS, which is equal to smoking about half a pack of cigarettes (9.9) a day and smoking for 12.9 years. PKYRS was log-transformed to adjust for skew (*M*=1.7, *Mdn*=1.8, *SD*=0.85, skew=0.1). Note that since non-smokers scored a zero for PKYRS, 1 point was added all scores to allow for transformation. See Table 1.1 for full sample descriptives for each cognitive and smoking measures.

All smoking behavior measures were significantly correlated with each cognitive task except for Digit Span (see Table 1.2). All associations were weak in magnitude and negative in direction, suggesting those with smoking experience (i.e., ever and current status) or those with greater smoking exposure (i.e., PKYRS) tend to show worse cognitive performance. The processing speed tasks showed the strongest association (*r*s=-.18, -.25, $p<<.0001$), with Picture Memory showing the lowest significant association

(*r*s=-.07, -.12, *p*<<.0001). Generally, PKYRS showed stronger associations with the cognitive tasks compared to the smoking status measures. For two tasks, current smoking was more strongly associated: Block Design (*r*=-.20, *p*<<.0001) and Vocabulary (*r*=-.17, *p*<<.0001). There was no association between TCS and any cognitive tasks.

Multilevel Regression Analyses

Episodic Memory (Picture Memory [PM], Names and Faces [NF])

Three smoking behavior measures were tested to evaluate the differential associations between measures with episodic memory. Table 1.3 (Picture Memory) and Table 1.4 (Names and Faces) show fixed, and random effects parameters and model fit statistics for Models 2-9 [M2-M9]. The base model (M1), not shown, includes just the baseline covariates. The first three models included (M2) ever smoking, (M3) current smoking, and (M4) PKYRS. Each smoking behavior measure was significantly associated with each episodic memory task. Smoking status measures had a small to moderate effect size across the tasks (Cohen's *d*=-.15-[-].30). Current smoking (B_{PM}=-1.89, *SE*= 0.81, *p*=.02; B_{NF}=-3.00, *SE*=0.79, *p*=.0002) was more strongly associated with episodic memory compared to ever smoking (B_{PM}=-1.54, *SE*= 0.62, *p*=.014; B_{NF}=-1.93, *SE*=0.61, *p*=.002). Across both tasks, the effect of PKYRS on episodic memory performance was very similar with Picture Memory score reduced by approximately B_{PM}=-1.07 (*SE*=.31, *p*<.001) and Names and Faces score reduced by B_{NF}=-1.09 (*SE*=.31, *p*<.001) points per log PKYRS. In other words, for those reporting the most amount of smoking or reporting around 4 log-PKYRS (i.e., about 53.6 pack years), their Picture Memory performance score was 4.28 or 0.43 *SD* points lower. When testing whether,

including an additional smoking measure in the model (i.e., current smoking and PKYRS; M5), Picture Memory resulted in a worse fit when compared to only including PKYRS (M4 vs. M5; $\chi 2(1)=0.5$, $p=.48$). Names and Faces did show an improved model fit when current smoking and PKYRS were both modeled (M3 vs M5; $\chi 2(1)=5.6$, $p<0.018$) and the lower AIC=8633.8, suggesting both current smoking (B=-2.13, *SE*=0.90, $p=.018$) and PKYRS (B=-.069, *SE*=0.35, $p=.049$) significantly and uniquely contributed to performance for Names and Faces.

The next series of analyses evaluated whether smoking behavior associations remained after including other potential explanatory variables. The best fitting model with a smoking measure, M6, included concurrent cardiovascular health (i.e., CVD and MAP). Across both tasks, cardiovascular health was not associated with episodic memory. Next, M7 included years of education (EDU_{yrs}) in the model. For both tasks, EDU_{yrs} attenuated the association but smoking behavior (current and PKYRS) was reduced to nonsignificance only for Names and Faces. Follow-up analyses (not shown in table) to examine whether a more parsimonious model would show the same pattern of attenuation with EDU_{yrs} was tested; models with only current smoking (B=-1.57, *SE*= 0.80, $p=.051$) or PCKYRS (B=-0.33, *SE*= 0.33, $p=.31$) failed to reach significance when EDU_{yrs} was included. No association with episodic memory was found when TCS was included (M8), and smoking behavior was not moderated by TCS (M9).

Working Memory (Digit Span [DSpa])

The model parameters and fit statistics for working memory can be found in Table 1.5. Smoking behavior was found to be nonsignificant across all measures, with

ever smoking showing positive, near-zero associations (B=0.07, *SE*=0.62, *p*=.59) and negative associations with current (B=-0.43, *SE*=0.80, *p*=.91) and PKYRS (B=-0.31, *SE*=0.31, *p*=.32). No model with a smoking measure included significantly improved model fit. Thus, no additional models were performed since smoking behavior was not significantly associated with working memory.

Processing Speed (Colorado Perceptual Speed [CPS], Digit Symbol [DSy])

Three smoking behavior measures were tested to evaluate the differential associations between measures with processing speed. Table 1.6 (Colorado Perceptual Speed) and Table 1.7 (Digit Symbol) shows fixed and random effects parameters and model fit statistics for models 2-9. The base model (M1), not shown, includes just the baseline covariates. The first three models included (2) ever smoking, (3) current smoking, and (4) PKYRS. Each smoking behavior measure was significantly associated with each processing speed task. Smoking status measures had a small to moderate effect size across the tasks (Cohen's *d*=-.24-[-].46). Current smoking (B_{CPS}=-3.84, *SE*= 0.77, *p*<.0001; $B_{DSy=}$-4.57, *SE*=0.75, *p*<.0001) was more strongly associated with processing speed compared to ever smoking (B_{CPS}=-2.35, *SE*= 0.60, *p*<.0001; $B_{DSy=}$-3.26, *SE*=0.58, *p*<.0001).

Processing speed performance was reduced by approximately B_{CPS}=-1.47 (SE_{CPS}=0.30, *p*<.0001) to B_{DSy}=-1.91 ($SE_{DSy=}$0.29, *p*<.0001) points per log packyear. In other words, for those reporting the most amount of smoking or reporting around 4 log-PKYRS (i.e., about 53.6 pack years), their Colorado Perceptual Speed performance score was 5.88 or 0.59 SD points lower. Similarly, Digit Symbol shows worse performance as

pack years increased with those reporting 4 log-PKYRS evidencing a reduced score of 7.64 points (Cohen's *d*=-.76). Including an additional smoking measure (i.e., current smoking and PKYRS; M5) resulted in a better fit when compared to a model only including pack years (M4 vs. M5) for both Colorado Perceptual Speed ($\chi 2(1)=9.2$, $p=.002$) and Digit Symbol Speed ($\chi 2(1)=11.6$, $p<.001$). Based on model fit comparisons, M5 was the best fitting model suggesting both current smoking (B_{CPS}=-2.67, SE_{CPS}=0.87, $p=.002$; B_{DSy}=-2.91, SE_{DSy}=0.84, $p<.001$) and pack years (B_{CPS}=-0.97, SE_{CPS}=0.34, $p=.004$; B_{DSy}=-1.37, SE_{DSy}=0.33, $p<.001$) significantly and uniquely contributed to performance for processing speed.

After selecting the best fitting model with a smoking measure, then M6 entered concurrent cardiovascular health (i.e., CVD and MAP). Across both tasks, cardiovascular health was not generally associated with processing speed, except for MAP on Colorado Perceptual Speed. Next, M7 included EDU_{yrs} in the model. For both tasks, EDU_{yrs} attenuated the association with smoking behavior with EDU_{yrs} weakening the association by about a third of the previous effect size. Under model 7, PKYRS (B_{cps}=-0.30, *SE*= 0.35, $p=.38$; $B_{DSy=}$-0.57, *SE*=0.34, $p=.09$) was no longer significant. No association with processing speed was found when TCS was included (M8), and smoking behavior was not moderated by TCS (M9).

Spatial Reasoning (Block Design [BD])

Three smoking behavior measures were tested to evaluate the differential associations between measures with spatial reasoning. Table 1.8 shows fixed and random effects parameters and model fit statistics for Models 2-9 (M2-M9). The base model

(M1), not shown, includes just the baseline covariates. The first three models included (2) ever smoking, (3) current smoking, and (4) PKYRS. Each smoking behavior measure was significantly associated with worse spatial reasoning. Smoking status measures had a small to moderate effect size across the tasks (Cohen's *d*=-.25-[-].46). Current smoking (B_B=-4.58, *SE*= 0.75, *p*<.0001) was more strongly associated with spatial reasoning compared to ever smoking (B_B=-2.52, *SE*= 0.58, *p*<.0001). Spatial reasoning performance was reduced by approximately 1.22 (*SE*=.30) points per log packyear. In other words, for those reporting the most amount of smoking or reporting around 4 log-PKYRS (i.e., about 53.6 pack years), their spatial reasoning performance score was 4.88 or 0.49 SD points lower. Including an additional smoking measure in the model (i.e., current smoking and PKYRS; M5) for Block Design showed a significantly better fit when compared to only including pack years (M4 vs. M5; $\chi 2(1)=21.3$, *p*<.001). However, M5 was not significantly different compared to only modeling current smoking (M3 vs. M5; $\chi 2(1)=2.3$, *p*=.129). Thus, the best performing model based was M3 with only current smoking.

After selecting the best fitting model with a smoking measure, Model 6 examined whether concurrent cardiovascular health (i.e., CVD and MAP) attenuated the association between smoking behavior and spatial reasoning. Cardiovascular health was not associated with spatial reasoning, and the estimated parameter for current smoking remained fairly consistent, albeit a bit smaller. Next, M7 included EDU_{yrs} in the model. Current smoking was attenuated when EDU_{yrs} were included (B_B=-3.55, *SE*=0.77, *p*<.0001) but remained significant, suggesting partial attenuation with EDU_{yrs}. No

association with spatial reasoning was found when TCS was included (M8), and smoking behavior was not moderated by TCS (M9).

Verbal Ability (Vocabulary [V])

Three smoking behavior measures were tested to evaluate the differential associations between measures with verbal ability. Table 1.9 shows fixed and random effects parameters and model fit statistics for Models 2-9 (M2-M9). The base model (M1), not shown, includes just the baseline covariates. The first three models included (2) ever smoking, (3) current smoking, and (4) PKYRS. Each smoking behavior measure was significantly associated with verbal ability, with smoking status measures evidencing a small to moderate effect size (Cohen's *d*=-.22-[-].33). Current smoking (B=-3.25, *SE*= 0.72, *p*<.0001) was more strongly associated with verbal ability compared to ever smoking (B=-2.21, *SE*= 0.56, *p*<.0001). Verbal ability performance was reduced by approximately 1.35 (*SE*=.28) points per log packyear. In other words, for those reporting the most amount of smoking or reporting around 4 log-PKYRS (i.e., about 53.6 pack years), their vocabulary performance score was 5.4 or 0.54 SD points lower. Including an additional smoking measure in the model (M5) showed an improved model fit when current smoking and PKYRS were both modeled ($\chi 2(1)=6.5$, $p=0.01$) and the lowest AIC=8412.6, suggesting both current smoking (B=-2.08, *SE*=0.81, *p*=.01) and pack years (B=-.99, *SE*=0.31, *p*=.002) significantly and uniquely contributed to performance for verbal ability performance.

M6 then examined whether concurrent cardiovascular health (i.e., CVD and MAP) attenuated the association between smoking behavior and verbal ability. CVD was

associated with Vocabulary (B=-2.27, *SE*=1.03, *p*=.03) but smoking behavior associations remained consistent ($B_{current}$=-2.07, *p*=.01; B_{PKYRS}=-1.01, *p*=.001). Next, M7 included EDU_{yrs} in the model. EDU_{yrs} attenuated the association with smoking behavior, with EDU_{yrs} weakening the association by about a half of the previous effect size for current smoking (B=-1.06, *SE*=0.77, *p*=.17) and about 90% for PKYRS (B=0.11, *SE*=.30, *p*=.72), neither effect remained significant. No association with Vocabulary was found when TCS was included (M8), and smoking behavior was not moderated by TCS (M9).

Sensitivity Analyses

Sensitivity analyses were conducted to examine whether random effects differed by state compared to between and within sibling type. ICCs were consistent in pattern across all sibling types ranging from near zero for siblings in adopted families to 68% among MZ siblings. State-level random effect accounted for at most 3.69%, suggesting clustering by sibling type was a more robust estimation for random effects between participants rather than state residence.

Additional sensitivity analyses were conducted to examine whether the association between smoking behavior and cognitive performance was derived from developmental cognitive differences. Parameter estimates and model fit indices are shown supplemental Table 1.4 in Appendix 1. Year 12 full scale IQ (FSIQ) was included in the selected smoking model for each cognitive task with the baseline covariates. For example, the best smoking model for Picture Memory included only PKYRS, while Names and Faces included both current smoking and PKYRS. The inclusion of year 12 IQ did not fully attenuate the smoking behavior association with cognition except for

Names and Faces. Further review was done with Names and Faces to examine whether the inclusion of two smoking measures in the model contributed to the reduced effect size. Two subsequent models only included one smoking measure at a time. Current smoking (B_{NF}=-2.15, SE=0.85, p=.01) and PKYRS (B_{NF}=-0.91, SE=0.34, p=.008) were significant in these more parsimonious models (not depicted). Overall, smoking behavior remained salient after including year 12 IQ suggesting the associations found between cognitive performance and smoking behavior are not attributable only to early developmental differences.

Discussion

The current study examined whether smoking is associated with worse cognitive performance for an adult sample approaching mid-life. Across all cognitive domains except for working memory, smoking behavior was associated with worse cognitive performance. The specific smoking behavior measure(s) associated vary by task with at least one smoking measure (i.e., current smoking and/or pack years). Moreover, the smoking behavior associated with each cognitive measure suggests meaningful differences in the degree of the smoking effect. For example, current use showed the largest effects of lower performance across all cognitive domains. For all tasks excluding Names and Faces, current smoking with the inclusion of pack years provided additional incremental contribution indexed by dosage. Pack years was solely associated with Picture Memory. Effects remained after controlling for cardiovascular health. Associations seen for Names and Faces and Vocabulary were no longer significant after including educational attainment, and attenuation was seen in the other cognitive tasks

ranging from a drop of 12% to 26% for smoking measures that remained significant. Lastly, current state-level tobacco control policies or early life intellectual differences did not influence the smoking-cognitive associations.

We found that the most pronounced effects appeared for processing speed and spatial reasoning. Our findings generally agree with past research that has found worse cognitive performance linked with smoking behavior among midlife and later-life adults (Bahorik et al., 2021; Conti et al., 2019; Durazzo et al., 2010; Lewis et al., 2021; Nadar et al., 2021; Starr et al., 2007; Swan & Lessov-Schlaggar, 2007). For example, among midlife adults, processing speed showed the strongest association with smoking behavior at baseline compared to memory function and global cognitive ability (Nooyens et al., 2008). Across all the domains assessed, processing speed is one of most robust findings with few studies failing to find significant differences with smoking behavior (Deal et al., 2020; Razani et al., 2004; Swan et al., 1992). Spatial reasoning tasks are often less assessed but past work has generally evidenced negative relations with smoking behavior (Glass et al., 2006; Hill et al., 2003; Kasl-Godley, 1996; Vermeulen et al., 2018) but inconsistency is more prevalent for this task compared to processing speed as some studies have not found associations (Durazzo et al., 2012; Fried et al., 2006; Meier et al., 2012; Starr et al., 2007).

We observed associations showing worse performance among current smokers and episodic memory, which aligns with observational work for middle-aged adults (Bahorik et al., 2021; Durazzo et al., 2012; Paul et al., 2006; Sabia et al., 2008) or across the lifespan (Lewis et al., 2021). Further, our evidence is consistent with meta-analytic

work of long-term memory where performance benefits were accrued to non-smokers (Conti et al., 2019). However, we found education attenuated associations with Names and Faces, but not for Picture Memory. Names and Faces is far more demanding as a memory binding task (James et al., 2008; Troyer et al., 2011) where participants are to freely recall names matched with faces from yearbook photos previously shown. Although this task represents a common real-world application of episodic memory, encoding and retrieval processes may differ between these tasks (Kremen et al., 2014; Mechie et al., 2021; Panizzon et al., 2015). In addition, education may help confer individual strategies that would directly impact performance that wouldn't be as readily apparent for Picture Memory which may rely on more recognition from simplified visual cues (Baadte & Meinhardt-Injac, 2019; Cohn et al., 2008; Hockley, 2008; James et al., 2008). In addition, associations of smoking and episodic memory for middle-aged adults find mixed results on the timing when smoking effects were found, where recall memory was unassociated with smoking at baseline but associated with subsequent decline (Nooyens et al., 2008). In a study examining class trajectories across 10 years separately for middle and older adults found current smoking was associated with less cognitive maintenance across time for both age groups (Olaya et al., 2017). Similarly, research using older adults found individuals older than 75 years old and smoke tends to influence only the rate of decline in memory but not level (Reitz et al., 2005). Thus, our findings prior to midlife, are nuanced suggesting that some effects may be present prior to midlife beyond education but further follow-up is warranted.

We did not find associations with Digit Span within this study. However, the measure captures both abilities of attention (Digits Forward) and short-term/working memory (Digits Backwards), which may have non-complementary associations with smoking behavior when the two subtests are combined (Castellanos-Ryan et al., 2017; Paul et al., 2006). Prior research has shown no significant difference in performance between middle-aged and older adult smokers and non-smokers for the Digit Span task (Razani et al., 2004), which was later replicated for young adults (Fried et al., 2006). In addition, one small younger adult sample of English university students showed evidence of worse working memory as measured by only Digits Backwards (Heffernan et al., 2014). A meta-analysis examining short-term memory and attention found negative associations with smoking behavior but with more pronounced effects on tasks representing working memory (Conti et al., 2019). Although working memory tends to show more robust effects than attention, the smoking-related associations are not always consistent, and age and measurement seem to play an important role. For example, the effects of smoking on working memory are often stronger and more consistently found in the N-back test (Ernst et al., 2001; Greenstein & Kassel, 2009; Jacobsen et al., 2005; Jacobsen et al., 2007; Mahedy et al., 2018; Mendrek et al., 2006) than the Digits Backwards task (Castellanos-Ryan et al., 2017; Conti et al., 2019; Fried et al., 2006; Heffernan et al., 2014; Lo et al., 2014; Nadar et al., 2021; Paul et al., 2006; Razani et al., 2004).

Notably, we found smoking associations with Vocabulary, considering that all the other tasks tend to represent more age-sensitive or fluid-type tasks (Horn & Cattell,

1967). Even though we did find associations with Vocabulary, these associations did not remain after adjusting for education, which has been observed previously (Batty et al., 2007; Sabia et al., 2008). Of the cognitive tasks, Vocabulary represents a task that may be more responsive to schooling, with gains continuing across the lifespan. The importance of early life influence of education and engagement in cognitive enriching activities, such as reading, is generally evident for Vocabulary. This measure has even been used as a proxy to capture cognitive reserve (Jones et al., 2011; Stern, 2009). Briefly, cognitive reserve is a measure of underlying "reserves" or early life experiences or resources that enable an individual to flourish cognitively. These earlier established reserves may allow an individual to bypass insults associated with cognitive aging (e.g., declines in performance) that would otherwise be observable.

We did find a status effect where associations are highest for current smokers compared to ever smokers. The higher status effect may align with findings from a study using the same CATSLife1 sample, where a persistent smoking indicator had larger effects with several physical health measures than a frequency measure (Ross et al., 2022). The combination of worse incremental performance by pack years and the additional effect for current users suggests there may be neurotoxic dosage effects that are more fully appreciable for current users. To say it another way, there appears to be a dosage effect that captures the combination of consumption and duration for those who ever smoked, including former smoking, on worse cognitive performance. Still, dosage does not solely capture the associations, and individuals who currently smoke further contribute to differences in cognitive ability. This finding may be due to a potential

recovery period for former smokers, where if matched on pack years, current users would show worse effects compared to former smokers. Indeed after controlling for pack years, former smokers have shown higher cognitive scores than current smokers, with a greater degree of difference as the years since cessation increased, suggesting a recovery for former smokers that were 65 years and older (Mons et al., 2013). Similarly, a study examining middle-aged adults found former smokers were not significantly at risk for worse cognitive functioning (Bahorik et al., 2021). Moreover, smoking in greater amounts was more strongly associated with cognitive decline than status alone.

The benefits of quitting smoking are intuitive, but our observations might not be completely due to recovery. Rather, worse cognitive performance by persistent users may indicate other individual differences in education or cognitive ability. Individuals with higher intellectual ability or educational attainment are more likely to quit smoking (Elwood et al., 1999; Johnson et al., 2009; Johnson et al., 2011). Additionally, those with higher educational attainment might have higher SES conditions that increase affordances to enriching environments that contribute to higher cognitive performance (Lövdén et al., 2020; Ritchie & Tucker-Drob, 2018) and increase the likelihood for those who smoked to quit successfully (Agaku et al., 2020; Garrett et al., 2014; Hill et al., 2014; van Wijk et al., 2019). Results showed that educational attainment completely weakened the effect of pack years across the board, except for Picture Memory, where educational attainment was not independently significant. Attenuation patterns may suggest individual differences contributing to the cognitive difference rather than recovery for former smokers. Thus, any effect from usage, especially from ex-smokers, is no longer seen

because ex-smokers may have a higher cognitive score. However, we repeated the analyses with year 12 IQ and found our effects were generally replicated, although attenuated, suggesting that the associations were not fully attributable to intellectual differences. Additionally, the attenuation observed could be a mixture of a timing effect between smoking duration indexed in pack years and educational attainment measured by years of education. The underlying cause for the attenuation patterns is unclear. Still, cessation-induced recovery, individual differences between former and current smokers, or a timing effect may mutually contribute to the patterns.

The risk smoking imposes on health may contribute to our findings. For example, smoking can influence cardiovascular health via increased inflammation and oxidation of low-density lipoprotein cholesterol (Ambrose & Barua, 2004). When smoking impacts this health pathway, this could be a mechanism that leads to changes in brain development and cognitive functioning. For example, oxidation stress via the elevated carbon monoxide within cigarette smoke can exacerbate cerebrovascular disease and cerebral hypoxia (Durazzo et al., 2010; Lahousse et al., 2015). Smoking behavior might contribute to accelerated brain aging that might have occurred prior to midlife. Work from Linli et al., (2022) found that current smokers tend to have brains that are 1.2 years older relative to their chronological age, and the brain age mediated the associations between smoking status and poorer cognitive performance. Causal evidence has been found using mendelian randomization methods for neurological outcomes and brain aging with smoking exposure (Logtenberg et al., 2021; Treur et al., 2021; Whitsel et al., 2022).

An alternative explanation for the smoking-cognitive associations we can't exclude entirely may be related to differential socioeconomic conditions that link smoking behavior and educational attainment (Ferraro et al., 2016; Pollitt et al., 2005). For example, individuals that are more likely to smoke may also experience worse socioeconomic conditions that likewise are associated with worse educational attainment (Cavelaars et al., 2000; Ferraro et al., 2016; Johnson et al., 2009; Pollitt et al., 2005) or that smoking behavior causally influences educational attainment but not cognition (Gage et al., 2022). Indeed, a large genome-wide association study of over one million individuals found genetic covariance of tobacco use with educational attainment, suggesting overlapping genetic influences (Liu et al., 2019). The links between education and smoking behavior may also arise from shared personality risks that increase the likelihood of smoking and attaining less education. For example, individuals with higher smoking polygenic scores were associated with worse educational attainment, outside phenotypic smoking behavior, suggestive of disinhibition partially connecting the two (Hicks et al., 2021). Further, higher impulsivity was also linked with smoking behavior found in a meta-analytic study (Conti et al., 2019).

Beyond examining how educational attainment alters the smoking-cognitive associations, we also sought to explore how the broader ecological context, such as contemporary tobacco control policy, may influence the smoking-cognitive effects. Overall, our study did not reveal that state-level tobacco control policy weakens the associations, nor did control policy moderate the smoking-cognitive associations. Thus, no support was found that the effects were attributable to a larger contextual factor of

state-level involvement in tobacco policy or that smoking effects were more pronounced for states with less policy action. Even though past work examining public health initiatives is suggestive of the benefits of implemented policies, especially for smoking-linked health conditions (Bradley et al., 2016; Gebreab et al., 2015; Jemal et al., 2003; Meyers et al., 2009), no study to date has examined how smoking control policies may influence cognitive health. However, we cannot completely rule out if control policies influence the smoking-cognitive effects across any age or cohort. Our study covers adulthood up to midlife (28-49 years), a period when cognitive decline begins to emerge for age-sensitive abilities (Hartshorne & Germine, 2015; Li et al., 2004; McArdle et al., 2002; Reynolds et al., 2005; Salthouse, 2009; Tucker-Drob, 2019). However, cognitive performance during this period typically will not reach functional declines that meet criteria for impairment or neurocognitive disorders such as dementia (Livingston et al., 2020; Tucker-Drob, 2019). Notably, a single measure of episodic memory, Names & Faces, evidenced an effect size of some note for tobacco control score by current smoking albeit not achieving significance (B=0.20, *SE*=0.10, *p*=.052). Names and Faces represents a cognitive domain that tends to reach plateaus in performance at earlier ages, around adolescence to mid-adulthood, compared to the other domains in the study (Hartshorne & Germine, 2015; Mechie et al., 2021; Thaler et al., 2013), and tends be relatively stable over adulthood with declines in later adulthood (Schaie, 1994). This trend finding may indicate policy measures could contribute to smoking-related effects on cognitive aging, but the current sample's age is too young to capture those deficits. Therefore, it is unclear if control policies saliency will function at ages with greater risk

of cognitive impairment and neurocognitive disorders. Likewise, contemporary policy scores will not capture the tobacco control climate before individuals start smoking. In particular, adolescence marks a period of dynamic growth and maturation for cognition (Fuster, 2002; Hartshorne & Germine, 2015; Mechie et al., 2021; Ricker et al., 2018; Romine & Reynolds, 2005; Thaler et al., 2013; Tucker-Drob, 2019; Wierenga et al., 2014) that also coincides when individuals often start smoking (Dutra et al., 2017; Fuemmeler et al., 2013; Huggett et al., 2019). Thus, future work could explore whether policies before adolescence that target smoking initiation processes influence the smoking-cognitive associations before midlife or if adulthood policies as assessed in this study, impact the likelihood of later cognitive dysfunction via increasing cessation rates.

Although this study provides insight into the influence of smoking behavior on cognitive performance, there are some limitations we must outline. First, given that the study is cross-sectional, there is limited causal inference one can glean from this work. Longitudinal work is needed to examine the smoking-cognitive functioning relationship further. We also do not know how context may influence smoking and cognition relationship, such as individual differences that inked with the propensity to smoke and lower cognitive functioning. Although we controlled for earlier life IQ, there may be other factors (e.g., personality) that could be important individual differences to consider. Second, the cognitive tasks we tested in this study represent important cognitive aging domains except for verbal ability, which has previously been shown to be associated with smoking behavior (Durazzo et al., 2010). Moreover, these tasks do not capture all cognitive domains that may be negatively associated with smoking behavior, such as

verbal fluency (Sabia et al., 2008), or other hierarchical cognitive domains including executive functioning (Amini et al., 2021) or general IQ (Mons et al., 2013; Wennerstad et al., 2010; Whalley et al., 2005). Lastly, individuals who smoke also tend to drink, and thus, there may mutual influences of smoking and alcohol use on brain health (Cardenas et al., 2020; Elbejjani et al., 2019), which may have later impacts on cognitive health (Anstey et al., 2009; Livingston et al., 2020). Smoking influences on brain age can be independently found outside of alcohol or the interaction between the two substances by early midlife (Whitsel et al., 2022). Although the impact of smoking influence on brain age may emerge separately from alcohol use, future research should explore whether there exist a possible synergic influence of smoking behavior and alcohol use to better capture polysubstance use.

This study examined the smoking-cognitive relationship before midlife, a time period scarcely represented in the cognitive aging literature. Our findings suggest that smoking-related associations may influence cognitive performance before later life. Notably, we found these associations since this period is when normative cognitive aging starts to emerge (Hartshorne & Germine, 2015; Li et al., 2004; McArdle et al., 2002; Salthouse, 2009; Tucker-Drob, 2019). Although these findings have important implications for intervention strategies, we did not, nor can we determine the causality with this work alone. Smoking represents a pernicious but modifiable health behavior, and our findings suggest interventions aimed at curbing persistent use or quitting before later adulthood may benefit cognitive health and aging.

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Table 1.1. Descriptives of Cognitive and Smoking Measures

	N	***M***	***SD***	**Median**	**Skew**	**MIN**	**MAX**
Picture Memory (PM)	1161	50.11	10.04	50.78	-0.22	16.08	75.57
Names & Faces (NF)	1174	49.98	9.98	48.33	0.48	29.10	85.03
Digit Span (Dspa)	1170	50.05	10.03	49.81	0.30	14.33	80.22
Perceptual Speed (CPS)	1175	50.08	10.01	50.16	-0.05	8.94	75.31
Digit Symbol (DSy)	1169	50.09	9.93	50.25	-0.10	19.05	81.44
Block Design (BD)	1170	50.10	9.96	52.01	-0.58	14.82	67.09
Vocabulary (V)	1170	49.99	9.99	51.63	-0.68	11.41	72.35
PKYRS (log)	1175	0.64	0.98	0.00	1.28	0.00	4.01
TCS	1175	50.26	8.09	49.33	-0.56	24.00	73.33
Sensitivity analytic sample							
FSIQ: Year 12 [CAP]	349	112.49	11.54	112.00	-0.006	75.00	144.00
FSIQ: Year 12 [LTS]	573	104.21	12.62	104.00	-0.01	68.00	136.00

Note. All cognitive measures are t-scored. CPS=Colorado Perceptual Speed; PKYRS=log-transformed pack years; TCS=tobacco control scale; FSIQ = full scale IQ using WISC-R (CAP) or WISC-III (LTS).

Table 1.2. Pearson Correlation Coefficients between Cognitive and Smoking Measures.

	Ever	Current	PKYRS	TCS
Picture Memory (PM)	**-.09**	**-.07**	**-.12**	.03
Names & Faces (NF)	**-.14**	**-.13**	**-.16**	.004
Digit Span (DSpa)	-.01	-.04	-.02	.06
Colorado Perceptual Speed (CPS)	**-.18**	**-.18**	**-.21**	.02
Digit Symbol (DSy)	**-.22**	**-.21**	**-.25**	.03
Block Design (BD)	**-.13**	**-.20**	**-.14**	.05
Vocabulary (V)	**-.12**	**-.17**	**-.12**	.03

Note. All cognitive measures are standardized on a t-scored scale. CPS=Colorado Perceptual Speed; TCS=tobacco control scale; Bolded parameters are significant $p < .05$; *N* range: 1161-1175

Table 1.3. Multilevel Models by Smoking Behavior with Random Effects for Siblings: Picture Memory (PM).

Model (M) parameters		M2	M3	M4	M5	M6	M7	M8	M9
Intercept	b1	**51.18**	**50.77**	**51.28**	**51.24**	**51.1**	**51.09**	**51.04**	**51.03**
	se	1.52	1.51	1.51	1.51	1.53	1.53	1.53	1.53
Age	b2	-0.01	-0.01	0.00	0.00	0.02	0.01	0.01	0.01
	se	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Sex	b3	**-3.18**	**-3.26**	**-3.07**	**-3.06**	**-2.88**	**-2.84**	**-2.83**	**-2.82**
	se	0.62	0.62	0.62	0.62	0.65	0.65	0.65	0.65
Adopted	b4	0.12	0.08	0.28	0.32	0.30	0.38	0.40	0.40
	se	0.89	0.89	0.89	0.89	0.89	0.89	0.90	0.9
Non-Hispanic	b5	-0.12	0.08	-0.19	-0.14	-0.11	-0.2	-0.17	-0.17
	se	1.63	1.63	1.63	1.63	1.63	1.63	1.63	1.63
White	b6	1.34	1.14	1.40	1.35	1.39	1.39	1.39	1.38
	se	1.54	1.54	1.53	1.54	1.53	1.53	1.53	1.53
Project	b7	-0.27	0.08	-0.32	-0.23	-0.31	-0.23	-0.2	-0.21
	se	1.26	1.26	1.25	1.26	1.25	1.26	1.26	1.26
MAP	b8					-0.03	-0.03	-0.03	-0.03
	se					0.03	0.03	0.03	0.03
CVD	b9					-0.19	-0.14	-0.12	-0.11
	se					1.16	1.16	1.16	1.16
EDU_{yrs}	b10						0.14	0.14	0.14
	se						0.15	0.15	0.15
TCS	b11							0.02	0.02
	se							0.04	0.04
TCS x PKYRS	b12								-0.01
	se								0.04
Ever	b13	**-1.54**							
	se	0.62							
Current	b14		**-1.89**		-0.66				
	se		0.81		0.93				
PKYRS (log)	b15			**-1.07**	**-0.95**	**-1.05**	**-0.93**	**-0.93**	**-0.93**
	se			0.31	0.35	0.31	0.33	0.33	0.33
$\sigma^2 BW_{AD*}$		0	0	0	0	0	0	0	0
$\sigma^2 BW_{Con}$		13.8	13.84	12.91	13.03	12.87	13.01	12.89	12.86
$\sigma^2 BW_{DZ}$		31.19	30.61	31.35	31.38	31.65	31.2	31.01	30.98
$\sigma^2 BW_{MZ}$		35.81	36.91	35.74	36.07	35.78	36.18	36.12	36.13
$\sigma^2 WI_{AD}$		88.69	88.33	88.38	88.13	87.79	87.46	87.35	87.37
$\sigma^2 WI_{Con}$		73.67	73.96	73.37	73.37	73.42	73.46	73.76	73.79
$\sigma^2 WI_{DZ}$		90.14	91.13	89.48	89.49	89.51	89.48	89.53	89.52
$\sigma^2 WI_{MZ}$		53.47	52.57	53.42	53.16	53.37	53.25	53.20	53.20
Model Fit									
-2ll		8561.4	8562.2	8555.3	8554.8	8554.4	8553.5	8553.1	8553.1

Model (M) parameters	M2	M3	M4	M5	M6	M7	M8	M9
AIC	8591.4	8592.2	8585.3	8586.8	8588.4	8589.5	8591.1	8593.1
Model (M) Comparison	M1 - M2	M1 - M3	M1 - M4	M4 - M5	M4 - M6	M6 - M7	M7 - M8	M8 - M9
$\Delta\chi^2$	6.1	5.3	12.2	0.5	0.9	0.9	0.4	0
df	1	1	1	1	2	1	1	1
p	**.014**	**.021**	**.0005**	.480	.638	.343	.527	--

Note. Adjusted for Age (centered at *M*=33.28), Sex (female=0, male=1), Adopted = adopted status (non-adopted=0, adopted=1), NotHispanic ethnicity (0=Hispanic, 1=Non-Hispanic), Project (CAP=0, LTS=1), and race (0=non-White, 1=White). MAP=mean arterial pressure (centered at *M*=85.21); CVD=count of cardiovascular conditions; EDU_{yrs}=ISCED years of education (centered at the median of 16 yrs); TCS=tobacco control scale (centered at *M*=50.26); TCS x PKYRS=moderation of TCS by PKYRS; PKYRS=log-transformed pack years; Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adopted, Con=control sibs, DZ=dizygotic twins, and MZ=monozygotic twins. Bolded parameters are significant $p < .05$; *N* (Individuals)=1161; *N* (Sibships)=687

Table 1.4. Multilevel Models by Smoking Behavior with Random Effects for Siblings: Name and Faces (NF).

Model (M) parameters		M2	M3	M4	M5	M6	M7	M8	M9
Intercept	b1	**52.28**	**51.83**	**52.25**	**52.17**	**52.38**	**52.42**	**52.48**	**52.42**
	se	1.54	1.53	1.54	1.54	1.55	1.52	1.52	1.52
Age	b2	-0.08	-0.07	-0.06	-0.07	-0.07	-0.13	-0.13	-0.13
	se	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Sex	b3	**-3.12**	**-3.18**	**-3.07**	**-3.04**	**-3.18**	**-2.97**	**-2.98**	**-2.99**
	se	0.61	0.61	0.61	0.61	0.65	0.64	0.64	0.64
Adopted	b4	-1.47	-1.41	-1.39	-1.24	-1.20	-0.68	-0.71	-0.68
	se	0.94	0.93	0.94	0.94	0.94	0.92	0.93	0.93
Non-Hispanic	b5	0.79	1.07	0.73	0.90	0.79	0.16	0.13	0.09
	se	1.59	1.59	1.58	1.59	1.59	1.55	1.55	1.55
White	b6	-0.03	-0.36	0.02	-0.18	-0.13	-0.12	-0.12	-0.03
	se	1.51	1.51	1.50	1.50	1.50	1.47	1.47	1.47
Project	b7	-1.15	-0.66	-1.18	-0.9	-0.94	-0.58	-0.61	-0.59
	se	1.31	1.31	1.31	1.31	1.31	1.29	1.29	1.29
MAP	b8					0.02	0.02	0.02	0.03
	se					0.03	0.03	0.03	0.03
CVD	b9					-1.01	-0.74	-0.77	-0.80
	se					1.14	1.12	1.12	1.12
EDU_{yrs}	b10						**0.95**	**0.95**	**0.94**
	se						0.15	0.15	0.15
TCS	b11							-0.02	-0.04
	se							0.03	0.04
TCS x Current	b12								0.20
	se								0.10
Ever	b13	**-1.93**							
	se	0.61							
Current	b14		**-3.00**		**-2.13**	**-2.14**	-1.50	-1.51	-1.47
	se		0.79		0.90	0.90	0.89	0.89	0.88
PKYRS (log)	b15			**-1.09**	**-0.69**	**-0.72**	-0.07	-0.06	-0.03
	se			0.31	0.35	0.35	0.36	0.36	0.36
$\sigma^2 BW_{AD}$		6.47	6.91	6.53	6.87	6.68	2.00	1.70	1.60
$\sigma^2 BW_{Con}$		33.60	34.19	33.34	33.84	33.10	31.43	31.54	33.19
$\sigma^2 BW_{DZ}$		24.93	27.10	24.29	25.51	25.60	21.52	21.70	21.65
$\sigma^2 BW_{MZ}$		47.01	47.88	47.16	47.14	47.07	45.85	45.88	45.78
$\sigma^2 WI_{AD}$		86.47	84.53	86.54	84.76	84.29	85.66	85.88	84.83
$\sigma^2 WI_{Con}$		66.50	65.40	66.15	65.44	66.41	67.42	67.35	66.91
$\sigma^2 WI_{DZ}$		67.77	67.71	67.54	67.65	67.55	66.29	66.20	65.99
$\sigma^2 WI_{MZ}$		47.25	45.93	47.42	46.50	46.43	44.28	44.19	43.86
Model Fit									
-2ll		8608.1	8603.7	8605.4	8599.8	8598.8	8559.5	8559.1	8555.4

Model (M) parameters	M2	M3	M4	M5	M6	M7	M8	M9
AIC	8640.1	8635.7	8637.4	8633.8	8636.8	8599.5	8601.1	8599.4
Model (M) Comparison	M1 - M2	M1 - M3	M1 - M4	M4 - M5	M4 - M6	M6 - M7	M7 - M8	M8 - M9
$\Delta\chi^2$	9.8	14.2	12.5	5.6	6.6	39.3	0.4	3.7
df	1	1	1	1	2	1	1	1
p	**.002**	**<.001**	**<.001**	**.018**	**.01**	**<.001**	.527	.054

Note. Adjusted for Age (centered at *M*=33.28), Sex (female=0, male=1), Adopted status (non-adopted=0, adopted=1), Non-Hispanic ethnicity (0=Hispanic, 1=Non-Hispanic), Project (CAP=0, LTS=1), and Race (0=non-White, 1=White); MAP=mean arterial pressure (centered at *M*=85.21); CVD=count of cardiovascular conditions; EDU_{yrs}= ISCED years of education (centered at the median of 16 yrs); TCS=tobacco control scale (centered at *M*=50.26); TCS x Current=moderation of TCS by Current smoking; PKYRS=log-transformed pack years. Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins. Bolded parameters are significant $p < .05$; *N* (Individuals)=1174; *N* (Sibships)=691

Table 1.5. Multilevel Models by Smoking Behavior with Random Effects for Siblings: Digit Span (DSpa).

Model (M) parameters		M2	M3	M4
Intercept	b1	**49.00**	**49.06**	**49.21**
	se	1.56	1.55	1.56
Age	b2	0.14	0.14	0.14
	se	0.12	0.12	0.12
Sex	b3	0.75	0.79	0.85
	se	0.62	0.62	0.62
Adopted	b4	**-2.72**	**-2.64**	**-2.57**
	se	0.96	0.96	0.96
Non-Hispanic	b5	**2.68**	**2.69**	**2.63**
	se	1.60	1.60	1.60
White	b6	-0.48	-0.50	-0.44
	se	1.52	1.52	1.52
Project	b7	-1.71	-1.68	-1.80
	se	1.32	1.32	1.32
Ever	b14	0.07		
	se	0.62		
Current	b15		-0.43	
	se		0.80	
PKYRS (log)	b16			-0.31
	se			0.31
σ^2BW_{AD}		9.95	9.63	9.00
σ^2BW_{Con}		30.40	30.63	30.20
σ^2BW_{DZ}		16.94	17.19	17.25
σ^2BW_{MZ}		53.10	52.55	52.68
σ^2WI_{AD}		89.90	89.66	89.51
σ^2WI_{Con}		68.24	68.28	68.78
σ^2WI_{DZ}		80.26	80.48	80.29
σ^2WI_{MZ}		45.28	45.34	45.50
Model Fit				
-2ll		8620.3	8620.0	8619.3
AIC		8652.3	8652.0	8651.3
Model (M) Comparison		M1 - M2	M1 - M3	M1 - M4
$\Delta\chi^2$		8652.3	8652	8651.3
df		1	1	1
p		-	.584	.317

Note. Adjusted for Age (centered at *M*=33.28), Sex (female=0, male=1), Adopted status (non-adopted=0, adopted=1), Non-Hispanic ethnicity (0=Hispanic, 1=Non-Hispanic), Project (CAP=0, LTS=1), and race (0=non-White, 1=White); MAP=mean arterial pressure (centered at *M*=85.21); CVD=count of cardiovascular conditions; EDU_{yrs}=

ISCED years of education (centered at the median of 16 yrs); TCS=tobacco control scale (centered at *M*=50.26); TCS x PKYRS=moderation of TCS by PKYRS; PKYRS=log-transformed pack years. Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adopted family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins. Bolded parameters are significant $p < .05$; *N* (Individuals)=1170; *N* (Sibships)=688

Table 1.6. Multilevel Models by Smoking Behavior with Random Effects for Siblings: Colorado Perceptual Speed (CPS).

Model (M) parameters		M2	M3	M4	M5	M6	M7	M8	M9
Intercept	b1	**53.02**	**52.48**	**53.06**	**52.95**	**53.54**	**53.63**	**53.62**	**53.59**
	se	1.55	1.54	1.54	1.54	1.55	1.49	1.49	1.49
Age	b2	**-0.36**	**-0.34**	**-0.33**	**-0.33**	**-0.36**	**-0.42**	**-0.42**	**-0.41**
	se	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Sex	b3	**-1.42**	**-1.48**	**-1.3**	**-1.28**	**-1.76**	**-1.43**	**-1.43**	**-1.44**
	se	0.62	0.62	0.62	0.62	0.65	0.63	0.63	0.63
Adopted	b4	**-2.24**	**-2.13**	**-2.07**	**-1.87**	-1.81	-1.22	-1.22	-1.19
	se	0.94	0.93	0.93	0.93	0.92	0.89	0.89	0.89
Non-Hispanic	b5	1.61	1.9	1.53	1.72	1.4	0.69	0.69	0.67
	se	1.60	1.60	1.60	1.59	1.6	1.54	1.54	1.54
White	b6	-0.44	-0.8	-0.37	-0.6	-0.48	-0.59	-0.59	-0.54
	se	1.49	1.48	1.48	1.48	1.48	1.43	1.43	1.43
Project	b7	**-3.82**	**-3.20**	**-3.90**	**-3.52**	**-3.58**	**-3.04**	**-3.04**	**-3.02**
	se	1.28	1.28	1.28	1.28	1.27	1.23	1.24	1.24
MAP	b8					**0.06**	**0.07**	**0.07**	**0.07**
	se					0.03	0.03	0.03	0.03
CVD	b9					-1.94	-1.67	-1.66	-1.68
	se					1.09	1.07	1.07	1.07
EDU_{yrs}	b10						**1.15**	**1.15**	**1.14**
	se						0.14	0.14	0.14
TCS	b11							0.001	-0.01
	se							0.03	0.03
TCS x Current	b12								0.11
	se								0.10
Ever	b13	**-2.35**							
	se	0.60							
Current	b14		**-3.84**		**-2.67**	**-2.72**	**-2.03**	**-2.03**	**-1.99**
	se		0.77		0.87	0.87	0.85	0.85	0.85
PKYRS (log)	b15			**-1.47**	**-0.97**	**-1.04**	-0.30	-0.30	-0.29
	se			0.30	0.34	0.34	0.35	0.35	0.35
σ^2BW_{AD}		10.87	10.52	11.25	10.88	8.90	4.83	4.83	4.80
σ^2BW_{Con}		12.22	13.43	11.32	12.47	13.15	10.21	10.18	10.40
σ^2BW_{DZ}		30.28	30.51	31.17	30.52	31.18	27.08	27.07	27.17
σ^2BW_{MZ}		62.43	63.1	62.2	60.95	60.83	51.73	51.72	51.48
σ^2WI_{AD}		92.61	91.54	89.76	88.97	89.08	85.01	85.02	84.73
σ^2WI_{Con}		76.44	74.24	77.56	75.95	74.13	73.48	73.49	73.81
σ^2WI_{DZ}		65.67	67.51	64.17	65.75	65.29	65.03	65.03	64.66
σ^2WI_{MZ}		30.47	28.75	30.57	29.70	29.79	30.51	30.51	30.47
Model Fit									
-2ll		8572.1	8562.7	8564.0	8554.8	8547.1	8485.7	8485.7	8484.5

Model (M) parameters	M2	M3	M4	M5	M6	M7	M8	M9
AIC	8604.1	8594.7	8596.0	8588.8	8585.1	8525.7	8527.7	8528.5
Model (M) Comparison	M1 - M2	M1 - M3	M1 - M4	M4 - M5	M4 - M6	M6 - M7	M7 - M8	M8 - M9
$\Delta\chi^2$	14.9	24.3	23	9.2	16.9	61.4	0.0	1.2
df	1	1	1	1	2	1	1	1
p	**<.001**	**<.001**	**<.001**	**.002**	**<.001**	**<.001**	-	.273

Note. Adjusted for Age (centered at *M*=33.28), Sex (female=0, male=1), Adopted = adopted status (non-adopted=0, adopted=1), Non-Hispanic ethnicity (0=Hispanic, 1=Non-Hispanic), Project (CAP=0, LTS=1), and race (0=non-White, 1=White). MAP=mean arterial pressure (centered at *M*=85.21); CVD=count of cardiovascular conditions; EDU_{yrs}= ISCED years of education (centered at the median of 16 yrs); TCS=tobacco control scale (centered at *M*=50.26); TCS x Current=moderation of TCS by Current smoking; PKYRS=log-transformed pack years. Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adopted family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins. Bolded parameters are significant $p < .05$; *N* (Individuals)=1175; *N* (Sibships)=692
[+]Model comparison is conducted with M3 as this model has the lowest AIC among smoking measures

Table 1.7. Multilevel Models by Smoking Behavior with Random Effects for Siblings: Digit Symbol (DSy).

Model (M) parameters		M2	M3	M4	M5	M6	M7	M8	M9
Intercept	b1	**53.3**	**52.48**	**53.32**	**53.18**	**53.48**	**53.55**	**53.53**	**53.53**
	se	1.51	1.49	1.5	1.49	1.5	1.43	1.43	1.44
Age	b2	-0.23	-0.21	-0.19	-0.20	-0.21	-0.27	-0.27	-0.27
	se	0.12	0.12	0.12	0.12	0.12	0.11	0.11	0.11
Sex	b3	**-3.89**	**-4.02**	**-3.77**	**-3.73**	**-3.92**	**-3.58**	**-3.58**	**-3.58**
	se	0.61	0.6	0.61	0.6	0.63	0.61	0.61	0.61
Adopted	b4	-1.58	-1.55	-1.43	-1.20	-1.12	-0.49	-0.48	-0.48
	se	0.92	0.91	0.91	0.90	0.90	0.87	0.87	0.87
Non-Hispanic	b5	2.94	3.46	2.88	3.19	3.01	2.17	2.18	2.18
	se	1.56	1.56	1.55	1.54	1.55	1.48	1.48	1.48
White	b6	-1.18	-1.77	-1.16	-1.49	-1.4	-1.38	-1.38	-1.38
	se	1.45	1.45	1.45	1.44	1.44	1.39	1.39	1.39
Project	b7	**-2.89**	-2.08	**-2.97**	**-2.57**	**-2.61**	-2.09	-2.08	-2.08
	se	1.27	1.27	1.27	1.26	1.26	1.21	1.21	1.21
MAP	b8					0.02	0.03	0.03	0.03
	se					0.03	0.03	0.03	0.03
CVD	b9					-1.70	-1.38	-1.37	-1.37
	se					1.07	1.05	1.05	1.05
EDU_{yrs}	b10						**1.24**	**1.24**	**1.24**
	se						0.14	0.14	0.14
TCS	b11							0.005	0.005
	se							0.03	0.03
TCS x PKYRS	b12								0.001
	se								0.10
Ever	b13	**-3.26**							
	se	0.58							
Current	b14		**-4.57**		**-2.91**	**-2.93**	**-2.18**	**-2.18**	**-2.18**
	se		0.75		0.84	0.84	0.82	0.82	0.82
	b15			**-1.91**	**-1.37**	**-1.41**	-0.57	-0.57	-0.57
PKYRS (log)	se			0.29	0.33	0.33	0.34	0.34	0.34
$\sigma^2 BW_{AD}$		0.13	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$\sigma^2 BW_{Con}$		26.58	26.94	25.07	25.80	25.48	19.77	19.79	19.79
$\sigma^2 BW_{DZ}$		29.11	28.77	30.39	29.14	29.39	24.40	24.42	24.42
$\sigma^2 BW_{MZ}$		54.13	56.04	53.79	53.40	52.92	44.30	44.25	44.26
$\sigma^2 WI_{AD}$		93.46	90.45	91.06	87.93	87.22	81.95	82.03	82.03
$\sigma^2 WI_{Con}$		65.30	64.40	66.53	65.40	65.03	63.14	63.08	63.08
$\sigma^2 WI_{DZ}$		55.05	57.25	52.99	54.99	55.30	55.45	55.43	55.42
$\sigma^2 WI_{MZ}$		31.65	30.41	31.93	31.13	31.15	30.83	30.84	30.84
Model Fit									
-2ll		8449.7	8444.3	8439.1	8427.5	8424.4	8347.5	8347.5	8347.5

Model (M) parameters	M2	M3	M4	M5	M6	M7	M8	M9
AIC	8481.7	8474.3	8469.1	8459.5	8460.4	8385.5	8387.5	8389.5
Model (M) Comparison	M1 - M2	M1 - M3	M1 - M4	M4 - M5	M4 - M6	M6 - M7	M7 - M8	M8 - M9
$\Delta\chi^2$	30.4	35.8	41.0	11.6	14.7	76.9	0	0
df	1	1	1	1	2	1	1	1
p	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	-	-

Note. Adjusted for Age (centered at *M*=33.28), Sex (female=0, male=1), Adopted = adopted status (non-adopted=0, adopted=1), Non-Hispanic ethnicity (0=Hispanic, 1=Non-Hispanic), Project (CAP=0, LTS=1), and race (0=non-White, 1=White). MAP=mean arterial pressure (centered at *M*=85.21); CVD=count of cardiovascular conditions; EDU_{yrs}=ISCED years of education (centered at the median of 16 yrs); TCS=tobacco control scale (centered at M=50.26); TCS x Current=moderation of TCS by Current smoking; PKYRS=log-transformed pack years. Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adopted family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins. Bolded parameters are significant $p < .05$; N (Individuals)=1169; N (Sibships)=688

Table 1.8. Multilevel Models by Smoking Behavior with Random Effects for Siblings: Block Design (BD).

Model (M) parameters		M2	M3	M4	M5	M6	M7	M8	M9
Intercept	b1	**49.61**	**49.12**	**49.47**	**49.36**	**48.91**	**49.18**	**49.07**	**49.07**
	se	1.55	1.52	1.54	1.52	1.53	1.50	1.50	1.50
Age	b2	-0.23	-0.22	-0.21	-0.22	-0.20	**-0.24**	**-0.24**	**-0.24**
	se	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Sex	b3	**3.4**	**3.35**	**3.43**	**3.46**	**3.63**	**3.89**	**3.92**	**3.92**
	se	0.61	0.60	0.61	0.60	0.63	0.62	0.62	0.62
Adopted	b4	**-2.86**	**-2.72**	**-2.87**	**-2.6**	**-2.63**	**-2.11**	**-2.05**	**-2.05**
	se	0.98	0.96	0.97	0.96	0.96	0.95	0.95	0.95
Non-Hispanic	b5	2.60	3.03	2.57	2.92	3.11	2.53	2.60	2.60
	se	1.57	1.57	1.58	1.57	1.57	1.54	1.53	1.53
White	b6	-0.17	-0.68	-0.15	-0.55	-0.66	-0.52	-0.53	-0.53
	se	1.46	1.46	1.47	1.46	1.45	1.43	1.43	1.43
Project	b7	**-3.59**	**-2.94**	**-3.61**	**-3.13**	**-2.89**	**-2.78**	**-2.74**	**-2.74**
	se	1.26	1.25	1.26	1.25	1.25	1.24	1.24	1.24
MAP	b8					-0.04	-0.04	-0.03	-0.03
	se					0.03	0.03	0.03	0.03
CVD	b9					-0.98	-0.82	-0.78	-0.78
	se					1.09	1.08	1.08	1.08
EDU_{yrs}	b10						**0.73**	**0.73**	**0.73**
	se						0.14	0.14	0.14
TCS	b11							0.04	0.04
	se							0.03	0.03
	b12								0.004
TCS x Current	se								0.10
Ever	b13	**-2.52**							
	se	0.58							
Current	b14		**-4.58**		**-3.13**	**-4.52**	**-3.55**	**-3.55**	**-3.55**
	se		0.75		1.25	0.75	0.77	0.77	0.77
	b15			**-1.22**	**-3.97**				
PKYRS (log)	se			0.30	0.85				
$\sigma^2 BW_{AD}$		30.04	25.88	28.62	25.04	27.60	24.19	24.63	24.62
$\sigma^2 BW_{Con}$		27.37	25.84	26.35	26.05	25.52	26.87	25.35	25.38
$\sigma^2 BW_{DZ}$		27.69	27.18	28.62	27.19	27.80	23.79	23.71	23.70
$\sigma^2 BW_{MZ}$		62.06	60.37	62.54	60.32	60.17	55.20	55.25	55.25
$\sigma^2 WI_{AD}$		83.61	82.53	83.01	82.32	80.50	79.40	78.79	78.78
$\sigma^2 WI_{Con}$		53.95	53.00	54.87	53.23	53.07	52.56	53.74	53.73
$\sigma^2 WI_{DZ}$		62.41	63.00	62.00	62.60	62.15	63.52	63.12	63.12
$\sigma^2 WI_{MZ}$		28.53	29.09	28.95	29.09	29.23	29.01	29.08	29.08
Model Fit									
-2ll		8485.4	8468.1	8487.1	8465.8	8464.9	8437.2	8435.7	8435.7

Model (M) parameters	M2	M3	M4	M5	M6	M7	M8	M9
AIC	8517.4	8500.1	8519.1	8499.8	8500.9	8475.2	8475.7	8477.7
Model (M) Comparison	M1 - M2	M1 - M3	M1 - M4	M4 - M5	M4 - M6	M6 - M7	M7 - M8	M8 - M9
$\Delta\chi^2$	18.3	35.6	16.6	21.3	22.2	27.7	1.5	0.0
df	1	1	1	1	2	1	1	1
p	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	.22	-

Note. Adjusted for Age (centered at *M*=33.28), Sex (female=0, male=1), Adopted=adopted status (non-adopted=0, adopted=1), Non-Hispanic ethnicity (0=Hispanic, 1=Non-Hispanic), Project (CAP=0, LTS=1), and race (0=non-White, 1=White). MAP=mean arterial pressure (centered at *M*=85.21); CVD=count of cardiovascular conditions; EDU_{yrs}= ISCED years of education (centered at the median of 16 yrs); TCS=tobacco control scale (centered at M=50.26); TCS x Current=moderation of TCS by Current smoking; PKYRS=log-transformed pack years. Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins. Bolded parameters are significant $p < .05$; *N* (Individuals)=1170; *N* (Sibships)=688

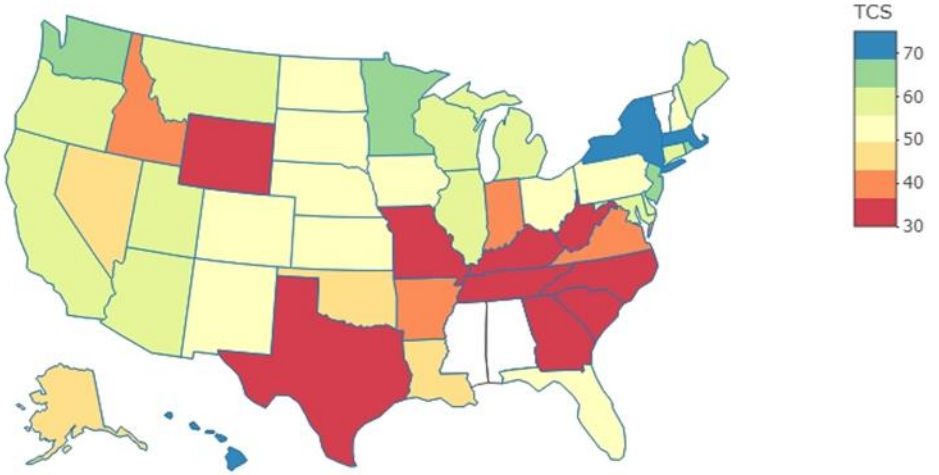
Table 1.9. Multilevel Models by Smoking Behavior with Random Effects for Siblings: Vocabulary (V).

Model (M) parameters		M2	M3	M4	M5	M6	M7	M8	M9
Intercept	b1	**50.73**	**50.22**	**50.78**	**50.71**	**50.77**	**50.52**	**50.54**	**50.49**
	se	1.52	1.5	1.51	1.5	1.51	1.39	1.39	1.39
Age	b2	**0.28**	**0.30**	**0.31**	**0.31**	**0.32**	**0.24**	**0.24**	**0.24**
	se	0.11	0.11	0.11	0.11	0.11	0.10	0.10	0.10
Sex	b3	-0.11	-0.20	0.00	0.02	0.09	0.62	0.61	0.67
	se	0.61	0.60	0.61	0.60	0.63	0.58	0.58	0.58
Adopted	b4	**-3.30**	**-3.27**	**-3.19**	**-3.03**	**-2.90**	**-1.99**	**-2.00**	**-2.02**
	se	0.86	0.85	0.86	0.85	0.85	0.80	0.80	0.80
Non-	b5	2.83	3.17	2.75	2.94	2.84	1.96	1.95	2.02
Hispanic	se	1.64	1.64	1.64	1.63	1.63	1.50	1.50	1.50
White	b6	-0.31	-0.72	-0.28	-0.5	-0.36	-0.35	-0.35	-0.40
	se	1.47	1.47	1.46	1.46	1.46	1.36	1.36	1.36
Project	b7	**-2.87**	-2.29	**-2.93**	**-2.63**	**-2.64**	-1.79	-1.80	-1.79
	se	1.19	1.19	1.19	1.19	1.18	1.08	1.08	1.08
MAP	b8					-0.02	-0.01	-0.01	-0.01
	se					0.03	0.02	0.02	0.02
CVD	b9					**-2.27**	-1.74	-1.75	-1.70
	se					1.03	0.98	0.98	0.98
EDU_{yrs}	b10						**1.73**	**1.73**	**1.74**
	se						0.13	0.13	0.13
TCS	b11							-0.005	0.02
	se							0.03	0.03
TCS x	b12								-0.04
PKYRS	se								0.03
Ever	b13	**-2.21**							
	se	0.56							
Current	b14		**-3.25**		**-2.08**	**-2.07**	-1.06	-1.06	-1.17
	se		0.72		0.81	0.81	0.77	0.77	0.77
PKYRS	b15			**-1.35**	**-0.99**	**-1.01**	0.11	0.11	0.15
(log)	se			0.28	0.31	0.31	0.30	0.30	0.30
$\sigma^2 BW_{AD}$		5.24	5.50	5.05	4.59	5.01	0.00	0.00	0.00
$\sigma^2 BW_{Con}$		17.33	17.24	16.53	16.66	16.19	11.55	11.57	11.37
$\sigma^2 BW_{DZ}$		57.92	58.26	58.21	57.73	57.84	41.08	41.02	40.94
$\sigma^2 BW_{MZ}$		75.77	75.50	76.32	75.24	74.93	56.53	56.55	56.21
$\sigma^2 WI_{AD}$		84.59	81.40	82.35	80.99	80.54	80.00	79.99	80.23
$\sigma^2 WI_{Con}$		48.09	47.46	48.67	48.25	48.07	40.67	40.62	40.46
$\sigma^2 WI_{DZ}$		42.42	42.90	41.85	42.34	41.91	41.20	41.27	41.33
$\sigma^2 WI_{MZ}$		27.10	27.80	27.11	27.26	27.16	26.81	26.80	26.78
Model Fit -2ll		8392.9	8388.6	8385.1	8378.6	8373.0	8214.4	8214.4	8212.4

Model (M) parameters	M2	M3	M4	M5	M6	M7	M8	M9
AIC	8424.9	8420.6	8417.1	8412.6	8411	8252.4	8254.4	8254.4
Model (M) Comparison	M1 - M2	M1 - M3	M1 - M4	M4 - M5	M4 - M6	M6 - M7	M7 - M8	M8 - M9
$\Delta\chi^2$	15.4	19.7	23.2	6.5	12.1	158.6	0.0	2
df	1	1	1	1	2	1	1	1
p	**<.001**	**<.001**	**<.001**	**.01**	**.002**	**<.001**	1.0	.16

Note. Adjusted for Age (centered at *M*=33.28), Sex (female=0, male=1), Adopted = adopted status (non-adopted=0, adopted=1), Non-Hispanic ethnicity (0=Hispanic, 1=Non-Hispanic), Project (CAP=0, LTS=1), and race (0=non-White, 1=White). MAP=mean arterial pressure (centered at *M*=85.21); CVD=count of cardiovascular conditions; EDU_{yrs}= ISCED years of education (centered at the median of 16 yrs); TCS=tobacco control scale (centered at M=50.26); TCS x PKYRS=moderation of TCS by PKYRS; PKYRS=log-transformed pack years. Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins. Bolded parameters are significant $p < .05$; *N* (Individuals)=1170; *N* (Sibships)=688

Figure 1.1. Tobacco Control Score Thematic Heat Map of the United States



Note. States not scored shown in white: Alabama, Missouri, and Vermont.

Chapter Three:

Evaluate longitudinal associations of smoking behavior with cognitive functioning from adolescence to midlife.

With the ever-aging world population, research investigating and promoting effective interventions for health are paramount. In particular, neurocognitive disorders represent a growing risk as more adults reach the oldest ages. Indeed, the United States population of adults 65 years and older is on track to increase to nearly 100 million by 2050 (Mather et al., 2015; U.S. Census Bureau, 2017). Thus, in the next 30 years, the number of individuals diagnosed with Alzheimer's disease, the most common type of neurocognitive disorder, is projected to more than double from nearly 6 to 13.8 million by 2050 (Hebert et al., 2013). Identifying factors contributing to the risk of later-life neurocognitive disorders will help alleviate the health and economic burden of these debilitating illnesses. One such factor is tobacco use (Dhana et al., 2020; Livingston et al., 2020). Tobacco, often smoked in cigarette products, represents a prevalent yet modifiable health behavior (Centers for Disease Control and Prevention, 2018; World Health Organization, 2019). Little debate exists on the putative harm chronic tobacco use imposes on general health (Centers for Disease Control and Prevention, 2018; Royal College of Physicians of London: Tobacco Advisory Group, 2000; U.S. Department of Health and Human Services, 2014; World Health Organization, 2019). However, research gaps remain in the study of tobacco use and its influence on cognitive health. Smoking is

associated with lower cognitive performance, worse cognitive declines, greater risk for cognitive impairment, and major neurocognitive disorders, such as dementia or Alzheimer's disease (Anstey et al., 2007; Conti et al., 2019; Durazzo et al., 2010; Livingston et al., 2020; Peters et al., 2008; Swan & Lessov-Schlaggar, 2007; Zhong et al., 2015) but little research has invested studying earlier life associations of smoking behavior with later cognitive functioning before major deficits and impairments present. Calls to disambiguate when risk emerges for later life neurocognitive disorders have been made, especially since antecedents such as smoking behavior typically originate in earlier life (Barnett et al., 2013b; Huggett et al., 2019). Clarifying the link and timing between cognitive functioning and tobacco use will inform policies and intervention measures that could remediate later neurocognitive health.

A recent review on the life course model for Alzheimer's disease and related dementias (ADRD) evaluated when risk factors were salient across the life course, and highlighted smoking as a later life risk factor in part due to the reduced risk, even in later life, for individuals that quit (Livingston et al., 2020). Situating the life course model of modifiable factors for ADRD within the broader life course theory framework posits that development is a dynamic process not situated entirely at a certain period of time but rather a process of continuity and change as individuals progress across historical time, life transitions, and experiences (Elder Jr, 1998). Thus, development for some traits is responsive across the lifespan to experiences and exposures, but certain age periods may be more vulnerable to exposure as in the case of smoking. It's important to note that the developmental range is not infinite but will be limited based on the underlying individual

genetic propensity and responsivity to the multi-level interaction between genetics, biology, and the environment (Gottlieb, 2007). Interestingly, even though regular smoking behavior is adopted by most before the age of 20 (Dutra et al., 2017; Fuemmeler et al., 2013; Huggett et al., 2019) the majority of research on the impact of smoking to cognitive health is studied with middle-aged or older adults, outside the perspective of the life course model. Research has focused on exploring the effects of smoking behavior in older adults, partly because former smokers, after abstaining for many years, tend to have a similar risk as never smokers for cognitive impairment and neurocognitive disorders (Anstey et al., 2007; Dhana et al., 2020; Peters et al., 2008). Another major reason is because cognitive aging is detectable at older ages (Hartshorne & Germine, 2015; Li et al., 2004; McArdle et al., 2002; Salthouse, 2009; Tucker-Drob, 2019).

Cognitive decline is characterized as a lost in efficiency and functionality and, broadly, declines increase as individuals age (Baltes, 1997; Cattell, 1971; Horn & Cattell, 1967; Lindenberger & Baltes, 1994; Lindenberger et al., 2001). Several theories exist to explain the mechanism and expected course of cognitive decline and thus explain processes of aging. The common cause theory (Lindenberger & Baltes, 1994) proposes that paired associations between visual and auditory deficiency with cognitive decline suggest a shared causal link in aging, possibly through changes in brain physiology integrity. Thus, the etiology of cognitive aging may arise from a single neurological cause. Over time less support has been found for the common cause theory as sensory-cognitive measures are less correlated than expected, suggesting functional mechanistic differences driving age-changes between cognitive abilities (Lindenberger & Ghisletta,

2009). Nevertheless, the common cause theory has gained a second life as recent research suggest there may be a domain general neurological mechanism of cognitive aging vis-à-vis the regulatory operations of the prefrontal cortex (PFC) on the sensorimotor cortices for older adults (Alain et al., 2022).

In contrast, other researchers delineated aging processes among two components of intelligence: aging-sensitive/fluid abilities and aging-resilient/crystallized abilities (Baltes, 1997; Cattell, 1971; Horn & Cattell, 1967; Lindenberger et al., 2001). Fluid abilities represent a broad spectrum of cognitive processes and involve abstract and problem-solving skills that are functionally dependent on neurobiology rather than cultural exposure, e.g., processing speed and spatial ability. In contrast, crystallized abilities capture culturally gained knowledge and experience-based reasoning skills, e.g., verbal ability or general knowledge. The fluid-crystallized components will differ based on the timing when declines are detected (Hartshorne & Germine, 2015; Li et al., 2004; McArdle et al., 2002; Reynolds et al., 2005; Salthouse, 2009; Tucker-Drob, 2019). Fluid abilities peak earlier, around age 20 to 30, than crystallized abilities with cognitive declines occurring sometime later varying by cognitive domain. For example, processing speed peaks in the early 20s with steeper declines across adulthood, while working memory peaks around age 30 with relatively stable but modest declines (Hartshorne & Germine, 2015). Crystallized abilities continue to grow until later ages, plateauing around 60 to 70 years and declining thereafter (Li et al., 2004; Pahlen et al., 2018; Reynolds et al., 2005; Salthouse, 2009). Even though there is renewed interest in the common cause theory of cognitive aging (Alain et al., 2022), more support has been gained for the two-

component theory. Moreover, heterogeneity between specific abilities on peak performance and trajectories, even within the same broad domain, suggest variation in development and etiology across tasks (Hartshorne & Germine, 2015; McArdle et al., 2002; Mella et al., 2018; Wilson et al., 2002). While the two-component theory of cognitive aging is conceptually helpful to illustrate which abilities vary as a function of age across the lifespan, it does not envisage uniformity in age-based curves for abilities falling broadly within fluid or crystallized components, especially since the two-component theory is inadequate to address the breadth and depth of the interrelations among various dimensions of intelligence (Horn & Blankson, 2005). Rather this theory is more descriptive than prescriptive for specific cognitive abilities.

Cognitive aging is not a process exclusive to older adults, and in fact, the emergence and detection of cognitive declines can begin as early as age 20 to 30 years of age (Hartshorne & Germine, 2015; Li et al., 2004; McArdle et al., 2002; Salthouse, 2009; Tucker-Drob, 2019). Therefore, much attention has been applied to study factors associated with accelerating decline beyond expected age-graded norms, otherwise termed nonnormative or pathological change (Deary et al., 2009). Smoking behavior represents one such pernicious health risk with worse cognitive functioning and greater declines evident by midlife (Bahorik et al., 2021; Durazzo et al., 2012; Kasl-Godley, 1996; Nooyens et al., 2008; Olaya et al., 2017; Richards et al., 2003; Sabia et al., 2012). Moreover, smoking behavior is associated with worse midlife neurological anatomical differences such as thinner cortical and smaller subregional volume and density (Elbejjani et al., 2019; Logtenberg et al., 2021; Prom-Wormley et al., 2015). Indeed,

smokers tend to have older brain age (i.e., the aggregate measure of expected brain health indices relative to predicted chronological age) based on length and amount of use (Franz et al., 2021; Linli et al., 2022; Ning et al., 2020; Whitsel et al., 2022). Smokers' brains tend to be 1.2 years older than non-smokers, and the difference in brain age predicts differences in cognitive performance with the brain age gap mediating the association between smoking and cognition (Linli et al., 2022).

Contributing pathways to accelerated brain aging include smoking-associated impairments to cardiovascular health (Ambrose & Barua, 2004; Finch, 2018; Gao et al., 2017), leading to a neurotoxicity effect via greater inflammation and oxidative stress (Finch, 2018; Swan & Lessov-Schlaggar, 2007). As research has predominately focused on the latter half of the lifespan only a partial picture is revealed. The long-reaching effects of smoking suggest an earlier risk window (Bourassa et al., 2022; Galanis et al., 1997; Karama et al., 2015; Mons et al., 2013; Whitsel et al., 2022). For instance, Whitsel et al. (2022) found at age 56, individuals had approximately one year older brain age if they had smoked about 10 pack years at age 40, after adjusting alcohol consumption, years of education, and health. Further, change in pack years wasn't associated with brain age in follow-up assessments at 62 or 68. In other words, early midlife smoking was associated with later neurological health that persisted, suggesting that the emergence of smoking impact occurs before midlife. Indeed, smoking daily during adolescence was associated with worse aging at early midlife, including older brain age, facial age, slower gait speed, and accelerated pace of aging or the projected biological age based on several biomarkers captured across adulthood (Bourassa et al., 2022). In addition, findings from

the Dunedin Study indicate that persistent tobacco users had more cognitive decline based on the difference between childhood and early midlife functioning (Meier et al., 2012) where midlife performance was assessed at year 38 and childhood performance was an average score ascertained from years 7, 9, 11, and 13. Notably, the Meier et al. (2012) study focused on cannabis use but included tobacco and other substance use behaviors as covariates. Including smoking behavior simply as a covariate is not uncommon (Castellanos-Ryan et al., 2017; Mahedy et al., 2018; Meier et al., 2012; Meier et al., 2022), especially in studies of adolescents and younger adults. However, it is surprising that relatively few studies that examined the smoking-cognitive relationship before middle age. Hamidullah and colleagues (2020) outlined in their review of adolescent substance use on brain and cognitive outcomes, that alcohol and cannabis research are more popular than tobacco, with more than twice the number of studies on the effects of cannabis use on cognitive functioning.

Smoking during adolescence may influence cognitive development by disrupting the maturation processes unfolding during this time. Adolescent cognitive development marks a fast-growing process across the first quarter of the lifespan (Hartshorne & Germine, 2015; Ricker et al., 2018; St Clair-Thompson, 2010; Tucker-Drob, 2019). As individuals age, cognitive processes adapt and become more efficient in resolving more complex tasks (Eccles et al., 2003; Kail & Salthouse, 1994). Further, neurological maturation occurs up to early adulthood, particularly with the PFC and the medial temporal lobe, including the hippocampus (Fuster, 2002; Romine & Reynolds, 2005; Wierenga et al., 2014). Thus, adolescence is a salient period for cognitive and brain

development. In addition, uptake for smoking behavior often develops during adolescence (Dutra et al., 2017; Fuemmeler et al., 2013; Huggett et al., 2019), about 5 to 10 years before the typical age individuals reach maximum cognitive performance (Hartshorne & Germine, 2015; McArdle et al., 2002; Salthouse, 2009; Tucker-Drob, 2019).

Beyond brain development, how does smoking affect human cognition if uptake occurs during adolescence? Much work has been devoted to unraveling the smoking exposure effect on neurological outcomes, specifically in the administration of nicotine, the major drug in cigarette products (c.f., Dwyer et al., 2009; Goriounova & Mansvelder, 2012; Mooney-Leber & Gould, 2018; Poorthuis et al., 2009; Thorpe et al., 2020; Zeid et al., 2018). Nicotine is of interest because this drug can pass the blood-brain barrier and acts as an agonist to acetylcholine and therefore binds to the same neural receptors termed neuronal nicotinic acetylcholine receptors (nAChRs). The nAChRs are expressed in the cholinergic system, a critical system involved in the brain formation and maturation occurring prenatally to later adolescence. The regulatory process of the cholinergic system thus is a vulnerable neurological mechanism susceptible to nicotine exposure which may alter the development of the PFC and medial temporal lobe, important regions for learning and memory. Thus, chronic nicotine exposure earlier in life may disrupt these brain regions' development and maturation, leading to impaired cognitive function persisting into adulthood (Goriounova & Mansvelder, 2012; Mooney-Leber & Gould, 2018; Poorthuis et al., 2009; Zeid et al., 2018).

Adolescent smoking signals a vulnerable developmental window of cognitive development, and much of our knowledge on the neurological effects comes from animal research (c.f., Dwyer et al., 2009; Goriounova & Mansvelder, 2012; Mooney-Leber & Gould, 2018; Poorthuis et al., 2009; Thorpe et al., 2020; Zeid et al., 2018). Observational work in humans has supported smoking-linked deficits in cognitive performance (Fried et al., 2006; Jacobsen et al., 2005; Mahedy et al., 2018; Mahedy et al., 2021). Even though smoking behavior is correlated with worse cognitive performance, prospective research is scant. If prospective work exists, many studies only typically evaluate the association between smoking behavior and cognitive functioning via a single follow-up (Castellanos-Ryan et al., 2017; Meier et al., 2012; Weiser et al., 2010). To date, no studies to our knowledge have examined how early adolescent smoking is associated with cognitive trajectories up to the verge of midlife.

Differences in socioeconomic status (SES) factors may represent a possible confounding pathway by which smoking and cognitive functioning are associated. Indeed, lower educational attainment assessed by parents or self-attained, individuals with lower childhood IQ, and more childhood deprivation show a greater risk of initiating smoking and persistent use (Corley et al., 2019; Daly & Egan, 2017; Kubička et al., 2001; Pampel et al., 2014; Silventoinen et al., 2022; Whalley et al., 2005). Moreover, earlier life SES conditions, such as higher parental education, have an enduring protective effect on smoking behavior across the life course (Corley et al., 2019; Pampel et al., 2014). SES conditions are likewise predictive of later cognitive functioning, which persist into later life (Lövdén et al., 2020; Ritchie & Tucker-Drob, 2018). Early education advantages may

contribute to compensatory mechanisms that allow some individuals with more resources to bypass or offset cognitive declines in later life (Stern, 2009; Stern et al., 2019), especially concerning unhealthy modifiable behaviors, including smoking (Franz et al., 2021). Thus, differences in SES might confound associations between cognition and smoking behavior during adolescence and later cognitive health. Health advantages can be gained from families with more resources and for individuals with higher IQ by preventing or delaying smoking initiation until college (Johnson et al., 2009). Further, the inclusion of SES indicators attenuated the smoking-cognitive associations during midlife (Sabia et al., 2008). Therefore, SES indicators such as parental educational attainment are important to include to avoid potential selection differences that influence the risk for smoking uptake and cognitive development.

Germaine to our study is elucidating when smoking influences cognitive development and later functioning. Our study examined cognitive development using combined data from two archival longitudinal projects and ending just prior to midlife with the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife1) assessment. We examined adolescent smoking via year 16 smoking consumption rates and adulthood smoking by the difference in smoking consumption at CATSLife1 compared to year 16. Thus, year 16 anchored smoking rates for adolescent smoking, and the smoking difference score allowed us to see how future adulthood smoking consumption (i.e., smoking difference) further influenced cognitive trajectories. The current study sought to answer if adolescent smoking and changes in smoking consumption from adolescence to midlife influences cognitive development and

change up to midlife. That is, do individuals who smoke more cigarettes at age 16 show worse cognitive developmental trends by the cusp of midlife (i.e., either dampened growth or cognitive decline)? Moreover, do changes in smoking, gains or reductions smoking predict differential cognitive change? In addition, do individuals who start regularly smoking after age 16, as captured by smoking consumption gains by the cusp of midlife, show differential adolescent cognitive functioning that may not be captured by extant adolescent smoking?

We expect the smoking difference score to have a more meaningful influence on cognitive trajectories than adolescent smoking. We reason that the smoking difference will provide a better index of the cumulative and more proximal impact of smoking behavior. Past work examining cognitive aging has demonstrated the stronger effect of current smoking on cognitive performance compared to former smokers (Amini et al., 2021; Collins et al., 2009; Lo et al., 2014; Nooyens et al., 2008; Sabia et al., 2012; Vermeulen et al., 2018; Weiser et al., 2010; Whalley et al., 2005). Moreover, we hypothesize that smoking influences the fluid/age-sensitive cognitive abilities trajectories more than the crystalized ability measure. In addition, although observational studies have shown the negative intercorrelation between cognitive ability and smoking behavior (Fried et al., 2006; Jacobsen et al., 2005; Mahedy et al., 2018; Mahedy et al., 2021), the few studies that have examined the impact of adolescent tobacco smoking on later cognitive function have found mixed results (Castellanos-Ryan et al., 2017; Meier et al., 2012; Weiser et al., 2010). Thus, the smoking effect in the cognitive aging literature is well documented, but the evidence is less clear for earlier initiated risk on cognitive

development. This study will be the first to help unravel how adolescent and later adulthood smoking may influence cognitive trajectories up to midlife.

Method

Participants

The current longitudinal study uses data derived from the Colorado Adoption Project (CAP; Plomin & DeFries, 1983; Rhea et al., 2013a), Longitudinal Twin Study (LTS; Rhea et al., 2013b), and the CATSLife study (Wadsworth et al., 2019). CATSLife1 is a combined follow-up of the LTS and CAP samples as they approach midlife. The CAP study began in 1976 and the LTS study was initiated in 1984 when participants were about one year of age. Until CATSLife1, yearly assessments were conducted through mid-adolescence for both studies (e.g., year 16) and continued periodically into later adulthood for CAP (e.g., year 30). Assessments between studies were nearly identical. The CAP sample consists of 490 families evenly split between adoptive and non-adoptive (i.e., control) families. In total there are 997 probands and their siblings (53% male; 479 adopted vs. 518 control). The LTS sample consists of same-sex twins from a total of 483 families (male–male twin pairs: 240; female–female twin pairs: 243) derived from the Twin Infant Project sample and from independent registry recruitment. The CATSLife1 assessment conducted between 2015 and 2021 tested participants derived from the CAP and LTS sample; ages ranged from 28 to 49 years old among the 1,327 individuals (M_{age}=33.3, Female=53.1%, 219 adopted individuals, 343 complete twin pairs). Overall, nearly all CATSLife1 participants (N=1,257 or 94.7%) completed at least one cognitive assessment examined in this study.

The current analysis sample of 1,236 individuals includes those with cognitive data from at least one assessment point between year 12 and the CATSLife1 assessments and available smoking consumption data at year 16 and CATSLife1 assessments. For the analytic sample, at least two waves were required since the smoking difference score was reliant on self-reported smoking consumption in year 16 and CATSLife1. Overall, the majority of CAP (75.3%) and LTS (99.3%) participants had cognitive data available for more than half of the available time points within each project (Appendix 2 Table A2.1). The analytic sample comprises individuals within 710 families and participants ranging in average age from 12.4 years (*SD*=0.4) at the year 12 assessment and up to 33.3 years of age (*SD*=5.0) at the CATSLife1 assessment. Age descriptives by project are reported in Table 2.1.

Measures

Cognitive Functioning

Seven cognitive tests were evaluated in this study, and assessments given were subtests taken from the Colorado Battery of Specific Cognitive Abilities (SCA) (Kent & Plomin, 1987) adopted from the Hawaii Family Study of Cognition protocol (DeFries et al., 1981; Wadsworth et al., 2019) or the Wechsler IQ battery. There were three subtests from the SCA: 1) Names and Faces [sum score of total correct across immediate and delayed], 2) Picture Memory [sum score of total correct across immediate and delayed], and 3) Colorado Perceptual Speed [sum score of total correct across, adjusting for errors].

The Wechsler IQ battery versions differed by age, where at year 12 and year 14 child versions were given (WISC-R or WISC-III) and the adult version administered

starting at year 16 (WAIS-R or WAIS-III; see Table 2.2). Versions for the WISC differed by project where CAP administered the WISC-R (Wechsler, 1974) and LTS the WISC-III (Wechsler, 1991). The adult WAIS IQ battery varied by project and year, with CAP administering the WAIS-R (Wechsler, 1981) in year 16 and year 21, then at year 30, this study gave the WAIS-III (Wechsler, 1993). LTS gave the WAIS-III at year 16. The CATSLife1 protocol included the WAIS-III. Based on other work, the WISC covariance structure among the subtests are essentially equivalent even though the item content differed between versions (Dixon & Anderson, 1995). Similarly, the WAIS-R and WAIS-III adult batteries are also highly correlated for the verbal subtests at .76-.90 and moderately for the .50-.77 performance subtests (Silva, 2008). The four IQ subtests included in the current study included Digit Span (year 16-33), Digit Symbol (year 16-33), Block Design (year 12, 14-33), and Vocabulary (year 12-33). Excluding Digit Symbol, all subtests were transformed from the original point scores to percent correct and scaled to the WAIS-III subtest point scores. Based on the time administration differences between the WAIS-R and WAIS-III for Digit Symbol, the WAIS-R was transformed to timed-based accuracy by dividing total correct by total amount of time for the test (e.g., 90 seconds) then multiplied by the duration of the WAIS-III test (e.g., 120 seconds).

Across the seven cognitive tasks, five specific cognitive ability domains are represented: 1) Episodic Memory: Picture Memory (PM) and Names and Faces (FM); 2) Working Memory/Attention: Digit Span (DSpa); 3) Perceptual Speed: Colorado Perceptual Speed (CPS) and Digit Symbol (DSy); 4) Spatial Reasoning: Block Design

(BD); 5) Verbal: Vocabulary (V). All cognitive scores were standardized to a t-score scale (*M*=50, *SD*=10) by anchoring to the year 16 score, which was represented across CAP and LTS. The year 16 assessment was the preferred anchor as this wave had better representation and intensified collection efforts were made in order to retest individuals before adulthood. There was a nearly 90% response rate for CAP and nearly 85% LTS (Rhea et al., 2013a; Rhea et al., 2013c) with approximately 86.9% across both projects. In addition, year 16 marks an important period of experimentation and early development of persistent smoking behavior (Huggett et al., 2019; Rose et al., 2009). Descriptives for each cognitive measure across wave and project are reported in Table 2.1.

Smoking Behavior

Smoking Consumption at Year 16. Smoking behavior was self-reported, and questions included smoking initiation, when they regularly started smoking, and the number of cigarettes an individual typically smoked in a day within the past 30 days (Jessor & Jessor, 1977). If individuals reported never smoking cigarettes or trying only once, their consumption rates were coded as 0. For those that indicated smoking a cigarette a few times, individuals responded with their consumption rates on a seven-point scale with restricted interval amounts. The scale was transformed to the number of cigarettes smoked to compare with later consumption rates. The scale was transformed to none=0, less than 1 cigarette a day=.5, 1–5 cigarettes a day=3, ½ pack a day=10, 1 pack a day=20, 1½ packs a day=30, and 2 packs a day=40. Analyses used rescaled consumption rates for clearer interpretation, and on average, individuals reported smoking about 1.4 (*SD*=4.9, *Skew*=4.4) cigarettes per day at the year 16 assessment wave. Given the skew in

the reported consumption rates, year 16 reported cigarettes was square-root transformed (*M*=0.4, *SD*=1.1, *Skew*=3.2). Descriptives for smoking at year 16 for the analytic sample are reported in Table 2.3. Descriptives for smoking at year 16 by project in Appendix 2 Table A2.2.

Smoking Consumption by CATSLife1. Smoking behavior was self-reported and followed the PhenX protocol (Hamilton et al., 2011). Smoking consumption was captured as the average number of cigarettes an individual reported smoking a day for current smokers. Former smokers reported their average daily consumption amount when they were regular smokers. If an individual identified as a non-smoker based on not smoking more than 100 cigarettes in their lifetime, their consumption was coded as 0. Regardless of current smoking status, smoking consumption at CATSLife1 indexes a history of smoking prior to the assessment.

Smoking Difference Score. A smoking difference score was created to examine the difference in smoking cigarette consumption from year 16 to CATSLife1. The reported year 16 wave consumption was subtracted from CATSLife1. Negative scores represent a loss in reported regular consumption, 0 will correspond to no change, and positive scores indicate gains in consumption by the CATSLife1 wave. Analyses used a difference score for clearer interpretation, and on average, individuals reported smoking about 2.3 (*SD*=7.0) more cigarettes per day at the CATSLife1 assessment wave compared to the year 16 assessment. To evaluate smoking differences among those that gain in cigarette consumption, and to adjust for skew, sensitivity analyses were completed with a modified difference score by only examining those that gained in cigarette consumption.

The gain score was then square-root transformed to adjust for skew (*M*=0.8, *SD*=1.5). Descriptives for the smoking difference score are reported in Table 2.3.

Parental Education

Parental education was collected for each parent at the year 14 assessment wave for CAP and LTS participants. The highest years of education attained between parents was used for analysis. The year 7 and 12 assessment waves were reviewed to refine parental education and supplement missing data at year 14. A few cases (*N*=6) in LTS were still missing after reviewing prior waves; hence, the year 16 highest years of parental education was used. All siblings were matched on parental education, and thus, it served as a family level measure. Parental education was centered at 16 years of education or equivalent to a bachelor's degree (*M*=16.3, *SD*=2.3)

Covariates

Several covariates were included in these analyses. The covariates included were sex (0=F, 1=M), project (-0.5=CAP, 0.5=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-Hispanic, 1=Hispanic), and race (0=White, 1=Non-White).

Statistical Analyses

All analyses were conducted using SAS 9.4 (SAS Institute Inc, 2016).

Attrition Analyses. Multilevel analyses were conducted to evaluate attrition for those in the analytic sample that participated during year 16 and those that did not participate by CATSLife1 (see Table 2.4). Year 16 was used to evaluate attrition given the high representation across LTS and CAP, as well as being the latest wave for both

projects to capture adolescent smoking. All analyses controlled for familial clustering, age, age^2, sex, and project. Attrition analyses revealed that fewer men participated by CATSLife1 (B=-0.10, *SE*=0.03, *p*=.0001), and the analytic sample had more educated parents with about 6 more months of education (B=0.47, *SE*=0.18, *p* = .009). In addition, those that didn't participate in CATSLife1 tended to have lower cognitive scores on all tasks (Bs=-2.0-[-]2.7), *p* < .009) except for Names and Faces (B=-0.17, *SE*=0.29, *p*=.57). There were no differences between the analytic and attrition sample on adoption status, race, ethnicity, or cigarettes reported smoking at year 16 (all *p*s > .26).

Unconditional Growth Models. Multilevel models were fitted to estimate unconditional growth (i.e., no added covariates) to find the general longitudinal trend for each cognitive measure, pooling data across the projects. All models accounted for family-level clustering, and random effects were estimated for the intercept and slope terms which were decomposed into within and between pair variances based on sibling type and the time-specific within-person residual. More specifically, random effects were split into four groups based on family type: adoptive (AD), control (Con), dizygotic twins (DZ), or monozygotic twins (MZ). The within-effect (σ^2 WI) represents differences in cognitive performance within a family, and the between-effect (σ^2BW) corresponds to the similarity between siblings. In addition, all models used full maximum likelihood estimation to account for missingness.

Table 2.5 provides an overview of all unconditional growth model runs and equations with parameter definitions. All models were age-based, meaning the time unit to capture the growth rate was age centered at 16 years old and scaled to half-decade

units (i.e., (age-16)/5). The age scaling was set to half-decade to aid in model convergence. The first model (M0) corresponds to the means-only model where only the intercept (β_{01}) was estimated. Next, the linear model (M1) included the intercept (β_{01}) and linear slope (β_{02}). Based on the age scale, the linear model intercept reflects the cognitive performance at age 16, and the slope reflects the individual rate of change at half-decade intervals. Several cognitive measures (Digit Span, Digit Symbol, and Block Design) supported a linear model only given three available waves across both projects (Grimm et al., 2016). For the remaining cognitive measures that had more than three assessment waves, the next model fitted (M2) included a quadratic term to capture nonlinear rates of growth. Last model (M3) was a bilinear spline model with a knot at age 16. The first slope is referred to as Spline1 and corresponds to the linear rate of change up to age 16 for each half-decade. The second slope is referred to as Spline2 and corresponds to the individual linear rate of change after age 16 for each half-decade. Thus, Spline1 represents growth during adolescence, and Spline2 captures, mostly, adulthood growth.

The chi-square difference test was used to assess the model fit between unconditional models. Comparisons were made with nested models that differed based on growth terms included. A significant difference in the chi-square indicated improvement in fit with the inclusion of the new terms (Grimm et al., 2016). The Akaike Information Criterion (AIC) was also reviewed, where models with lower AIC values suggested better fitting models calibrated on the parameters (K) included (Akaike, 1987). In other words, AIC favors parsimony and penalizes models based on the number of parameters estimated. Thus, even though a model may have a lower negative 2-loglikelihood (-2lnL),

the penalty imposed (i.e., -2lnL+K*2) may suggest the difference in included parameters is not sufficient to retain the more complex model.

To further examine whether intraindividual differences were significant, thus allowing between person predictors on the slope term(s), additional follow-up models were fitted, dropping random effects on the slope(s). One additional model was fitted for linear models (M1a), while two additional follow-up models (M3a and M3b) were tested for bilinear models. In the original sample analyses, all cognitive tasks assessing nonlinear growth demonstrated a preference for bilinear growth over quadratic growth; thus, no follow-up was completed for quadratic models. The random effects were dropped, and the follow-up model (M1a) was compared with the base linear (M1) model to test if there was a significant reduction in fit, suggesting significant random effects. Similarly, the bilinear spline model then dropped random effects on the 1st spline (M3a), and the 2nd model dropped random effects across both slope terms (M3b). Model fit for the follow-up models (i.e., M1a, M3a, and M3b) used the same chi-square test, but a significant difference suggested a reduction in fit indicating important between-person slope heterogeneity should be retained.

Conditional Growth Models. Once a baseline growth model could be determined, the next series of model runs were conditional on a set of included time-invariant predictors to evaluate the smoking consumption associations with cognitive functioning. The bottom half of Table 2.5 provides an example series of conditional linear growth models runs as well as equations with predictors bolded and defined. The base conditional model (M0) includes the noted covariates on the intercept and slope(s).

The time-invariant covariates accounted for between-person differences in cognitive performance and growth rates. Based on the coding for the covariates, the fixed effects represent the average cognitive performance and the growth rate for female, non-adopted, white and non-Hispanic individuals, controlling for project. Next, Model 1 (M1) retained the outlined covariates and included the time-invariant smoking behavior (smoking consumption at age 16 and smoking difference) measures on the intercept. After adjusting for covariates, the average cognitive performance represents non-smokers plus any deviations to average performance based on smoking consumption at age 16.

In addition, the difference in smoking consumption up to midlife captured any contribution to the average level of cognitive performance not captured by extant smoking consumption at age 16. It is important to note we are using time-invariant smoking behavior measures that occur after the first cognitive assessment (i.e., year 12), but the age-based growth models are centered at age 16. Thus, the smoking measures allow us to observe from CATSLife1 whether there are any intercept differences in cognitive performance at a consequence of smoking consumption at age 16 and the additional impact of any gains from smoking consumption after age 16. The smoking measures were then entered on the slope for the second model (M2). Under this model, after covariate adjustment, the average slope represents non-smokers plus any deviations to the average slope based on smoking consumption at age 16 and the difference in smoking consumption up to midlife. In other words, the time-invariant smoking measures allow us to trace backward from CATSLife1 the rate differences in cognitive trajectories associated with adolescent smoking consumption. The difference score will then capture

any additional impact for each cigarette reported on the slope of cognitive trajectories outside the baseline adolescent smoking consumption. The third model (M3) only included smoking behavior on the slope to test whether associations of smoking behavior influenced the cognitive growth rate but not intercept. The last model (M4) was the best fitting model with a smoking measure and with parental education on the intercept and slope entered. Parental education was added to test whether smoking behavior fixed effects were attenuated based on a proximate SES measure.

Random Effects Variances and Sibling Similarity. In the results section, we will focus on describing fixed effect patterns. However, for both unconditional and conditional growth model results, we present random effects variances for completeness where, as noted, the within-effect (σ^2 WI) represents differences in cognitive performance within a family, and the between-effect (σ^2BW) corresponds to the similarity between siblings. The random effect variances for conditional growth models are reported in Appendix 2 Table A2.3 to A2.9 and are similar to the unconditional growth models (c.f., Table 2.8).

As a rule, variance components for the intercept estimates conform to genetic and environmental relatedness patterns of siblings (Berglund et al., 2016; Knopik et al., 2017; Luna et al., Under Review), where sequentially MZ twin pairs tend to show relatively smaller σ^2 WI and larger σ^2BW, followed by DZ pairs, followed by siblings in control families, then siblings in adoptive families. This suggests that genetic and environmental factors contribute to individual differences in cognitive performance at age 16. Patterns

for slopes tend to show relatively greater σ^2 WI than σ^2BW across sibling types, suggesting relatively greater (non-shared) environmental contributions to change.

Sensitivity Analyses. Sensitivity analyses for Digit Span, Colorado Perceptual Speed, Digit Symbol, and Block Design were conducted with only the CAP project participants to review whether the cognitive gains observed in adulthood were replicated in CAP participants alone. We repeated analyses with only the CAP participants for two reasons. First, CAP participant birth years are about a decade earlier compared to the LTS sample, although there is overlap. Moreover, the assessment coverage during early adulthood for CAP participants is greater (e.g., year 21 and 30) than LTS. Given the fewer waves available for LTS compared to CAP, we limited the growth models to assess simple linear growth for the Digit Span, Digit Symbol, and Block Design tasks. We then tested whether a difference was observed between growth patterns in the pooled analysis compared to the CAP-only analysis.

Prior work with later adulthood samples tends to observe the emergence of cognitive decline before midlife for fluid or age-sensitive traits (Baltes, 1997; Hartshorne & Germine, 2015; Horn & Cattell, 1967; Li et al., 2004; McArdle et al., 2002; Salthouse, 2006; Tucker-Drob, 2019). Based on our observations of growth for these tasks, we are testing whether the increased rate of cognitive performance across adulthood is due to age curves being anchored to a time period (~30 years) before more precipitous cognitive decline may occur (Hartshorne & Germine, 2015). Thus, sensitivity analyses will test if the age curves for only the CAP project potentially captures decline for these cognitive tasks across early adulthood up to midlife. CAP-only unconditional growth model will

test nonlinear growth models, where only linear models were tested in the pooled analysis. Additionally, we will test if changing the knot point in a spline model to 21 or 30 years provides a better proximation to the bilinear growth pattern than the year 16.

Another series of sensitivity tests were done to evaluate whether skewness in smoking behavior measures contributed to our findings. Model 4 for each cognitive test was retested with the square-root adjusted measures for the year 16 consumption and the smoking gains only score.

Results

Cognitive Measures

On average, all cognitive tasks show performance increases up until age 30 within each project (see Table 2.1). At CATSLife, for CAP participants who are on average 38 years, some average declines are notable with more pronounced differences in episodic memory and processing speed tasks. Variability generally increased up to age 14 for episodic memory tasks (i.e., PM & NF) and remained relatively stable thereafter. WAIS tasks, such as Digit Span, Block Design, and Vocabulary showed moderate to large increases from the first assessment to CATSLife1.

Smoking Measures

Smoking behavior descriptives are provided in Table 2.3. At year 16, the average consumption rate is approximately 1.4 (*SD*=4.9) cigarettes, and most of the sample (84.4%) did not report smoking cigarettes in the last month. Individuals who reported smoking at least 1 cigarette a day tended to smoke on average about 8.9 (*SD*=9.5) cigarettes. CAP participants also smoke more (*M*=9.7, *SD*=9.9) than LTS (*M*=7.5,

SD=8.8); see Appendix 2 Table A2.2 for smoking consumption descriptives by project. There was an inverse relationship between age at regular smoking and smoking consumption (*r*=-.19, *p*=.01). The younger an individual started smoking, the more consumption they report by year 16, with the average age of regular smoking reported as 13.5 (*SD*=2.0) years.

By CATSLife1, about 63.1% of the sample identified as non-smokers, with 21.0% as former smokers and 15.9% as current smokers. Interestingly, former smokers (*M*=10.9, *SD*=8.9) reported, on average, smoking more before quitting than current smokers (*M*=8.6, *SD*=6.3). Ever smokers (i.e., the combination of current and former) tend to report smoking about half a pack (*M*=9.9, *SD*=8.0) and reported starting regularly smoking at 15.2 (*SD*=3.4) years with about 9.7% of the sample starting at age 18 or after. Overall, there is a general gain in smoking consumption, with ever smokers reporting about 6.3 (*SD*=10.1) more cigarettes by CATSLife1, which was higher for former (*M*=7.8, *SD*=10.8) compared to current smokers (*M*=4.4, *SD*=8.8). Few ever smokers (*N*=52) reported smoking fewer cigarettes by CATSLife1 compared to year 16 at about 11.2 (*SD*=7.3) fewer cigarettes.

Correlations

Correlations of key study measures and covariates with cognitive measures at year 16 and CATSLife1 are presented in Table 2.6. All partial correlations are adjusted for age, age^2, and sex for all variables excluding sex and age, where reported correlations are only adjusted for age effects on sex and sex effects for age. Small and negative associations were observed between smoking consumption at year 16 (e.g., Cigs16) and

year 16 cognitive performance across all cognitive measures (*rs* = -.11-[-].07, *p*s < .02), suggesting minor relations between adolescent smoking consumption and worse cognitive performance. A similar pattern was seen for smoking consumption at year 16 and CATSLife1 cognitive performance (*rs* = -.13-[-].06, *p*s < .05). Smoking difference (e.g., SmkDiff) was significantly associated with year 16 Colorado Perceptual Speed only (*r* = -.07, *p* = .018) and likewise observed for CATSLife1 Colorado Perceptual Speed (*r* = -.07, *p* = .012). Relations between smoking consumption measures and year 16 and CATSLife1 cognitive performance were very consistent with the exception of Digit Symbol and Vocabulary. Parental education was correlated with all cognitive measures across assessment wave with the exception of Picture Memory (*rs* = .02-.04, $p \geq .20$). Correlations between parental education and cognitive performance were positive and consistent in magnitude across assessment waves and ranged from small for most tasks (*rs* = .06-.14, $p \leq .033$) to moderate for Vocabulary ($r \geq .28$, *p* <.0001).

Growth models

Picture Memory (PM)

Unconditional Growth Model. The best fitting growth model for Picture Memory was the bilinear spline with a knot point at age 16 with random effects only on the intercept (see Table 2.7). Due to convergence issues, random effects could not be simultaneously modeled on both slope terms. The bilinear model showed a significant improvement in fit relative to the linear model ($\chi 2(1)=309.6$, *p*<.001). Random effects could be dropped without appreciable effects on model fit ($\chi 2(16)=25.6$, *p*=.06) and had the lowest AIC compared to all other models (AIC=35801.5). The bilinear slope model

suggested a linear increase from age 12 of 7.79 (*SE*=0.46, *p*<.001) points per half-decade up until age 16 (see Table 2.8). After age 16, Picture Memory decreased in performance by -1.12 (*SE*=0.08, *p*<.001) points per half-decade up until midlife.

Conditional Growth Model. For Picture Memory, the best fitting conditional growth model with smoking measures included was Model 1 (see Table 2.9). The chi-square difference test suggests an improvement in fit relative to the base model (M0) with only covariates ($\chi 2(2)=17.2$, $p<.001$). For Model 1, when entering the smoking behavior, smoking at 16 was significant. According to this model, individuals with a smoking history had a lowered average cognitive performance at age 16 after controlling for covariates. For every additional cigarette smoked at age 16, individuals had approximately -0.20 (*SE*=0.05, *p*<.001) points lower performance on their Picture Memory task. Model 4 entered parental education on the intercept. Parental education was not a significant predictor and smoking behavior effects on the intercept remained consistent. For completeness, Figure 2.1 shows predicted Picture Memory scores across age for non-smokers, year 16 non-smokers that gain in consumption of a half and full pack, and year 16 smokers that smoke 9 cigarettes and gain in consumption of a half and full pack. Ultimately as shown by the Figure 2.1, there were larger performance differences for those who smoked more at age 16 than those who changed their smoking consumption (i.e., started smoking after age 16 or increased smoking amount) or remained non-smokers.

Names & Faces (NF)

Unconditional Growth Model. The best fitting growth model for Names and Faces was the bilinear spline with a knot point at age 16 with random effects on the intercept and both slopes (see Table 2.7). The bilinear model showed a significant improvement in fit relative to the linear model ($\chi2(25)=1260.7$, $p<.001$) and also had a lower AIC compared to all other models (AIC= 34249.8). Slope variances for both adolescent and adulthood growth were necessary to retain based on the significant reduction in fit when Spline1 ($\chi2(24)=181.8$, $p<.001$) and Spline2 ($\chi2(16)=73.1$, $p<.001$) were dropped suggesting important intraindividual differences in change across age.

The bilinear slope model suggested a linear increase from age 12 of 14.30 (*SE*=0.37, $p<.0001$) points per half-decade up until age 16 (see Table 2.8). After age 16, there was a linear decrease in performance of -0.33 (*SE*=0.07, $p<.0001$) points per half-decade up until midlife.

Conditional Growth Model. For Names and Faces, the best fitting conditional growth model with smoking measures included was Model 3 based on the lowest AIC, although the difference between models was trivial (see Table 2.10). Model fit for M3 did not suggest a significant improvement in fit relative to the base model (M0) with only covariates ($\chi2(2)=5.9$, $p=.052$). Model 3 included smoking at 16 and smoking difference on the slope but only smoking at 16 was significant (B=-0.03, SE=0.01, $p=.02$). According to this model, for every additional cigarette an individual smoked at age 16, individuals had approximately -0.03 points lower performance on their Names and Faces task, after controlling for covariates and smoking difference by midlife. Model 4 entered

parental education on the intercept and slope. Parental education was a significant predictor on the intercept (B=0.28, *SE*=0.13, *p*=.04), with individuals showing about 0.28 points higher on average performance for every additional year increase in education. Further, the smoking at age 16 effect on the intercept remained consistent after parental education was included. Figure 2.2 shows predicted change in Names and Faces scores across age for non-smokers, year 16 non-smokers that gained in consumption of half and full pack, and year 16 smokers that smoked 9 cigarettes and gained in consumption of half and full pack. According to Figure 2.2, individuals that smoked more at age 16 show more declines in performance than those who changed their smoking consumption or remained non-smokers.

Digit Span (Dspa)

Unconditional Growth Model. The best fitting growth model for Digit Span was the linear model with random effects on the intercept and slope (see Table 2.7). Note, based on the number of waves shared between CAP and LTS, only the linear model was fitted. The linear model showed a significant improvement in fit relative to the means only model ($\chi 2(17)=346.1$, $p<.001$) and also had a lower AIC compared to all other models (AIC= 21364.4). There was significant slope variation that was necessary to retain based on a significant reduction in fit when linear random effects ($\chi 2(16)=47.4$, $p<.001$) were dropped, suggesting important intraindividual differences in change across age. The linear slope model suggested a linear increase from age 16 of 1.25 (*SE*=0.07, $p<.0001$) points per half-decade up until midlife (see Table 2.8).

Conditional Growth Model. For Digit Span, the best fitting conditional growth model with smoking measures included was Model 1 based on the lowest AIC (see Table 2.11). The chi-square difference test suggests an improvement in fit relative to the base model (M0) with only covariates ($\chi 2(2)=8.5$, $p=.014$). Model 1 included smoking at 16 and smoking difference on the intercept but only smoking at 16 was significant (B=-0.12, *SE*=0.06, $p=.03$). According to this model, for every additional cigarette an individual smoked at age 16, individuals had approximately -0.12 points lower performance on their Digit Span task, after controlling for covariates and smoking difference by midlife. Model 4 entered parental education on the intercept and slope. Parental education was not a significant predictor, but inclusion did attenuate the smoking at age 16 effect on the intercept (B=-0.11, SE=0.06, $p=.06$) where the effect was no longer significant. Although smoking behavior is non-significant after parental education was entered, for completeness Figure 2.3 shows predicted Digit Span scores across age for non-smokers, year 16 non-smokers that gained in consumption of half and full packs, and year 16 smokers that smoked 9 cigarettes and gained in consumption of half and full packs.

Colorado Perceptual Speed (CPS)

Unconditional Growth Model. The best fitting growth model for Colorado Perceptual Speed was the bilinear spline with a knot point at age 16 with random effects on the intercept and the Spline2 (see Table 2.7). The bilinear model showed a significant improvement in fit relative to the linear model ($\chi 2(1)=2360.6$, $p<.001$) and also had a lower AIC compared to all other models (AIC= 33264.5). Random effects on both linear terms could not be modeled simultaneously as boundaries were hit when estimating slope

variance across sibling type. Thus, model M3a retains random effects only on Spline2 (i.e., M3a). There was significant slope variation based on a significant reduction in fit when the Spline2 random effects ($\chi 2(16)=118.8$, $p<.001$) were dropped, suggesting important intraindividual differences in change after age 16. The bilinear slope model suggested a linear increase from age 12 of 20.52 (*SE*=0.30, $p<.0001$) points per half-decade up until age 16 (see Table 2.8). After age 16, there was still a linear increase but at a slower rate in growth in performance of 1.14 (*SE*=0.07, $p<.0001$) points per half-decade up until midlife.

Conditional Growth Model. For Colorado Perceptual Speed, the best fitting conditional growth model with smoking measures included was Model 1 (see Table 2.12). The chi-square difference test suggests an improvement in fit relative to the base model (M0) with only covariates ($\chi 2(2)=20.0$, $p<.0001$). Model 1 included smoking at 16 and smoking difference on the intercept. According to this model, individuals with a smoking history had a lower average cognitive performance at age 16 after controlling for covariates. For every additional cigarette smoked at age 16, individuals showed -0.22 (*SE*=0.05, $p<.0001$) points lower performance on the Colorado Perceptual Speed task.

Additionally, an individual's performance at age 16 was lower by -0.12 (*SE*=0.04, $p=.0007$) points for every additional cigarette smoked by CATSLife1, suggesting biases such that age 16 smoking does not by itself capture performance differences at age 16 without taking into account future gains in smoking. Model 4 entered parental education on the intercept and slope. Parental education was a significant predictor on the intercept (B=0.33, *SE*=0.12, $p=.01$) only, with individuals showing about 0.33 points higher on

average performance for every additional year increase in parental education. Further, the intercept effects of smoking behavior remained fairly consistent after parental education was included. Figure 2.4 shows predicted Colorado Perceptual Speed scores across age for non-smokers, year 16 non-smokers that gain in consumption of a half and full pack, and year 16 smokers that smoked 9 cigarettes and consumption gains by CATSLife1 of half and full pack. According to Figure 2.4, any history of smoking was associated with lower average performance with worst performance observed for those that smoke about a half pack of cigarettes at age 16 and increase their consumption by a full pack before midlife.

Digit Symbol (DSy)

Unconditional Growth Model. The best fitting growth model for Digit Symbol was the linear model with random effects on the intercept and slope (see Table 2.7). Note, based on the number of waves shared between CAP and LTS, we only fitted a linear model. The linear model showed a significant improvement in fit relative to the means only model ($\chi 2(17)=225.8$, $p<.001$) and also had a lower AIC compared to all other models (AIC= 20871.9). Slope variation was significant and therefore necessary to retain based on a significant reduction in fit when linear random effects ($\chi 2(16)=35.9$, $p=.003$) were dropped, suggesting important intraindividual differences in change across age. The linear model suggested a linear increase from age 16 of 0.93 ($SE=0.07$, $p<.0001$) points per half-decade up until midlife (see Table 2.8).

Conditional Growth Model. For Digit Symbol, the best fitting conditional growth model with smoking measures included was Model 2 based on the lowest AIC

(see Table 2.13). The chi-square difference test suggests an improvement in fit relative to the base model (M0) with smoking measures on the intercept for Model 1 ($\chi 2(2)=23.5$, $p<.001$). Moreover, the inclusion of smoking measures on the slope (M3) also showed improved fit compared to M1 ($\chi 2(2)=9.3$, $p=.01$). Model 2 included smoking at 16 and smoking difference on the intercept and slope where smoking at 16 was significant on the intercept (B=-0.22, *SE*=0.06, $p<.001$) and slope (B=-0.03, *SE*=0.01, $p=.03$). Smoking difference was only significant on the slope (B=-0.03, *SE*=0.01, $p=.005$). According to this model, for every additional cigarette an individual smoked per day at age 16, individuals had approximately -0.22 points lower performance on their Digit Symbol test and a dampened growth of -0.03 after controlling for covariates and smoking difference by midlife. Moreover, if an individual smoked more by midlife then for every additional cigarette in their daily smoking consumption by midlife, their growth in performance was dampened by -0.03 after controlling for covariates and smoking at age 16. Model 4 entered parental education on the intercept and slope. Parental education was a significant predictor on the intercept (B=0.45, *SE*=0.13, $p=.0007$), with individuals showing about 0.45 points higher on average performance for every additional year of parental education. Further, the smoking at age 16 effect on the intercept remained consistent after parental education was included. Figure 2.5 shows predicted change in Digit Symbol scores across age for non-smokers, year 16 non-smokers that gained in consumption of half and full pack, and year 16 smokers that smoked 9 cigarettes and gained in consumption of half and full pack.

Block Design (BD)

Unconditional Growth Model. The best fitting growth model for Block Design was the linear model with no random effects on the slope (see Table 2.7). Note, we limited to testing only a linear due to fewer measurement occasions shared between CAP and LTS. The linear model showed a significant improvement in fit relative to the means only model ($\chi 2(17)=257.1$, $p<.001$). Random effects could be dropped without appreciable effects on model fit ($\chi 2(16)=18.3$, $p=.307$). The linear slope model suggested a linear increase from age 12 of 0.76 (*SE*=0.05, $p<.0001$) points per half-decade up until midlife (see Table 2.8).

Conditional Growth Model. For Block Design, the best fitting conditional growth model with smoking measures included was Model 1 (see Table 2.14). The chi-square difference test suggests an improvement in fit relative to the base model (M0) with only covariates ($\chi 2(2)=17.7$, $p=.0001$) when smoking measures were entered on the intercept. According to this model, for every additional cigarette an individual smoked per day at age 16, individuals had approximately -0.21 (*SE*=0.05, $p<.0001$) points lower performance on their Block Design task after controlling for covariates and smoking difference by midlife. Additionally, an individual's performance at age 16 was lower by -0.09 (*SE*=0.03, $p=.008$) points for every additional cigarette smoked by midlife, suggesting biases such that age 16 smoking does not by itself capture performance differences at age 16 without taking into account future gains in smoking. Model 4 entered parental education on the intercept and slope. Parental education was a significant predictor on the intercept (B=0.38, *SE*=0.12, $p=.003$), with individuals showing about

0.38 points higher on average performance for every additional year increase in parental education. Further, smoking measures effects remained consistent after parental education was included. Figure 2.6 shows predicted Block Design scores across age for non-smokers, year 16 non-smokers that gain in consumption of a half and full pack, and year 16 smokers that smoke 9 cigarettes and gain in consumption of a half and full pack.

Vocabulary (V)

Unconditional Growth Model. The best fitting growth model for Vocabulary was the linear model with random effects only on the intercept (see Table 2.7). Note, similar to Block Design we only fitted a linear model based on available measurement occasions. The linear model showed a significant improvement in fit relative to the means-only model ($\chi 2(17)=1547.3$, $p<.001$). Random effects could be dropped without appreciable effects on model fit ($\chi 2(16)=7.2$, $p=.969$) and had the lowest AIC compared to all other models (AIC=31682.2). The linear slope model suggested a linear increase from age 12 of 1.90 ($SE=0.04$, $p<.0001$) points per half-decade up until midlife (see Table 2.8).

Conditional Growth Model. For Vocabulary, the best fitting conditional growth model with smoking measures included was Model 1 (see Table 2.15). The chi-square difference test suggests an improvement in fit relative to the base model (M0) with only covariates ($\chi 2(2)=13.6$, $p=.001$). Model 1 included smoking at 16 and smoking difference on the intercept but only smoking at 16 was significant (B=-0.16, $SE=0.04$, $p=.0002$). According to this model, for every additional cigarette an individual smoked per day at age 16, individuals showed approximately -0.16 points lower performance on their

Vocabulary task after controlling for covariates and smoking difference by midlife. Model 4 entered parental education on the intercept and slope. Parental education was a significant predictor on the intercept (B=0.88, *SE*=0.11, $p<.0001$), with individuals showing about 0.88 points higher on average performance for every additional year of parental education. Further, smoking behavior effects on the intercept remained consistent albeit slightly weakened for smoking at age 16 (M1: B_{cigs16}=-.16 vs. M4: B_{cigs16}=-.12). Figure 2.7 shows predicted Vocabulary scores across age for non-smokers, year 16 non-smokers that gain in consumption of a half and full pack, and year 16 smokers that smoked 9 cigarettes and gain in consumption of a half and full pack.

Sensitivity Analysis

CAP-only: Unconditional Models

The unconditional growth models for the CAP-only analyses were conducted for Digit Span, Colorado Perceptual Speed, Digit Symbol, and Block Design, given these tasks demonstrated growth after age 16 up to midlife in the full analysis. Since adults reach peak cognitive performance sometime between age 20 to 30, the linear or bilinear model centered at 16 years was incapable of capturing decline in adulthood (Baltes, 1997; Hartshorne & Germine, 2015; Horn & Cattell, 1967; McArdle et al., 2002; Salthouse, 2006). These age-curves conflict with past research in cognitive aging, and thus we repeated analyses with CAP-only sample since this project is the older of two projects and includes more measurement occasions after age 16. Unconditional models first evaluated different knot points for bilinear spline models: at age 21 or 30 years. For tasks with at least five measurement occasions, we also tested a three-part spline at age 16 and

age 30, or at age 21 and age 30. Appendix 2 Table A2.10 includes model fits based on differing age knots for spline models. Best fitting spline models were then compared to the means only, linear, and quadratic models (see Table A2.11). Based on AIC comparisons, the preferred model differed from the full analysis. We found the Digit Span and Block Design supported a bilinear or 2-part spline model. The processing speed tasks differed with Colorado Perceptual Speed supporting a 3-part spline with two knot points and the quadratic model was the preferred model for Digit Symbol.

CAP-only: Digit Span

The best fitting unconditional growth model was bilinear spline model centered at age 21 with no random effects on slope. For Digit Span, the spline model supported accelerated growth (B=6.36) up to age 21 (see Appendix 2 Table A2.12). After age 21, there was not a significant change in growth for Digit Span. Figure A2.1 in Appendix 2 illustrates the nonlinear trend in the plotted expected trajectory along with observed trajectories for the CAP sample. Conditional analyses were not repeated with smoking measures as predictors, given prior analyses didn't suggest significant associations with intercept or slope after including parental education.

CAP-only: Colorado Perceptual Speed

Overall, the best fitting unconditional model was spline at age 16 and 30, with intraindividual differences on growth rates prior to age 30. For fixed effects see Appendix 2 Table A2.12. The CAP-only analysis supported the rapid acceleration in cognitive growth during adolescence (B_{CAP_Only}=20.33 vs. $B_{Analysis}$=20.52), and weaker trends in gain from 16 to 30, (B_{CAP_Only}=3.00) and the trend becomes negative after age 30

(B_{CAP_Only}=-2.68). The increased growth rate after age 16 in the full analysis ($B_{Analysis}$=1.14) is attributable to collapsing of age effects across the early up to mid adulthood years.

Analyses were then repeated with smoking measures as predictors (See Table A2.13 for model fixed effects and model fit statistics). We found similar results, with the best fitting model being one with smoking consumption on the intercept but not slopes (M1: $\chi 2(2)$=10.6, *p*=.005). After the inclusion of parental education, there was a significant influence of smoking consumption at year 16 (B=-0.19, *SE*=0.07, *p*=.004) and smoking difference (B=-0.13, *SE*=0.04, *p*=.005) on the average performance. The magnitude of the effect was also similar in size between the full sample and CAP-only analysis. Figure A2.2 shows predicted Colorado Perceptual Speed scores across age for non-smokers, year 16 non-smokers that gained in consumption of half and full pack, and year 16 smokers that smoked 9 cigarettes and gain in consumption of a half and full pack.

CAP-only: Digit Symbol

The best fitting model was the quadratic model centered at age 21, with no intraindividual differences suggestive for the growth rate. The quadratic model suggested a linear increase of 2.24 (*SE*=0.18, *p*<.0001) points at age 21, but the increasing trend is damped by the quadratic term of -0.63 (*SE*=0.06, *p*<.0001) per half-decade after 21 years (see Table A2.12). Based on the dampening effect of the quadratic term, the trend changes from increasing to decreasing around 29.9 years.

Analyses were then repeated with smoking measures as predictors given prior pooled analysis (See Table A2.14 for model fixed effects and fit statistics). We found,

generally, similar results, but the best fitting model did differ. When comparing M1 between analyses, we did find similar smoking behavior effects on the intercept. There was a significant influence of smoking consumption at year 16 (B=-0.25, *SE*=0.07, *p*=.0003) but not significantly so for smoking difference (B=-0.09, *SE*=0.05, *p*=.06) on average performance. Associations remained consistent for smoking behavior after the inclusion of parental education. Figure A2.3 shows predicted Digit Symbol scores across age for non-smokers, year 16 non-smokers that gain in consumption of a half and full pack, and year 16 smokers that smoked 9 cigarettes and gain in consumption of a half and full pack.

CAP-only: Block Design

The preferred model was a bilinear spline at age 21 and random effects were meaningful on the growth approaching early adulthood (Spline1) but slope variation on the early adulthood slope (Spline2) could be dropped. The CAP-only analysis supported the increase in cognitive growth as the full sample, but the effect was stronger when centered at age 21 instead of 16 (B_{CAP_Only}=2.34 vs $B_{Analysis}$=0.76). The muted linear increase from the full sample is most likely attributable to the collapsing of age effects across adulthood, where detectable cognitive decline can be observed after age 21 (B_{CAP_Only}=-0.22).

Analyses were then repeated with smoking measures as predictors (See Table A2.15 for model fixed effects and model fit statistics). We found similar results, with the best fitting model including smoking consumption on only average performance at age 21 (M1: $\chi 2(2)$=10.9, *p*=.004). After the inclusion of parental education, there remained a

significant influence of smoking consumption at year 16 (B=-0.22, *SE*=0.07, *p*=.0009) on the average performance. Figure A2.4 shows predicted Block Design scores across age for non-smokers, year 16 non-smokers that gain in consumption of a half and full pack, and year 16 smokers that smoked 9 cigarettes and gain in consumption of a half and full pack.

Skew Adjusted and Gains only Smoking Measures

Sensitivity analyses were conducted to test whether the smoking behavior associations were attributable to outliers in the reported consumption rates. In addition, we examined only gains in the smoking difference score to only examine those that either started smoking after year 16 or increased by CATSLife1. Smokers who decline in their consumption may represent experimental smokers, former smokers, or smokers attempting to quit. Gain scores, square-root transformed, thus evaluates the direct influence of additional cigarettes on average performance compared to year 16 usage rates. Model 4 for all cognitive measures was repeated with square-root and gain score smoking measures (see Appendix 2 Table A2.16). We found similar patterns across the cognitive measures compared to the original analyses. Cigarettes at year 16 was significant on the intercept for all cognitive tasks excluding Names and Faces where only the interaction of the smoking behavior on the slope was fitted. In addition, the smoking gains score significantly predicted the intercept for Colorado Perceptual Speed and Block Design, which was likewise seen in the original analyses. Although patterns were relatively similar there were a couple differences. We observed that smoking consumption at year 16 on Digit Span (B=-0.52, SE=0.24, p=.03) was significant, which

differed from the original analysis. Also in the original analysis, we observed a significant slope interaction of year 16 consumption for Digit Symbol, but the effect was no longer significant for the skew-adjusted score (B=-0.10, *SE*=0.06, *p*=.09).

Our original findings are unlikely driven by outliers based on the consistency between analyses. The magnitude of the effect increased for both measures, although all smoking measures remain to be small in magnitude. Table A2.17 in Appendix 2 lists the expected intercept and slope interactions for the sensitivity analyses and original analyses for each smoking measure. When comparing the skew-adjusted year 16 consumption measure with the original scale, we found a Cohen's *d* equivalent decrease on average cognitive performance ranging from -0.14 to -0.26 for 9 cigarettes smoked per day. The effect size is approximately a third larger of an effect compared to the original scale. For the gain score, we also found an elevation in effect size compared to the difference score of approximately 40% for the significant associations on the intercept. There was a Cohen's *d* equivalent decrease in average cognitive performance ranging from -0.09 to -0.11 for 10 cigarettes. The Names and Faces slope interaction of smoking 9 cigarettes at year 16 had a Cohen's *d* equivalent decrease of -0.04 per every 5 years. The Digit Symbol slope interaction of gaining 10 cigarettes in smoking had a Cohen's *d* equivalent decrease of -0.03 per every 5 years.

Discussion

This study investigated the longitudinal associations between smoking consumption and cognitive functioning in a sample from early adolescence up to midlife.

First, we sought to answer if changes in smoking consumption influence average cognitive performance and trajectories up to midlife that may not be captured by extant adolescent smoking. Contrary to our expectations, we found limited evidence of smoking after age 16 or increases in smoking consumption to impact cognitive development, thus suggesting smoking influence occurs during early life. For the tasks that had significant effects with smoking difference on average cognitive performance at age 16 (i.e., Colorado Perceptual Speed & Block Design), the effect was half the size compared to adolescent smoking. Our findings show that higher smoking consumption at year 16 was associated with lower average performance on all cognitive tasks, excluding the episodic memory binding task Names and Faces. In addition, the rate of cognitive growth was moderated by smoking behavior for Names and Faces and Digit Symbol, where a more rapid decline (Names and Faces) or dampened cognitive growth (Digit Symbol) was associated with both greater levels of adolescent smoking and adulthood smoking gains. Parental education did not account for smoking-cognition patterns apart from Digit Span, suggesting that smoking associations with Digit Span were confounded with a common vulnerability for this task. Overall, findings suggest small detrimental associations of smoking on cognitive performance and change from adolescence up to midlife that do not seems to be due to selection effects.

Cognitive Trajectories and Aging

The shape of the observed cognitive trajectories generally captured growth patterns seen during adolescence and early adulthood, but patterns diverge, covering the middle adulthood range, namely 30 to 40 years old (Baltes, 1997; Hartshorne & Germine,

2015; Horn & Cattell, 1967; Li et al., 2004; McArdle et al., 2002; Salthouse, 2009; Tucker-Drob, 2019). As expected, we show growth in the younger ages, and when methods allowed for nonlinear age curves, there was an accelerated pace after age 16. Notably, we observed growth during middle adulthood for Digit Span, Colorado Perceptual Speed, Digit Symbol, and Block Design which was contrary to expected patterns as either decline in performance should begin to emerge or growth plateaus and stabilize over this age period. For example, performance in working memory, as measured by Digit Span, peaks around age 30 (c.f., Hartshorne & Germine, 2015). In the full analysis, we tested only a linear model for some tasks due to the limited shared waves across projects. We were therefore restricted to growth only age-curve patterns. Hence, we conducted sensitivity analyses to evaluate if these known age trends could be recovered for the older CAP project. The CAP-only analysis showed the more expected normative cognitive aging patterns for the four tasks tested. Digit span peaked around age 21 and showed a small, nonsignificant increase, thus suggesting stability approaching midlife. This finding is in line with past work that suggests less steep changes in Digit Span compared to Block Design and processing speed tasks (Hartshorne & Germine, 2015; Reynolds et al., 2005), albeit the peak is observed earlier than others have seen (c.f., Hartshorne & Germine, 2015). Processing speed peaked around the same age (i.e., age 30) for both tests and declined rate afterward. Peak age is older compared to past work (c.f., Hartshorne & Germine, 2015) but is close to the age range across different tests (i.e., 22-27 years; Salthouse, 2009). Block Design peaked at age 21, which aligns with prior work (Hartshorne & Germine, 2015; McArdle et al., 2002; Salthouse, 2009).

Beyond replicating age curves observed in the cognitive aging literature, CAP-only sensitivity analyses allowed us to review whether smoking consumption effects remained consistent. We examined if smoking consumption slope effects could be found when cognitive losses begin to emerge but didn't find any new slope effects. Further, we couldn't reproduce the smoking interaction found with Digit Symbol where more smoking at age 16 and greater gains in future smoking was associated with dampened growth. However, the difference in findings is more attributable to low slope heterogeneity for older ages in the CAP-only sample.

Adolescent Smoking Consumption

It's difficult to compare our smoking findings with the extant literature as the majority of research exploring the smoking-cognitive relationship is studied in the latter half of the lifespan (Bahorik et al., 2021; Conti et al., 2019; Durazzo et al., 2010; Hill et al., 2003; Nadar et al., 2021; Nooyens et al., 2008; Starr et al., 2007; Swan & Lessov-Schlaggar, 2007). Moreover, very few studies are prospective, and to our knowledge, no study has examined whether smoking influences cognitive trajectories from early adolescence to the cusp of midlife. We found worse cognitive performance the more one smokes at year 16, which aligns with observational work (Fried et al., 2006; Jacobsen et al., 2005; Mahedy et al., 2018; Mahedy et al., 2021). Two studies have explored the associations between early adolescent tobacco use and cognitive change by early adulthood (Castellanos-Ryan et al., 2017) or midlife (Meier et al., 2012), but their findings contradict. Our findings align more closely with the Dunedin Multidisciplinary Health and Development Study that investigated the effect of substance use on cognitive

change from childhood to the single follow-up at midlife (Meier et al., 2012). Meier et al. (2012) assessed tobacco use across five waves from age 18 to 38 and found more persistent tobacco use suggested more declines in cognitive performance. The effects of tobacco persistence on full-scale, verbal, and performance IQ were larger in magnitude compared to our findings when participants met criteria for tobacco persistence on three or more waves (d>-.31). In contrast, our findings differ from the male-only study that explored cannabis effects on change in cognitive performance from age 13-14 to 20 while including tobacco, alcohol, and other drug use as covariates (Castellanos-Ryan et al., 2017). Very limited evidence was found for tobacco use where frequency at age 20 was associated with improved performance on attention, and no associations were found between cognitive change and average tobacco use from age 13 to 17. It is unclear what may account for the divergent findings across these studies. Nevertheless, the studies only examined cognitive change and did not examine cognitive trajectories across time. Thus, our study findings help elucidate the impact of early smoking exposure on developmental patterns on cognitive functioning.

In our study, we generally found more level effects than smoking slope interactions, specifically year 16 smoking consumption. These findings somewhat align with cognitive aging literature as past work has shown baseline-only effects of smoking behavior for some studies (Kasl-Godley, 1996; Lo et al., 2014), but many more studies show the contribution of smoking at baseline or on cognitive decline varies by cognitive ability domain (Amini et al., 2021; Nooyens et al., 2008; Reitz et al., 2005; Richards et al., 2003; Sabia et al., 2012; Vermeulen et al., 2018). When research was inconsistent

between studies on the longitudinal cognitive trends, authors speculated whether the divergence was driven by cohort or methodological differences and smoking-specific timing effects on cognitive tasks. For example, several studies found smoking behavior-related effects on baseline performance levels for processing speed, but findings for episodic memory are somewhat more mixed on whether the associations were more attributable to baseline or cognitive decline (Lo et al., 2014; Nooyens et al., 2008; Vermeulen et al., 2018). Thus, smoking effects on processing speed in earlier adult periods might signal a cognitive trait more susceptible to smoking than episodic memory. However, the current study findings suggest that the influence of smoking exposure might emerge far earlier than when cognitive decline is typically observed. Further, adolescent smoking seems to impact various abilities, excluding working memory/attention after adjusting for parental education. In other words, smoking during adolescence may have an enduring effect up to later adulthood when cognitive performance tends to peak (Baltes, 1997; Hartshorne & Germine, 2015; Horn & Cattell, 1967; Li et al., 2004; McArdle et al., 2002; Salthouse, 2006; Tucker-Drob, 2019).

Our year 16 smoking consumption level effects and limited evidence of slope effects across all tasks may support preserved differentiation rather than differential preservation (Salthouse, 2006; Tucker-Drob, 2019). That is, cognitive-related consequences accrued by age 16 persist into older ages. Thus, smoking influences impacting the average cognitive performance across age but not the rate is suggestive of preserved differentiation given the effects emerged prior to adulthood and the risk to cognitive decline is maintained up to midlife. To illustrate the preserved differentiation

pattern, smoking behavior would affect level but not slope; thus, smokers would have a lower overall cognitive score, but their cognitive trajectories would be parallel across age. A common early life experience that tends to exhibit preserved differentiation would be education (Tucker-Drob et al., 2019), where education influences the level of cognitive performance (Sala et al., 2022) and potentially plays a protective role up until later adulthood (Kremen et al., 2019). Smoking may parallel education, albeit in a negative direction. For example, lifestyle factors, including smoking behavior, have a modest effect on later cognitive outcomes after controlling for earlier adulthood (i.e., age 20) cognitive ability (Franz et al., 2021). Thus, if smoking behavior contributes to earlier life cognitive functioning, then the influence of smoking behavior may be most salient prior to adulthood and only be modestly associated with those that start smoking later in life especially since approximately only 10% of regular smokers try smoking after the age of 18 (Centers for Disease Control and Prevention, 2022).

Although our findings evince more preserved differentiation across tasks, notably results from Names and Faces supported, albeit with small effects, differential preservation (Salthouse, 2006; Tucker-Drob, 2019). For Names and Faces, smoking moderated cognitive growth rate with a more rapid decline associated with greater levels of adolescent smoking. Differential preservation is distinguished from preserved differentiation based on the rate of cognitive aging that is influenced by risk factors, such as greater amount of smoking consumption at age 16. Moderation of growth rate, thus, further widens the difference in cognitive ability between peers that vary by adolescent smoking amount across age. It is unclear why only Names and Faces from the two

episodic memory tasks demonstrated this pattern compared to Picture Memory. Slope moderation may have emerged earlier for Picture Memory due to the difference in difficulty between tasks (Troyer et al., 2011). In addition, trajectories may differ based on test modalities that might be indicative of different episodic memory factors (Kremen et al., 2014; Panizzon et al., 2015). Lastly, we are uncertain whether other tasks would demonstrate differential preservation if measurement continued into middle and older ages. Based on prior cognitive aging and health, smoking may mediate cardiovascular health, thus leading to greater rates of cognitive decline via this health pathway (Sabia et al., 2009; Samieri et al., 2018; Yaffe et al., 2020). Future work will be needed to examine whether smoking coupled with health accelerates cognitive decline from middle age to older adults, thereby demonstrating differential preservation.

The limited impact of later lifestyle factors may explain why smoking consumption at year 16 had a more meaningful influence on cognitive trajectories before midlife than adulthood smoking difference. In other words, those who smoke by year 16 demonstrate overall lower cognitive performance above and beyond those who increase their smoking amount or start smoking later. Thus, these findings may signal the neurotoxicity of tobacco use, specifically nicotine, especially during a vulnerable developmental window of adolescence (Dwyer et al., 2009; Goriounova & Mansvelder, 2012; Mooney-Leber & Gould, 2018; Thorpe et al., 2020). Notably, the PFC and the medial temporal lobe, including the hippocampus, continue to develop across adolescence into adulthood (Fuster, 2002; Romine & Reynolds, 2005; Wierenga et al., 2014). Thus, nicotine exposure as administered via cigarettes may contribute to long-term

deficits in learning and memory that is more sensitive to adolescent use than adulthood use (Zeid et al., 2018). Moreover, chronic nicotine exposure, which is marked by alterations and reduced activation of neurotransmitter and receptor systems, including nAChRs, may influence the development of mood regulatory, executive functioning, memory, and learning systems (DeBry & Tiffany, 2008; Dwyer et al., 2009; Goriounova & Mansvelder, 2012; Thorpe et al., 2020; Zeid et al., 2018). Indeed, even the lowest amount of cigarette smoking at age 16 was associated with reduced gray matter volume in ventromedial PFC from ages 14 to 16 (Chaarani et al., 2019). Notably, we found evidence of smoking at year 16 with worse verbal ability even after adjusting for parental education. This pattern is somewhat unexpected given prior work examining verbal ability with smoking behavior (Durazzo et al., 2010; Reitz et al., 2005; Sabia et al., 2012; Sabia et al., 2008). Moreover, as well documented in cognitive health literature, verbal abilities on average continue to grow until the 7th decade and decline the latest (Li et al., 2004; Pahlen et al., 2018; Reynolds et al., 2005; Salthouse, 2009). Recent research may suggest neural regions linked with language function as well as verbal ability show marked differences in children as young as 9 years old that initiate smoking (Dai et al., 2022). Thus, certain neurological regions may be differentially sensitive to smoking exposure that could persist across time.

Another mechanism by which smoking may impose on cognitive health during adolescence that may compromise later cognitive functioning is via the social environment. In other words, smoking may not directly impact cognitive functioning but, in contrast, influence educational attainment (Gage et al., 2022). Thus, smoking behavior

may be operating by limiting scholastic opportunities and achievement available to students with higher externalizing traits (Erskine et al., 2016; Fergusson & Horwood, 1995) than directly altering neurobiological health that disrupts general cognitive functioning. However, a recent Mendelian randomization study found causal evidence of smoking impacting education attainment but not cognitive ability (Gage et al., 2022). Why this study failed to find evidence linking smoking behavior and cognitive functioning may be due to a possible shared common vulnerability with impulsivity or, more broadly, externalizing psychopathology (Hicks et al., 2021; Krueger et al., 2002) and/or maternal smoking during pregnancy (Fried et al., 2003; Marceau et al., 2019). Additionally, genetic variants for smoking initiation had a direct effect on childhood IQ measured at 8 years old, before initiation of smoking behavior. These findings may also partially explain the childhood smoking initiation associations with lower cognitive performance found by Dai and colleagues (2022). Thus, the argument of social environmental mechanisms is suggestive via disruptions individuals high in externalizing traits may experience within academic settings. Further, the bidirectional influence of externalizing behavior and educational attainment may, in turn, have later impacts on cognitive development and functioning, but the causal and predictive evidence is not entirely settled (Kulkarni et al., 2021). Future research is needed to explore the potential reciprocal influence of smoking and education.

Change in Smoking

Even though we found stronger associations with year 16 smoking consumption, we found selective associations with the smoking difference score, where the rate of

cognitive growth was moderated by smoking difference for Digit Symbol, with dampened cognitive growth associated with greater levels of adulthood smoking gains. Moreover, additional dosage exposure was associated with worse average performance at age 16 on Colorado Perceptual Speed and Block Design for each additional cigarette smoked.

Findings for Digit Symbol parallel dosage-response findings, either measured as the number of cigarettes smoked or pack years, seen in the cognitive aging literature (Kasl-Godley, 1996; Nooyens et al., 2008; Richards et al., 2003; Sabia et al., 2012; Vermeulen et al., 2018; Weiser et al., 2010). We found less evidence of smoking difference effects for the CAP-only study, but the study may have been underpowered alone to find associations compared to the combined analysis. Results for processing speed and spatial reasoning suggested that after accounting for adolescent smoking, overall average performance was lower for those that increased consumption by CATSLife1. These findings may suggest a continuous temporal impact of smoking. Or these findings may be appropriately interpreted such that lower age 16 Colorado Perceptual Speed and Block Design performance are predictive of increases in smoking by CATSLife1. Coupled with findings of smoking dosage on the intercept, this may suggest some smoking-cognition dynamics. Notably, these tasks represent age-sensitive cognitive abilities as well as speed-based tasks. The processing speed theory in cognitive aging (Salthouse, 1996) posits losses in processing speed mediate the progressive declines in other age-sensitive or fluid-type cognitive abilities. Past work has found some support for this theory, with a study of a Swedish twin sample finding processing speed

to be a leading indicator in memory and spatial composite functioning scores but not verbal ability across middle age (Finkel et al., 2007). Thus, the smoking differences could capture the early additive effects of smoking on cognitive health via health mechanisms such as worse cardiovascular and pulmonary health (Bahorik et al., 2021; Elliott et al., 2021; Lahousse et al., 2015). Indeed, we found the support of global health, as indexed by frailty, significantly associated with worse processing speed performance (e.g., Digit Symbol) in prior cross-sectional work (Luna et al., Under Review).

Why we failed to find evidence of smoking difference on episodic memory, another age-sensitive task, is unclear. A large cross-sectional study covering ages 18 to 85 years found current cigarette smoking was associated with worse episodic memory (Lewis et al., 2021). Moreover, these findings coincide with worse cardiovascular disease detected as early as 18 years old. The study did find sex differences with the smoking effect more pronounced for women and a greater impact of cardiovascular disease on memory performance for men. Thus, future research could explore sex differences in health-mediated pathways. In addition, smoking influences on episodic memory may be more complicated compared to processing speed. For example, the Doetinchem Cohort Study (ages 43-70 years) found current smokers tend to perform worse at baseline on processing speed, and current smoking was related to a greater difference in decline after 5 years for verbal episodic memory (Nooyens et al., 2008). In contrast, a female-only study covering a similar age range (40-79 years) found current smoking was associated with worse baseline performance on processing speed, working memory, and visual episodic memory but not verbal episodic memory (Lo et al., 2014). Further, Lo et al.

(2014) found current smoking was not associated with the rate of cognitive change. Although these two studies' findings align regarding processing speed, they do differ in their episodic memory findings. These divergent findings may suggest different timing effects for episodic memory than processing speed, where smoking effects on processing speed are evident by midlife, but episodic memory may emerge later via affected health pathways. In contrast, smoking effects on episodic memory may be influenced by other underlying factors such as genetic risk. For example, individuals may differ on genetic risk factor for Alzheimer's Disease, such as carriers for the *APOE*-ε4 allele, that could interact with smoking exposure (Durazzo et al., 2015; Reitz et al., 2005).

The smoking difference score may also obscure the heterogeneous usage patterns across ages (Bahorik et al., 2021; Dutra et al., 2017; Fuemmeler et al., 2013). For example, we can't distinguish from the difference score alone whether those that report less smoking at CATSLife1 correspond to former smokers or experimenters (i.e., individuals that try smoking at year 16 but never transition to persistent smoking and thus do not report any regular consumption rates at CATSLife1). Future work could include status measures to gauge more proximal effects of smoking at CATSLife1 or develop latent class trajectories to better capture smoking history profiles. Notably, we observed former smokers report higher rates of smoking relative to adolescent smoking rates than current smokers. It could be that former smokers represent a group of individuals who may have quit at their highest consumption rates due to health concerns. Quitters may also represent individuals with more SES affordances, where health concerns could be identified more quickly, and individuals could have resources to quit successfully. Even

though usage rates tend to be less reliable for former smokers, it is unlikely rates are biased in a certain direction, such as under or overreporting (Soulakova et al., 2012). Delineating these differences across studies is made more difficult with the attrition bias known based on cognitive functioning and smoking behavior (Hernán et al., 2008; Weuve et al., 2012), especially with studies of older adults (Chatfield et al., 2005).

Strengths

Strengths of this study included the longitudinal design, the multiple cognitive abilities, and the analysis covering several important age periods in cognitive development (i.e., adolescence to the cusp of midlife). Indeed, this study was able to capture cognitive trajectories across age that was unavailable in other studies (Dai et al., 2022; Mons et al., 2013; Nooyens et al., 2008; Richards et al., 2003; Sabia et al., 2012; Swan et al., 1992; Vermeulen et al., 2018; Weiser et al., 2010; Whalley et al., 2005). Another strength of this study was that fact attrition might be less of a concern compared to extant smoking-cognitive literature, which is chiefly studied in middle-aged and older adults. Inconsistent findings in the literature may have arisen from attrition bias in older adult samples, especially since individuals who smoke tend to have higher rates of risk for mortality which may weaken the smoking effects on cognitive performance and decline in other studies (Peterson et al., 2020; Weuve et al., 2012). Lastly, this study investigated the distal and proximal impacts of smoking influence on cognitive age curves, narrowing the literature gap as it relates to the timing effect of smoking. In other words, our findings bridge the gap between earlier life exposure and the additive effect of

continued smoking, thus, providing a more nuanced picture of the smoking effect on cognitive development with implications to aging.

Limitations

Although this study has several strengths, there are also limitations. First, although the study projects were representative of the Colorado population at the time of recruitment (Rhea et al., 2013a; Rhea et al., 2013b), the study sample is still predominately White. Thus, our findings may not generalize to more diverse populations. For example, smoking disparities among race and ethnic populations may moderate the smoking-cognitive relations (Amini et al., 2021); however, current evidence remains mixed (Peterson et al., 2020). Second, while we controlled for sex, we did not investigate sex-smoking moderation. Past research has generally shown limited evidence of sex differences in cognitive functioning. When effects were found, they tended to be small (Keith et al., 2008) and the underlying quantitative genetic and environmental contributions did not vary between males and females (Pahlen et al., 2018)**.** By and large, sex differences in cognitive functioning may partially be explained by limited access for women compared to men in older generations (Lövdén et al., 2020), and indeed, the sex differences observed between smoking-education link tend to shrink in younger generations (Silventoinen et al., 2022). Thus, the mixed findings between sex-specific effects found in the smoking and cognitive functioning literature may be mediated in part by social-cultural factors influencing differences in education and smoking behavior across cohorts (Boardman et al., 2011; Wedow et al., 2018), as well as social attitudes and policies surrounding tobacco use (Gao et al., 2022; Kendler et al., 2000; Lee et al.,

2020). Even though combining LTS and CAP projects nearly doubles the analytic sample, the projects do not fully overlap regarding birth cohorts. Although we included project as a covariate in the analysis, the nearly ten-year difference between the projects may contribute to cohort differences that also influence patterns of cognitive trajectories in a combined analysis that are not attributable fully to age (Flynn, 1987; Schaie & Strother, 1968; Schaie et al., 2005). Thus, future research could further explore the impact of cohort effects between the two study projects. Fourth, smoking behavior is comorbid with several other conditions and disorders, namely schizophrenia, ADHD, alcohol use disorders, and anxiety (De Leon & Diaz, 2005; Grant et al., 2004; Thorpe et al., 2020). It is likely that the influence of smoking on cognitive development is not an isolated effect, and future research should explore how polysubstance use, health, and other individual characteristics (e.g., personality) may impact the smoking-cognitive associations. Last, smoking effects may emerge earlier than year 16, especially for individuals that initiate smoking during childhood (Dai et al., 2022). Thus, although we included ages starting at 12 years old, a time before most start smoking regularly, this doesn't exclude the emergence of tobacco-related consequences that may be detected prior to what our investigations found.

Conclusion

Elucidating how smoking may operate and impact cognitive function is important. Disambiguating the mechanisms at play is necessary when developing intervention strategies and understanding the wider implications of the smoking-cognitive relationship from birth to death. Our findings are neither more suggestive of neurobiological nor

social-environmental pathways, however. Even so, we speculate our findings are more likely representative of the coaction of these systems along with underlying genetic propensities and broader ecological contextual factors such as attitudes and policies surrounding environmental smoke exposure and cigarette access (Bronfenbrenner, 2005; Knopik et al., 2017). Future work should investigate these different pathways with the comprehensive data available and the informative genetic family structure in these samples. Therefore, we caution readers from interpreting our findings as causal and deterministic of the neurotoxicity effect of adolescent smoking that persists across the lifespan. This study helps reveal the potential early effects of tobacco smoking on cognitive development and health. Moreover, our findings suggest factors that influence cognitive aging, such as tobacco smoking, are not limited to older adults. Factors influencing aging can start early (Barnett et al., 2013a; Bourassa et al., 2022); the more attention we pay to viewing the lifespan in a holistic matter, not dissociable segments, the better we may fare across the continuum.

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Table 2.1. Descriptives of Age and Cognitive Measures across Assessment Years.

		Age			PM		NF		Dspa		CPS		DSy		BD		V	
Year	Project	*M*	*SD*	*N* Range	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
12	CAP	12.4	0.4	390-395	45.5	9.8	40.6	7.3			36.8	7.8			49.2	9.4	53.9	5.9
	LTS	12.4	0.4	589-590	44.0	9.9	40.0	6.7			36.6	7.6			50.5	9.2	51.9	7.3
14	CAP	14.5	0.4	387-390	46.6	10.5	46.3	10.5			42.3	8.9					57.1	6.7
	LTS	14.4	0.4	501-511	46.1	11.0	45.1	9.3			41.2	8.4					57.2	7.5
16	CAP	16.7	1.7	524-562	50.0	10.1	50.4	9.8	51.2	10.2	51.2	10.2	51.7	9.8	50.9	10.0	52.0	10.3
	LTS	16.5	0.7	670-673	49.8	9.8	49.9	9.9	50.0	9.8	50.4	9.9	50.4	10.0	50.0	10.0	50.6	10.2
21	CAP	21.5	0.7	408-410	49.6	9.7	52.2	10.3	56.7	10.4	55.5	10.3	54.5	9.4	52.9	9.0	57.3	8.2
	LTS																	
30	CAP	31.8	1.3	230-231	49.3	9.3	53.5	10.8	58.0	10.6	57.7	10.4	56.1	9.8	53.3	9.5	63.3	7.5
	LTS																	
C1	CAP	38.2	3.3	517-532	45.2	9.9	48.8	9.9	56.8	10.5	54.5	10.7	54.3	10.1	52.3	9.0	62.1	7.0
	LTS	29.4	1.3	641-652	45.2	10.4	48.9	9.9	53.7	11.4	53.2	9.9	55.2	10.6	54.2	8.9	59.4	8.3
	Total	33.4	5.0	1158-1184	45.2	10.2	48.9	9.9	55.1	11.1	53.8	10.3	54.8	10.4	53.4	9.0	60.6	7.8

Note. All cognitive measures are t-scored and scaled to year 16. Analyses included up to six assessment times; each assessment year corresponds to the approximate testing age of the participants. CAP=Colorado Adoption Project; LTS=Longitudinal Twin Study, C1=CATSLife1. PM=Picture Memory, NF=Names & Faces, Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, BD=Block Design, V=Vocabulary.

Table 2.2. IQ Subtest Assessments by Year and Project.

Assessment	Project	WISC–R	WISC–III	WAIS–R	WAIS–III
Year 12	CAP	BD, V			
	LTS		BD, V		
Year 14	CAP	V			
	LTS		V		
Year 16	CAP			X	
	LTS				X
Year 21	CAP			X	
	LTS				
Year 30	CAP				X
	LTS				
CATLife1 (*M*=33)	CAP				X
	LTS				X

Note. CAP=Colorado Adoption Project; LTS=Longitudinal Twin Study. BD=Block Design, V=Vocabulary, X=All 4 cognitive tests were given (Digit Span, Digit Symbol, Block Design, and Vocabulary). Grayed-out rows indicate years not assessed for the project.

Table 2.3. Descriptives of Smoking Measures for Analytic Sample N=1236.

						Smoking Status at C1			
						Former *N*=259		Current *N*=197	
Measure	***M***	***SD***	***Min***	***Max***	***Skew***	***M***	***SD***	***M***	***SD***
Cigs16	1.4	4.9	0	40.0	4.4	3.1	7.1	4.2	7.8
CigsC1	3.6	6.8	0	60.0	2.5	10.9	8.9	8.6	6.3
SmkDiff	2.3	7.0	-35.0	60.0	1.5	7.8	10.8	4.4	8.8
Sensitivity Analysis									
Cigs16sq	0.4	1.1	0	6.3	3.2	0.9	1.5	1.2	1.7
SmkGainsq	0.8	1.5	0	7.7	1.6	2.5	1.6	2.0	1.4

Note. CAP=Colorado Adoption Project; LTS=Longitudinal Twin Study; C1=CATSLife1. Cigs16=Number of cigarettes reported smoking at year 16, CigsC1= Number of cigarettes reported smoking at CATSLife1, SmkDiff=Difference in the number of cigarettes smoked from CATSLife1 (*M*=33 years) and year 16, Cigs16sq=square-root transformation of Cigs16. SmkGainsq=square-root transformation of SmkDiff for only those that gain in consumption by CATSLife1

Table 2.4. Descriptives Statistics for Analytic and Attrition Sample at Year 16.

	Analytic Sample		Attrition Sample					
	N	%	*N*	%	Total *N*	B	*SE*	*p*
Female	1236	53.6%	469	43.6%	1705	-0.10	0.03	**.0001**
Adopted	1236	1.5%	469	1.8%	1705	-0.002	0.01	.82
Non-white	1236	6.5%	469	8.0%	1705	-0.01	0.01	.26
Hispanic	1236	5.3%	469	5.2%	1705	0.001	0.008	.95
		M		*M*				
PEdu	633	18.0	217	17.5	850	0.47	0.18	**.009**
Cigs16	1236	0.8	386	1.0	1691	-0.17	0.29	.57
PM	1235	51.7	395	49.8	1700	-1.96	0.58	**<.0001**
NF	1231	52.2	388	51.9	1693	-0.30	0.55	.58
Dspa	1198	50.0	339	48.5	1644	-1.51	0.58	**.009**
CPS	1235	51.5	393	48.9	1698	-2.61	0.56	**<.0001**
DSy	1195	53.2	334	50.8	1639	-2.37	0.55	**<.0001**
BD	1197	49.1	338	47.0	1643	-2.15	0.58	**.0002**
V	1197	49.6	338	46.9	1643	-2.74	0.56	**<.0001**

Note. Multilevel regression analyses are adjusted for familial clustering, age, age^2, sex, and project. PEdu=Parental Education, matched between siblings (i.e., family-level measure), Cigs16=Number of cigarettes reported smoking at age 16, PM=Picture Memory, NF=Names & Faces, Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, BD=Block Design, V=Vocabulary.
Bolded parameters are significant $p < .05$

Table 2.5. Equations for Unconditional and Conditional Growth Models.

Model		Equation
Unconditional Growth Models		
M0_un	Means Only	$cog_{tij} = (\beta_{01} + d_{1ij})$
M1_un	Linear	$cog_{tij} = (\beta_{01} + d_{1ij}) + (\beta_{02} + d_{2ij}) *(age\_c) + u_{tij}$
M2_un	Quadratic	$cog_{tij} = (\beta_{01} + d_{1ij}) + (\beta_{02} + d_{2ij}) *(age\_c) + (\beta_{03} + d_{3ij}) *(age\_c^2) + u_{tij}$
M3_un	Bilinear Spline	$cog_{tij} = (\beta_{01} + d_{1ij}) + (\beta_{04} + d_{4ij}) *(Spline1) + (\beta_{05} + d_{5ij}) *(Spline2) + u_{tij}$
M1a_un	Linear (no slope random effects)	$cog_{tij} = (\beta_{01} + d_{1ij}) + (\beta_{02}) *(age\_c) + u_{tij}$
M3a_un	Bilinear Spline (no random effects on Spline1)	$cog_{tij} = (\beta_{01} + d_{1ij}) + (\beta_{04}) *(Spline1) + (\beta_{05} + d_{5ij}) *(Spline2) + u_{tij}$
M3b_un	Bilinear Spline (no slope random effects on Spline1 and Spline2)	$cog_{tij} = (\beta_{01} + d_{1ij}) + (\beta_{04}) *(Spline1) + (\beta_{05}) *(Spline2) + u_{tij}$

Age-based measures

age_c= Age centered at 16 scaled to half decade ([age-16]/5)

Spline1= age_c if age_c<16

= 0 if age_c≥16

Spline2= age_c if age_c>16

= 0 if age_c≤16

Parameters

$cog_{tij=}$ cognitive score at the *t* time point (i.e., age) for the *i*th individual within the *j*th sibling

β_{01}= Individual's expected intercept

β_{02}= Individual's expected linear slope

β_{03}= Individual's expected quadratic slope

β_{04}= Individual's expected linear slope through age 16

β_{05}= Individual's expected linear slope after age 16

Random effects

$d_{1ij=}$ residual deviations for the individual from the expected intercept

d_{2ij}= residual deviations for the individual from the expected linear slope

$d_{4ij=}$ residual deviations for the individual from the expected linear slope through age 16

d_{5ij}= residual deviations for the individual from the expected linear slope after age 16

u_{tij} = time specific residual

Model		Equation
Conditional Growth Models *Example Linear Model*		
M0	+covariates	$cog_{tij} = (\beta_{01} + \mathbf{\beta_{p1}(Cov_{ijp})} + d_{1ij}) + (\beta_{02} + \mathbf{\beta_{p2}(Cov_{ijp})} + d_{2ij}) *(age\_c) + u_{tij}$
M1	+SMK on I	$cog_{tij} = (\beta_{01} + \beta_{p1}(Cov_{ij}) + \mathbf{\beta_{21}(Cigs16_{ij})} + \mathbf{\beta_{31}(SmkDiff_{ij})} + d_{1ij}) + (\beta_{02} + \beta_{p2}(Cov_{ij}) + d_{2ij}) *(age\_c) + u_{tij}$
M2	+SMK on I & S	$cog_{tij} = (\beta_{01} + \beta_{p1}(Cov_{ij}) + \mathbf{\beta_{21}(Cigs16_{ij})} + \mathbf{\beta_{31}(SmkDiff_{ij})} + d_{1ij}) + (\beta_{02} + \beta_{p2}(Cov_{ij}) + \mathbf{\beta_{22}(Cigs16_{ij})} + \mathbf{\beta_{32}(SmkDiff_{ij})} + d_{2ij}) *(age\_c) + u_{tij}$
M3	+SMK on S	$cog_{tij} = (\beta_{01} + \beta_{p1}(Cov_{ij}) + d_{1ij}) + (\beta_{02} + \beta_{p2}(Cov_{ij}) + \mathbf{\beta_{22}(Cigs16_{ij})} + \mathbf{\beta_{32}(SmkDiff_{ij})} + d_{2ij}) *(age\_c) + u_{tij}$
M4	Best model [M1] +PEdu	$cog_{tij} = (\beta_{01} + \beta_{p1}(Cov_{ij}) + \mathbf{\beta_{21}(Cigs16_{ij})} + \mathbf{\beta_{31}(SmkDiff_{ij})} + \mathbf{\beta_{31}(PEdu_{j})} + d_{1ij}) + (\beta_{02} + \beta_{p2}(Cov_{ij}) + \mathbf{\beta_{13}(PEdu_{j})} + d_{2ij}) *(age\_c) + u_{tij}$

Cov= Covariates where p = 1 to P covariates [Sex, Adopted, Hispanic, Non-white, and Project]
Cigs16= smoking consumption at year 16
SmkDiff= Smoking difference score from CATSLife1 and Year 16
PEdu= Parental education, matched between siblings

Table 2.6. Partial Correlations Between Key Study Variables with Cognitive Measures at Year 16 and CATSLife1.

		PM	NM	Dspa	CPS	DSy	BD	V
	N	1235	1231	1198	1235	1195	1197	1197
Year 16	Cigs16	**-.08**	**-.07**	**-.08**	**-.11**	**-.10**	**-.09**	**-.10**
	SmkDiff	-.0002	-.05	.04	**-.07**	-.04	-.02	-.03
	Age	**-.10**	.03	.05	**.06**	**.07**	.03	**.13**
	Sex	**-.11**	**-.20**	.02	**-.13**	**-.28**	**.14**	**.06**
	Adopted	-.003	-.02	-.04	-.03	.01	-.03	-.04
	Hispanic	-.02	**-.08**	**-.08**	.01	.01	-.04	**-.10**
	Non-white	-.04	-.03	**-.06**	.003	-.001	-.05	**-.08**
	Project	-.02	-.03	-.05	-.04	**-.08**	-.04	**-.06**
	PEdu	.04	**.07**	**.07**	**.12**	**.13**	**.12**	**.29**
	N	1171	1182	1158	1184	1158	1158	1158
CATSLife1	Cigs16	**-.06**	**-.09**	**-.09**	**-.11**	**-.13**	**-.12**	**-.12**
	SmkDiff	-.03	-.04	.04	**-.07**	**-.09**	-.03	**-.06**
	Age	.01	-.004	**.13**	.01	**-.07**	**-.14**	**.17**
	Sex	**-.16**	**-.17**	.03	**-.08**	**-.22**	**.14**	-.02
	Adopted	-.03	-.06	**-.07**	**-.06**	**-.06**	**-.11**	**-.12**
	Hispanic	.01	-.02	**-.06**	-.03	-.05	**-.06**	**-.09**
	Non-white	-.03	-.02	-.04	.00	-.04	-.06	-.05
	Project	.02	-.01	-.06	**-.09**	-.04	-.02	-.03
	PEdu	.02	**.09**	**.06**	**.10**	**.14**	**.13**	**.28**

Note. Partial correlations adjusted for age, age^2, and sex., Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=Difference in the number of cigarettes smoked from CATSLife1 (*M*=33 years) and year 16, PEdu=Parental Education, PM=Picture Memory, NF=Names & Faces, Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, BD=Block Design, V=Vocabulary.
Bolded parameters are significant $p < .05$

Table 2.7. Model Fit Statistics for Unconditional Growth Curves.

	K	-2lnL	AIC	Model (M) Comparison	$\Delta\chi^2$	df	*p*
PM*							
M0_un: Means only	10	36092.7	36112.7				
M1_un: Linear	27	36061.5	36115.5	M0-M1	31.2	17	**.019**
M2_un: Quadratic	52	35912.8	36016.8	M1-M2	148.7	25	**<.001**
M3_un: Spline at 16 years	--	--	--	--	--	--	**--**
M3a_un: Spline- no random effects Spline1	28	35751.9	35807.9	M1-M3a	309.6	1	**<.001**
M3b_un: Spline- no random effects slopes	12	35777.5	35801.5	M3b-M3a	25.6	16	.06
NF							
M0_un: Means only	10	35776.2	35796.2				
M1_un: Linear	27	35406.5	35460.5	M0-M1	369.7	17	**<.001**
M2_un: Quadratic	28	34746.2	34802.2	M1-M2	660.3	1	**<.001**
M3_un: Spline at 16 years	52	34145.8	34249.8	M1-M3	1260.7	25	**<.001**
M3a_un: Spline- no random effects Spline1	28	34327.6	34383.6	M3a-M3	181.8	24	**<.001**
M3b_un: Spline- no random effects slopes	12	34400.7	34424.7	M3b-M3a	73.1	16	**<.001**
Dspa							
M0_un: Means only	10	21656.5	21676.5				
M1_un: Linear	27	21310.4	21364.4	M0-M1	346.1	17	**<.001**
M1a_un: Linear- no random effects on slope	11	21357.8	21379.8	M1a-M1	47.4	16	**<.001**

	K	-2lnL	AIC	Model (M) Comparison	$\Delta\chi^2$	df	*p*
CPS*							
M0_un: Means only	10	37398.4	37418.4				
M1_un: Linear	27	35569.1	35623.1	M0-M1	1829.3	17	**<.001**
M2_un: Quadratic	52	33590.3	33694.3	M1-M2	1978.8	25	**<.001**
M3_un: Spline at 16 years	--	--	--	--	--	--	**--**
M3a_un: Spline- no random effects Spline1	28	33208.5	33264.5	M1-M3a	2360.6	1	**<.001**
M3b_un: Spline- no random effects slopes	12	33327.3	33351.3	M3b-M3a	118.8	16	**<.001**
DSy							
M0_un: Means only	10	21043.7	21063.7				
M1_un: Linear	27	20817.9	20871.9	M0-M1	225.8	17	**<.001**
M1a_un: Linear- no random effects on slope	11	20853.8	20875.8	M1a-M1	35.9	16	**.003**
BD							
M0_un: Means only	10	26977.4	26997.4				
M1_un: Linear	27	26720.3	26774.3	M0-M1	257.1	17	**<.001**
M1a_un: Linear- no random effects on slope	11	26738.6	26760.6	M1-M1a	18.3	16	.307
V							
M0_un: Means only	10	33200.3	33220.3				
M1_un: Linear	27	31653.0	31707.0	M0-M1	1547.3	17	**<.001**
M1a_un: Linear- no random effects on slope	11	31660.2	31682.2	M1-M1a	7.2	16	.969

Note. PM=Picture Memory, NF=Names & Faces, Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, BD=Block Design, V=Vocabulary; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Best fitting models are highlighted as green; Bolded parameters are significant $p < .05$; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=2991-4943.
*Model couldn't converge with random effects simultaneously modeled on Spline1 and 2.

Table 2.8. Best Fitting Unconditional Growth Models across Cognitive Measures.

		PM	NF	Dspa	CPS	DSy	BD	V
		Spline^{+} B (*SE*)	Spline B (*SE*)	Linear B (*SE*)	Spline B (*SE*)	Linear B (*SE*)	Linear^{+} B (*SE*)	Linear^{+} B (*SE*)
Performance at age 16		**49.67** (0.29)	**50.38** (0.31)	**51.22** (0.32)	**50.51** (0.29)	**51.45** (0.32)	**50.60** (0.29)	**54.19** (0.25)
Spline1		**7.79** (0.46)	**14.30** (0.37)		**20.52** (0.30)			
Spline2 or Linear		**-1.12** (0.08)	**-0.33** (0.07)	**1.25** (0.07)	**1.14** (0.07)	**0.93** (0.07)	**0.76** (0.05)	**1.90** (0.04)
Random Effects								
Residual σ^2		62.17	38.78	36.06	26.64	26.57	26.60	24.66
Intercept	σ^2BW_{AD}	0.00	15.83	0.00	25.51	8.97	27.43	7.84
	σ^2BW_{Con}	8.91	22.28	31.15	9.91	19.55	21.19	16.35
	σ^2BW_{DZ}	23.68	24.76	37.66	27.59	36.14	32.14	40.70
	σ^2BW_{MZ}	28.74	60.01	60.52	50.03	73.27	55.60	53.01
	σ^2WI_{AD}	41.62	43.68	68.70	45.04	61.20	53.93	42.03
	σ^2WI_{Con}	27.32	45.20	43.31	50.51	43.53	29.68	17.97
	σ^2WI_{DZ}	25.35	33.35	17.56	27.87	32.82	33.11	15.50
	σ^2WI_{MZ}	8.74	8.12	4.98	5.84	7.32	6.59	0.00
COV Intercept & Spline1	σ^2BW_{AD}		15.34					
	σ^2BW_{Con}		-0.71					
	σ^2BW_{DZ}		19.87					
	σ^2BW_{MZ}		36.88					
	σ^2WI_{AD}		19.37					
	σ^2WI_{Con}		29.50					
	σ^2WI_{DZ}		15.35					
	σ^2WI_{MZ}		7.97					
Spline1	σ^2BW_{AD}		0.00					
	σ^2BW_{Con}		0.00					
	σ^2BW_{DZ}		13.78					
	σ^2BW_{MZ}		26.66					
	σ^2WI_{AD}		38.02					
	σ^2WI_{Con}		0.00					
	σ^2WI_{DZ}		0.00					
	σ^2WI_{MZ}		0.00					

		PM	NF	Dspa	CPS	DSy	BD	V
		Spline^{+} B (*SE*)	Spline B (*SE*)	Linear B (*SE*)	Spline B (*SE*)	Linear B (*SE*)	Linear^{+} B (*SE*)	Linear^{+} B (*SE*)
COV Intercept & Spline2/Linear	σ^2BW_{AD}		-1.01	1.30	-1.97	-0.70		
	σ^2BW_{Con}		1.02	2.39	1.32	0.75		
	σ^2BW_{DZ}		0.90	-2.30	1.41	-0.15		
	σ^2BW_{MZ}		-2.87	0.41	1.30	-1.50		
	σ^2WI_{AD}		0.88	-0.33	2.99	-0.24		
	σ^2WI_{Con}		-1.54	-1.53	0.26	-0.93		
	σ^2WI_{DZ}		-2.12	9.38	1.62	1.16		
	σ^2WI_{MZ}		0.95	1.92	0.93	0.41		
COV Spline1 & Spline2	σ^2BW_{AD}		-1.64					
	σ^2BW_{Con}		3.21					
	σ^2BW_{DZ}		-1.58					
	σ^2BW_{MZ}		-4.95					
	σ^2WI_{AD}		6.25					
	σ^2WI_{Con}		0.47					
	σ^2WI_{DZ}		-1.32					
	σ^2WI_{MZ}		2.52					
Spline2/Linear	σ^2BW_{AD}		0.07	0.00	0.00	0.33		
	σ^2BW_{Con}		0.02	0.00	0.02	0.11		
	σ^2BW_{DZ}		0.00	0.27	0.66	1.61		
	σ^2BW_{MZ}		0.91	0.76	0.53	1.95		
	σ^2WI_{AD}		0.22	0.10	1.58	0.73		
	σ^2WI_{Con}		0.70	0.09	0.75	0.53		
	σ^2WI_{DZ}		0.81	0.08	0.00	0.00		
	σ^2WI_{MZ}		0.00	1.52	0.00	0.00		

Note. PM=Picture Memory, NF=Names & Faces, Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, BD=Block Design, V=Vocabulary; Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=2991-4943.

$^{+}$No random effects on slopes.

Table 2.9. Conditional Growth Model Fixed Effects: Picture Memory (PM) from year 12 to CATSLife1.

	Model 1		Model 4	
	B	*SE*	B	*SE*
Performance at age 16	**51.23**	0.39	**51.19**	0.39
Sex	**-2.47**	0.46	**-2.48**	0.46
Adopted	0.23	0.66	0.21	0.66
Hispanic	0.67	1.22	0.68	1.22
Non-white	-1.81	1.11	-1.76	1.11
Project	**-1.75**	0.54	**-1.69**	0.54
PEdu			0.07	0.11
Cigs16	**-0.20**	0.05	**-0.20**	0.05
SmkDiff	-0.05	0.03	-0.05	0.03
Spline1	**7.76**	0.46	**7.76**	0.46
Spline2	**-1.14**	0.08	**-1.14**	0.08
Goodness-of-fit				
K	19		20	
-2lnL	35716.5		35716.0	
AIC	35754.5		35756.0	
Model Comparison	M0-M1		M1-M4	
$\Delta\chi 2$	17.2		1	
df	2		0.5	
p	**<.001**		.48	

Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), project (-0.5=CAP, 0.5=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Random effects are not estimated on the bilinear terms, thus Model 2 & 3 with smoking behavior interaction on the slope is not shown. Model 1 refers to adding smoking behavior on the intercept; Model 4 refers to the model with smoking behavior on the intercept and entering parental education; ; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=4923.

Table 2.10. Conditional Growth Model Fixed Effects: Names and Faces (NF) from year 12 to CATSLife1.

	Model 1		Model 2		Model 3		Model 4	
	B	*SE*	B	*SE*	B	*SE*	B	*SE*
Performance at age 16	**52.83**	0.44	**52.80**	0.44	**52.67**	0.44	**52.58**	0.44
Sex	-4.14	0.57	-4.15	0.57	-4.25	0.56	**-4.29**	0.56
Adopted	-0.82	0.83	-0.86	0.83	-0.94	0.83	-0.97	0.83
Hispanic	-2.11	1.45	-2.13	1.45	-2.19	1.45	-2.19	1.45
Non-white	-0.07	1.31	-0.06	1.31	0.04	1.32	0.25	1.32
Project	-1.93	0.69	-1.92	0.69	-1.84	0.69	**-1.64**	0.70
PEdu							**0.28**	0.13
Cigs16	-0.06	0.04	-0.04	0.05				
SmkDiff	**-0.06**	0.03	-0.05	0.03				
Spline1	**15.93**	0.55	**15.93**	0.55	**15.94**	0.55	**15.94**	0.56
Sex	**-2.34**	0.74	**-2.31**	0.74	**-2.30**	0.74	**-2.32**	0.74
Adopted	-2.05	1.18	-2.07	1.18	-2.09	1.18	-2.04	1.18
Hispanic	**-4.87**	1.88	**-4.86**	1.88	**-4.85**	1.88	**-4.81**	1.88
Non-white	1.35	1.78	1.34	1.78	1.33	1.78	1.32	1.78
Project	**-1.72**	0.88	**-1.74**	0.88	**-1.77**	0.88	**-1.76**	0.89
PEdu							0.04	0.17
Spline2	**-0.45**	0.11	**-0.41**	0.11	**-0.40**	0.11	**-0.40**	0.11
Sex	**0.30**	0.14	**0.31**	0.14	**0.32**	0.14	**0.32**	0.14
Adopted	-0.16	0.18	-0.13	0.18	-0.12	0.18	-0.12	0.18
Hispanic	0.72	0.42	0.75	0.42	0.75	0.42	0.76	0.42
Non-white	-0.27	0.37	-0.29	0.37	-0.29	0.37	-0.30	0.37
Project	-0.05	0.18	-0.08	0.18	-0.09	0.18	-0.08	0.18
PEdu							0.003	0.03
Cigs16			**-0.03**	0.01	**-0.03**	0.01	**-0.03**	0.01
SmkDiff			-0.01	0.01	-0.01	0.01	-0.01	0.01
Goodness-of-fit								
K	69		71		69		72	
-2lnL	34061.6		34057.3		34060.2		34053.1	
AIC	34199.6		34199.3		34198.2		34197.1	
Model Comparison	M0-M1		M1-M2		M0-M3		M3-M4	
$\Delta\chi 2$	4.5		4.3		5.9		3	
df	2		2		2		7.1	
p	.11		.12		.05		.07	

Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), project (-0.5=CAP, 0.5=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White,

1=Non-White); Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and 2nd slope; Model 3 refers to only including smoking behavior on the 2nd slope; Model 4 refers to the model with smoking behavior on the 2nd slope and entering parental education; ; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=4926.

Table 2.11. Conditional Growth Model Fixed Effects: Digit Span (Dspa) from year 16 to CATSLife1.

	Model 1		Model 2		Model 3		Model 4	
	B	*SE*	B	*SE*	B	*SE*	B	*SE*
Performance at age 16	**51.60**	0.48	**51.57**	0.48	**51.53**	0.47	**51.50**	0.49
Sex	0.53	0.62	0.50	0.62	0.58	0.61	0.50	0.62
Adopted	**-1.91**	0.90	**-1.91**	0.90	**-2.00**	0.90	**-1.96**	0.90
Hispanic	-0.60	1.43	-0.57	1.43	-0.64	1.43	-0.44	1.43
Non-white	-1.74	1.57	-1.73	1.58	-1.87	1.58	-1.73	1.57
Project	**-3.46**	0.74	**-3.44**	0.74	**-3.43**	0.74	**-3.25**	0.75
PEdu							0.25	0.14
Cigs16	**-0.12**	0.06	-0.12	0.06			-0.11	0.06
SmkDiff	0.04	0.04	0.05	0.04			0.04	0.04
Linear	**1.25**	0.11	**1.26**	0.11	**1.27**	0.11	**1.25**	0.11
Sex	0.13	0.14	0.15	0.14	0.14	0.14	0.13	0.14
Adopted	-0.02	0.17	-0.005	0.17	0.01	0.17	-0.01	0.17
Hispanic	-0.23	0.43	-0.23	0.43	-0.21	0.43	-0.23	0.43
Non-white	0.24	0.38	0.23	0.38	0.24	0.38	0.23	0.38
Project	0.29	0.18	0.28	0.18	0.28	0.18	0.28	0.18
PEdu							-0.01	0.03
Cigs16			-0.01	0.01	-0.02	0.01		
SmkDiff			-0.01	0.01	-0.004	0.01		
Goodness-of-fit								
K	39		41		39		41	
-2lnL	21270.1		21269.4		21277.2		21267.0	
AIC	21348.1		21351.4		21355.2		21349.0	
Model Comparison	M0-M1		M1-M2		M0-M3		M1-M4	
$\Delta\chi 2$	8.5		0.7		1.4		3.1	
df	2		2		2		2	
p	**.014**		.705		.497		.212	

Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), project (-0.5=CAP, 0.5=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and slope; Model 3 refers to only including smoking behavior on the slope; Model 4 refers to the model with smoking behavior on the intercept and entering parental education; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=2994.

Table 2.12. Conditional Growth Model Fixed Effects: Colorado Perceptual Speed (CPS) from year 12 to CATSLife1.

	Model 1		Model 2		Model 3		Model 4	
	B	*SE*	B	*SE*	B	*SE*	B	*SE*
Performance at age 16	**52.42**	0.41	**52.40**	0.41	**52.02**	0.40	**52.28**	0.41
Sex	**-2.34**	0.52	**-2.35**	0.52	**-2.60**	0.52	**-2.39**	0.51
Adopted	-1.13	0.77	-1.15	0.77	-1.44	0.79	-1.17	0.78
Hispanic	0.81	1.28	0.79	1.28	0.57	1.29	0.89	1.27
Non-white	-0.98	1.15	-0.96	1.15	-0.78	1.16	-0.80	1.15
Project	**-2.12**	0.60	**-2.11**	0.60	**-1.88**	0.61	**-1.86**	0.61
PEdu							**0.33**	0.12
Cigs16	**-0.22**	0.05	**-0.20**	0.05			**-0.20**	0.05
SmkDiff	**-0.12**	0.04	**-0.11**	0.04			**-0.11**	0.04
Spline1	**20.45**	0.31	**20.46**	0.31	**20.46**	0.31	**20.46**	0.31
Spline2	**1.04**	0.09	**1.08**	0.10	**1.09**	0.10	**1.04**	0.09
Sex	**0.38**	0.12	**0.41**	0.12	**0.42**	0.12	**0.38**	0.12
Adopted	-0.29	0.16	-0.26	0.16	-0.25	0.16	-0.29	0.16
Hispanic	-0.36	0.35	-0.32	0.35	-0.32	0.34	-0.35	0.35
Non-white	0.30	0.31	0.28	0.31	0.27	0.31	0.29	0.31
Project	0.07	0.14	0.04	0.14	0.04	0.14	0.07	0.14
PEdu							-0.003	0.03
Cigs16			**-0.03**	0.01	**-0.03**	0.01		
SmkDiff			-0.01	0.01	-0.01	0.01		
Goodness-of-fit								
K	40		42		40		42	
-2lnL	33140.5		33135.9		33153.5		33153.5	
AIC	33220.5		33219.9		33233.5		33237.5	
Model Comparison	M0-M1		M1-M2		M0-M3		M1-M4	
$\Delta\chi 2$	20.0		4.6		7.0		13.0	
df	2		2		2		2	
p	**<.001**		.100		**.030**		**.002**	

Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), project (-0.5=CAP, 0.5=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and 2nd slope; Model 3 refers to only including smoking behavior on the 2nd slope; Model 4 refers to the model with smoking behavior on the intercept and entering Pedu; ; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=4943.

Table 2.13. Conditional Growth Model Fixed Effects: Digit Symbol (DSy) from year 16 to CATSLife1.

	Model 1		Model 2		Model 3		Model 4	
	B	*SE*	B	*SE*	B	*SE*	B	*SE*
Performance at age 16	**54.40**	0.45	**54.28**	0.45	**53.93**	0.44	**54.09**	0.45
Sex	**-5.22**	0.58	**-5.30**	0.58	**-5.45**	0.58	**-5.36**	0.58
Adopted	-0.60	0.81	-0.65	0.82	-0.91	0.82	-0.73	0.82
Hispanic	-0.23	1.33	-0.15	1.33	-0.07	1.34	0.11	1.33
Non-white	1.01	1.48	0.99	1.48	0.82	1.50	1.06	1.47
Project	**-3.07**	0.68	**-2.99**	0.68	**-2.80**	0.68	**-2.64**	0.68
PEdu							**0.45**	0.13
Cigs16	**-0.27**	0.05	**-0.22**	0.06			**-0.20**	0.06
SmkDiff	**-0.11**	0.04	-0.07	0.04			-0.06	0.04
Linear	**1.09**	0.10	**1.17**	0.10	**1.20**	0.10	**1.17**	0.11
Sex	**0.39**	0.13	**0.44**	0.13	**0.45**	0.13	**0.45**	0.13
Adopted	-0.08	0.17	-0.03	0.17	-0.01	0.17	-0.03	0.17
Hispanic	-0.74	0.39	-0.70	0.39	-0.69	0.39	-0.67	0.39
Non-white	0.09	0.35	0.04	0.35	0.04	0.35	0.02	0.35
Project	**1.38**	0.16	**1.32**	0.16	**1.31**	0.16	**1.33**	0.16
PEdu							0.01	0.03
Cigs16			**-0.03**	0.01	**-0.05**	0.01	**-0.03**	0.01
SmkDiff			**-0.03**	0.01	**-0.03**	0.01	**-0.03**	0.01
Goodness-of-fit								
K	39		41		39		43	
-2lnL	20622.5		20613.2		20626.3		20600.4	
AIC	20700.5		20695.2		20704.3		20686.4	
Model Comparison	M0-M1		M1-M2		M0-M3		M1-M2	
$\Delta\chi 2$	23.5		9.3		19.7		12.8	
df	2		2		2		4	
p	**<.001**		**.010**		**<.001**		**.012**	

Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), project (-0.5=CAP, 0.5=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and slope; Model 3 refers to only including smoking behavior on the slope; Model 4 refers to the model with smoking behavior on the intercept and slope and entering parental education; ; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=2991

Table 2.14. Conditional Growth Model Fixed Effects: Block Design (BD) from year 12 to CATSLife1.

	Model 1		Model 4	
	B	*SE*	B	*SE*
Performance at age 16	**50.15**	0.41	**50.00**	0.41
Sex	**2.92**	0.52	**2.86**	0.51
Adopted	**-1.72**	0.78	**-1.78**	0.78
Hispanic	-2.06	1.19	-1.85	1.19
Non-white	0.33	1.35	0.42	1.34
Project	-0.11	0.62	0.18	0.63
PEdu			**0.38**	0.12
Cigs16	**-0.21**	0.05	**-0.20**	0.05
SmkDiff	**-0.09**	0.03	**-0.09**	0.03
Linear	**0.76**	0.05	**0.76**	0.05
Goodness-of-fit				
K	18		19	
-2lnL	26681.5		26672.7	
AIC	26717.5		26710.7	
Model Comparison	M0-M1		M1-M4	
$\Delta\chi 2$	17.7		8.8	
df	2		1	
p	**.0001**		**.003**	

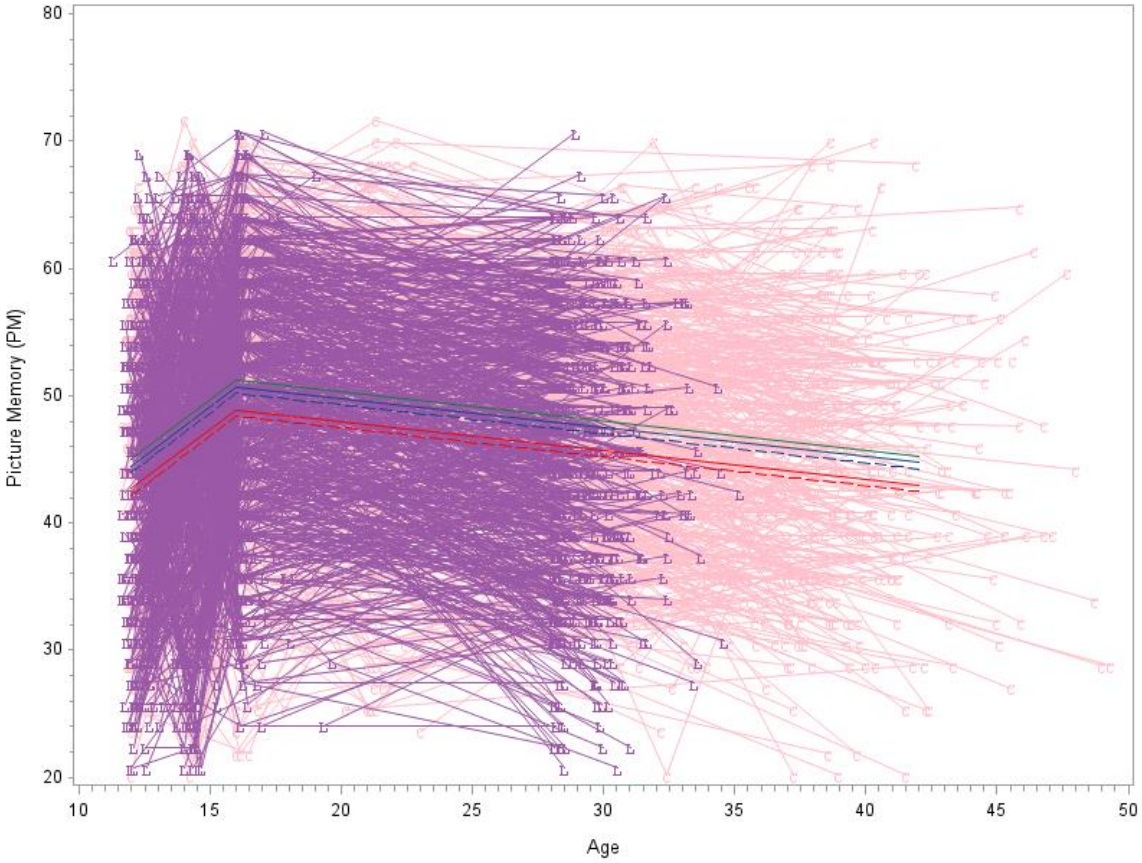
Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), project (-0.5=CAP, 0.5=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Random effects are not estimated on the linear term, thus Model 2 & 3 with smoking behavior interaction on the slope is not shown. Model 1 refers to adding smoking behavior on the intercept; Model 4 refers to the model with smoking behavior on the intercept and entering parental education; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=3977.

Table 2.15. Conditional Growth Model Fixed Effects: Vocabulary (V) from year 12 to CATSLife1.

	Model 1		Model 4	
	B	*SE*	B	*SE*
Performance at age 16	**54.40**	0.36	**54.07**	0.35
Sex	**0.95**	0.45	0.84	0.44
Adopted	**-1.88**	0.65	**-2.01**	0.65
Hispanic	-0.32	0.98	0.07	0.96
Non-white	-1.17	1.18	-1.16	1.13
Project	**-1.92**	0.55	**-1.26**	0.53
PEdu			**0.88**	0.11
Cigs16	**-0.16**	0.04	**-0.12**	0.04
SmkDiff	-0.05	0.03	-0.03	0.03
Linear	**1.89**	0.04	**1.90**	0.05
Goodness-of-fit				
K	18		19	
-2lnL	31623.6		31562.7	
AIC	31659.6		31600.7	
Model Comparison	M0-M1		M0-M4	
$\Delta\chi 2$	13.6		60.9	
df	2		1	
p	**.001**		**<.001**	

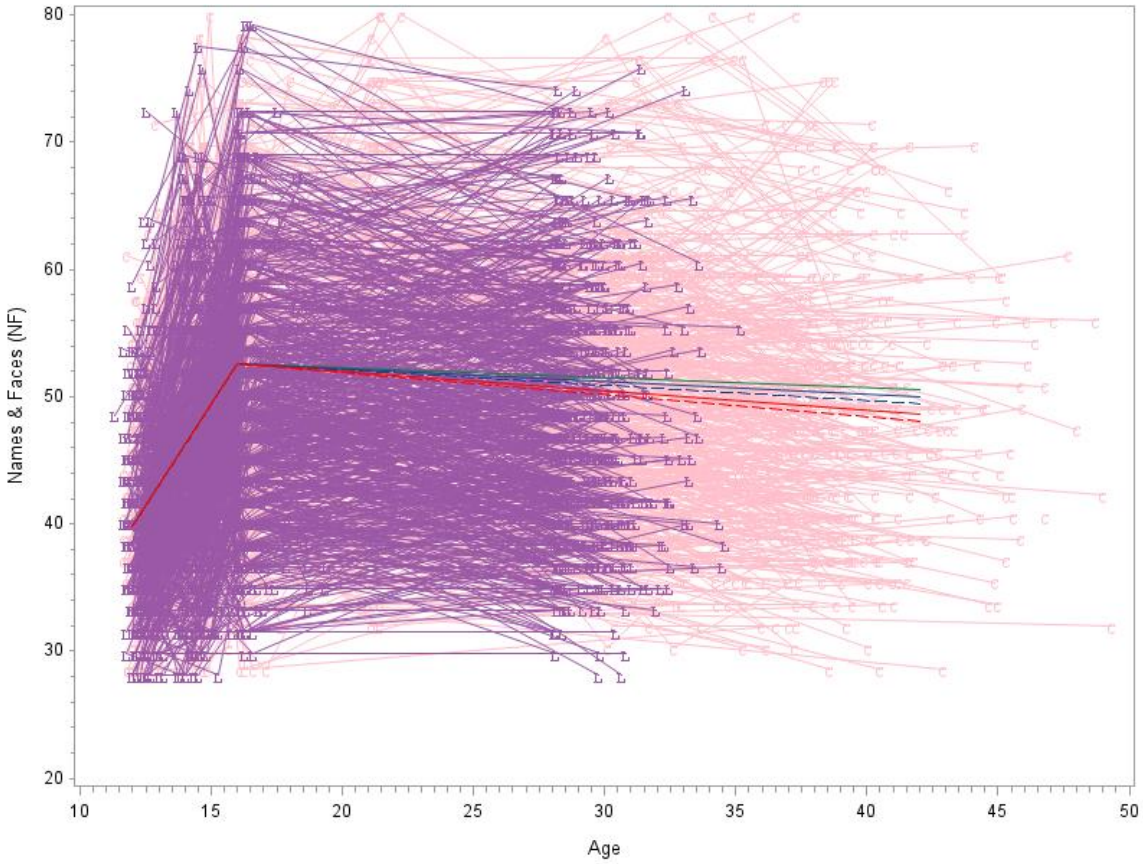
Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), project (-0.5=CAP, 0.5=LTS), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Model 1 refers to adding smoking behavior on the intercept; Random effects are not estimated on the linear term, thus Model 2 & 3 with smoking behavior interaction on the slope is not shown. Model 1 refers to adding smoking behavior on the intercept; Model 4 refers to the model with smoking behavior on the intercept and entering parental education; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=4868.

Figure 2.1. Trajectories of Picture Memory (PM) between assessment points 12 through CATSLife1.



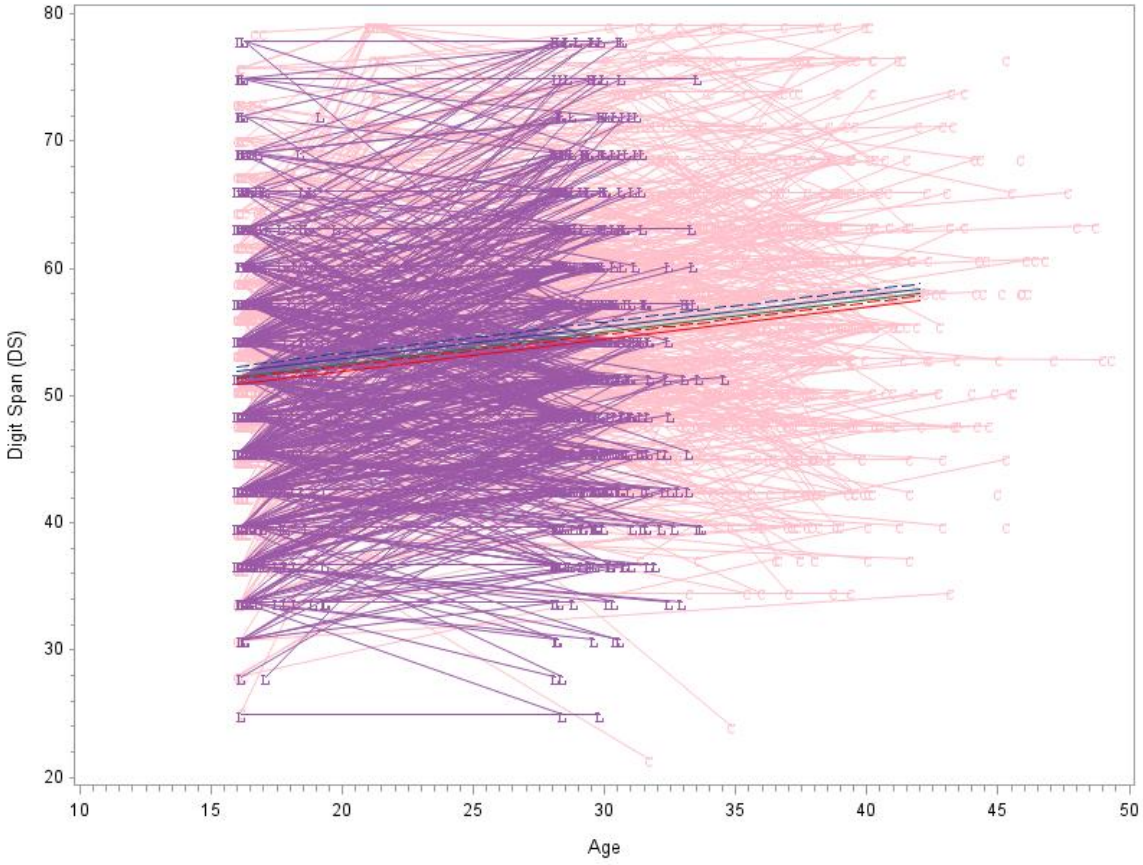
Note. Observed Picture Memory *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants; Purple solid lines with the letter L reflect the raw trajectories of LTS participants.
All plotted spline models knot point at age 16 represent expected trajectories with year 16 smoking consumption and gains in smoking amount by year CATSLife1; adjusting for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.

Figure 2.2. Trajectories of Names and Faces (NF) between assessment points 12 through CATSLife1.



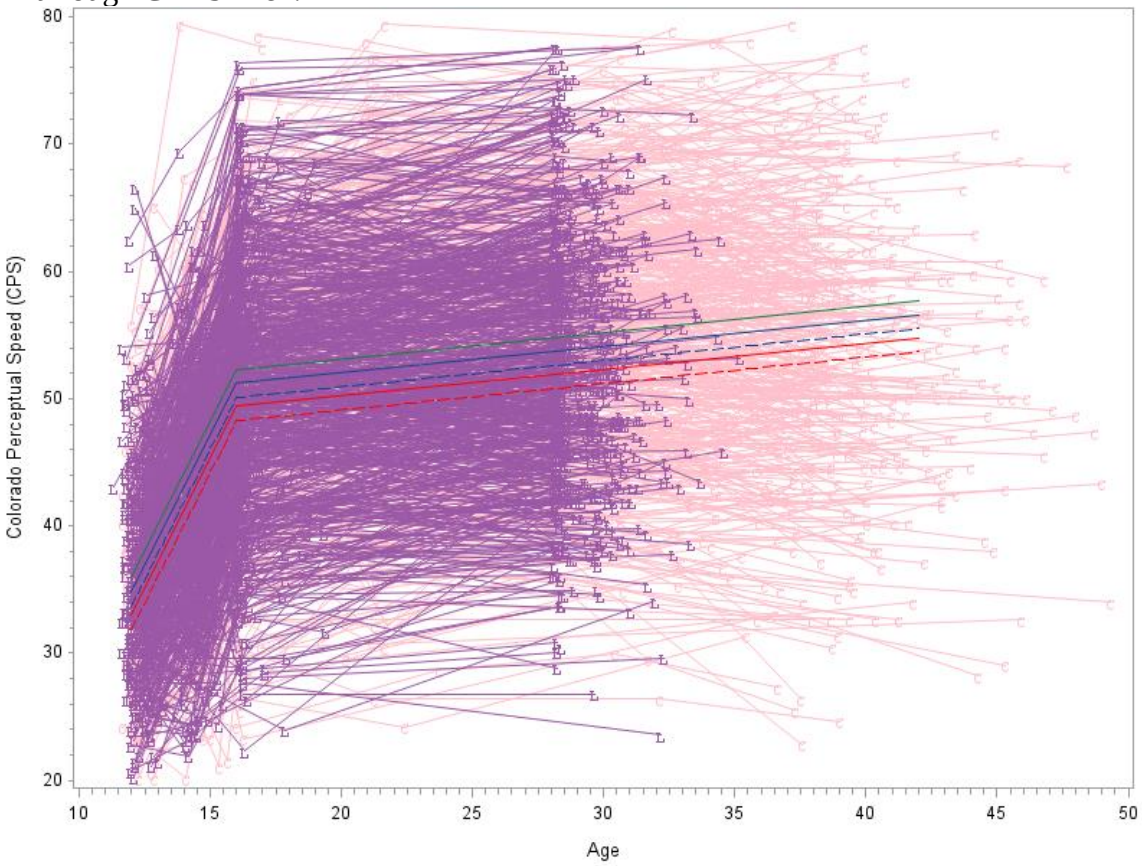
Note. Observed Names and Faces *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants; Purple solid lines with the letter L reflect the raw trajectories of LTS participants.
All plotted spline models knot point at age 16 represent expected trajectories with year 16 smoking consumption and gains in smoking amount by year CATSLife1; adjusting for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.

Figure 2.3. Trajectories of Digit Span (Dspa) between assessment points 16 through CATSLife1.



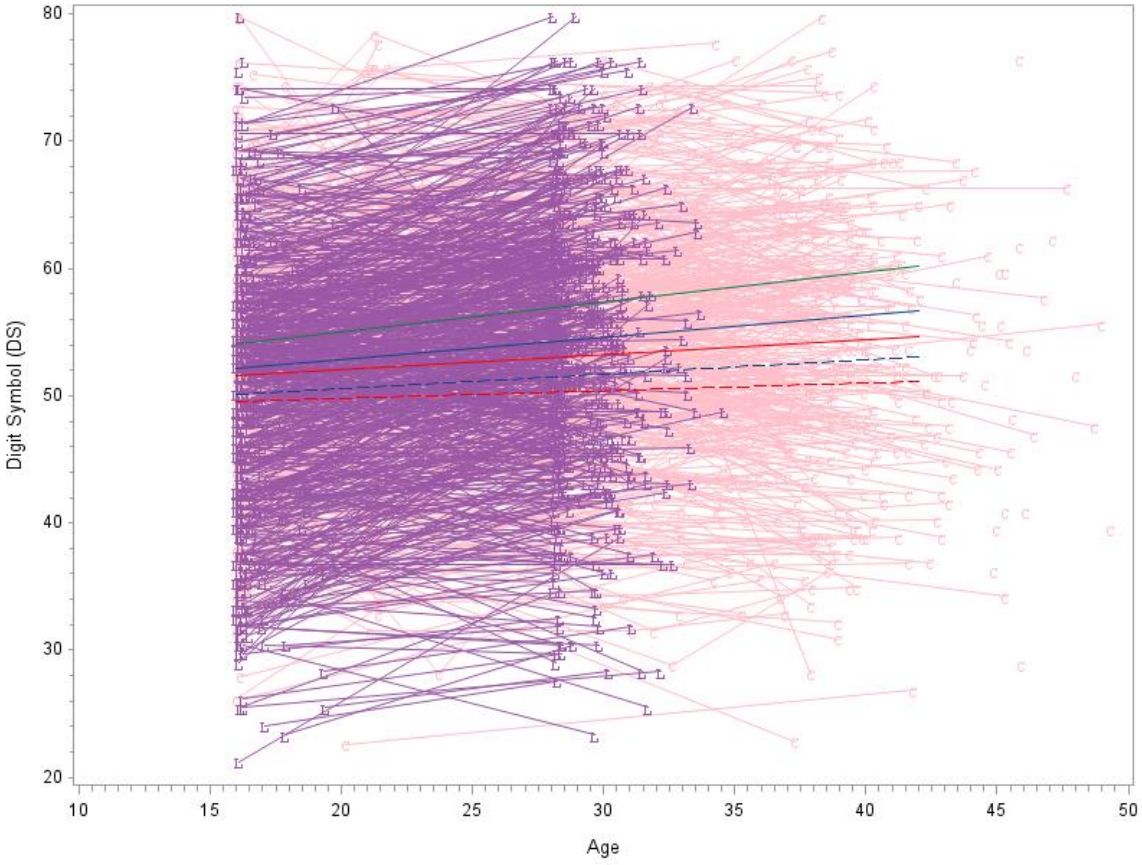
Note. Observed Digit Span *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants; Purple solid lines with the letter L reflect the raw trajectories of LTS participants.
All plotted linear models centered at age 16 represent expected trajectories with year 16 smoking consumption and gains in smoking amount by year CATSLife1; adjusting for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.

Figure 2.4. Trajectories of Colorado Perceptual Speed (CPS) between assessment points 12 through CATSLife1.



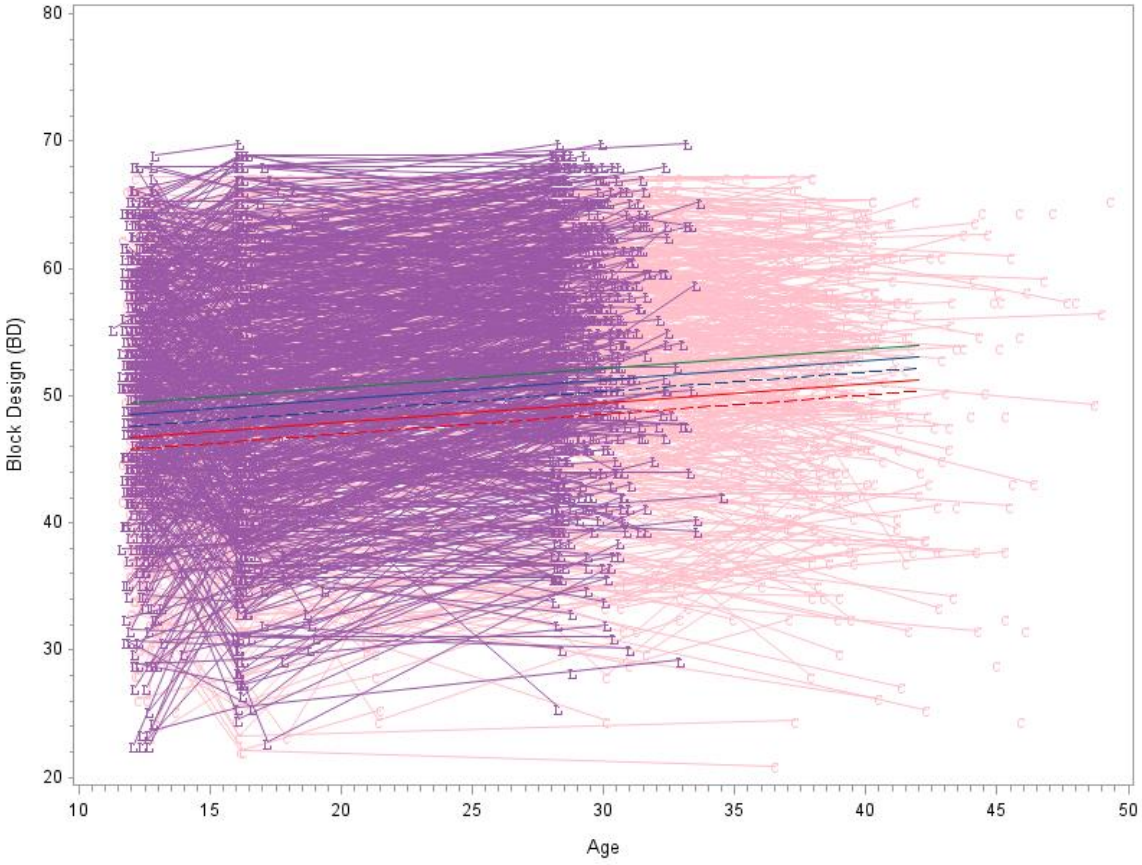
Note. Observed Colorado Perceptual Speed *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants; Purple solid lines with the letter L reflect the raw trajectories of LTS participants.
All plotted spline models with knot point at age 16 represent expected trajectories with year 16 smoking consumption and gains in smoking amount by year CATSLife1; adjusting for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.

Figure 2.5. Trajectories of Digit Symbol (DSy) between assessment points 16 through CATSLife1.



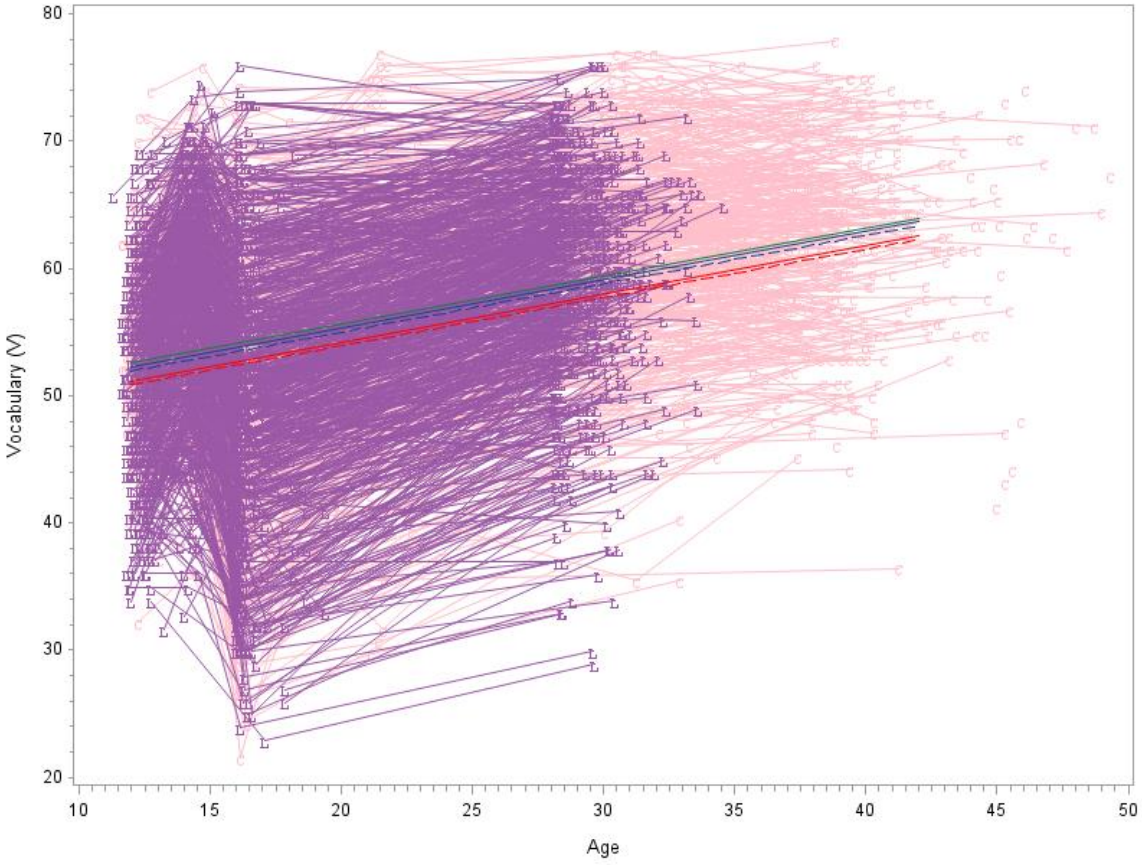
Note. Observed Digit Symbol *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants; Purple solid lines with the letter L reflect the raw trajectories of LTS participants.
All plotted linear models, centered at age 16, represent expected trajectories with year 16 smoking consumption and gains in smoking amount by year CATSLife1; adjusting for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.

Figure 2.6. Trajectories of Block Design (BD) between assessment points 12 through CATSLife1.



Note. Observed Block Design *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants; Purple solid lines with the letter L reflect the raw trajectories of LTS participants.
All plotted linear models centered at age 16 represent expected trajectories with year 16 smoking consumption and gains in smoking amount by year CATSLife1; adjusting for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.

Figure 2.7. Trajectories of Vocabulary (V) between assessment points 12 through CATSLife1.



Note. Observed Vocabulary *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants; Purple solid lines with the letter L reflect the raw trajectories of LTS participants.
All plotted linear models, centered at age 16 represent expected trajectories with year 16 smoking consumption and gains in smoking amount by year CATSLife1; adjusting for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.

Chapter Four:

GENERAL DISCUSSION

Cognition is a mutable trait (Horn & Cattell, 1967; Reynolds et al., 2014; Salthouse, 2009; Tucker-Drob, 2009), and individuals can be active agents in their own development for better or worse (Bronfenbrenner, 2005; Bronfenbrenner & Ceci, 1994; Scarr & McCartney, 1983). Processes of aging may take shape earlier in life (Barnett et al., 2013; Bourassa et al., 2022), such as lifestyle factors, including smoking behavior which tends to start before adulthood (Dutra et al., 2017; Fuemmeler et al., 2013; Huggett et al., 2019). Moreover, our experiences and contexts, both proximal and historical, can influence the developmental course for numerous age-relevant outcomes (Bronfenbrenner, 2005; Bronfenbrenner & Ceci, 1994; Elder Jr, 1998; Gottlieb, 2007). With that developmental perspective in mind, we examined how the known health risk, smoking, may influence cognitive health while considering individual differences and contextual factors, including the policy environment surrounding tobacco control.

Health risks and observable deficits, but not yet functional impairments, can emerge earlier in the lifespan (Barnett et al., 2013; Bourassa et al., 2022) and can serve as a warning or "smoke signal" for future age deficits and dysfunction. For that reason, we explored the effect of smoking behavior on cognitive functioning and change in a sample covering the ages of early adolescence to midlife. The extant literature has consistently linked smoking with worse cognitive outcomes, but nearly all studies have been focused on the latter half of the lifespan (Anstey et al., 2007; Conti et al., 2019; Durazzo et al.,

2010; Swan & Lessov-Schlaggar, 2007). Determining whether smoking behavior imposes a risk of cognitive impairment or neurocognitive disorders is important, but research that exclusively examines smoking and cognition only in older adults adds little to identifying the earliest period for the onset of the detrimental effects on cognition. The primary purpose of this dissertation was to elucidate directly earlier life smoking-cognitive associations, and the impact smoking may have on cognitive development and aging. Indeed, until this dissertation, no study has examined whether smoking behavior may impact cognitive trajectories from early adolescence to the cusp of midlife. This dissertation aims to address the gaps in the literature and clarify the emergence of smoking-cognitive associations within the first half of the lifespan. Across two studies, the dissertation investigated five research questions:

Research Q1: What is the association between cigarette smoking behavior (e.g., smoking status and pack years) and cognitive performance, and do the associations vary by smoking measure for each cognitive domain?

Research Q2: Are the associations between smoking behavior and cognitive performance attenuated by cardiovascular health status, educational attainment, or childhood IQ?

Research Q3: Are associations between smoking behavior and cognitive performance attenuated by state-level tobacco control policy? Do state-level tobacco control policy measures moderate smoking and cognition associations?

Research Q4: Does smoking consumption at age 16 influence cognitive development up to mid-life? That is, do individuals who smoke more cigarettes at age 16

show worse cognitive developmental trends by the cusp of midlife (i.e., either dampened growth or cognitive decline)?

Research Q5: Do changes in smoking consumption influence cognitive development and change up to midlife? Moreover, do individuals who start regularly smoking after age 16, as captured by smoking consumption gains by the cusp of midlife, show differential adolescent cognitive functioning that may not be captured by extant adolescent smoking?

As outlined in the conceptual model shown in Figure 0.1 in Chapter 1, this dissertation explored the influence of smoking behavior on cognition within the first half of lifespan. Two studies were conducted to test (1) smoking behavior influence on cross-sectional cognitive associations at Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife1) (Wadsworth et al., 2019) with consideration of moderation by tobacco control score (TCS) (Joossens et al., 2019; Joossens & Raw, 2006) and (2) evaluate the influence of smoking consumption on longitudinal cognitive trajectories from adolescence to CATSLife1. In addition, the first study examined different smoking behavior measures cross-sectionally to further explore the unique contribution each smoking measure had on cognitive performance before midlife. Across both studies, we also explored possible confounding factors to evaluate the level of possible attenuation (not depicted in the model).

Smoking behavior is theorized to influence cognitive performance through processes of accelerated aging (Bourassa et al., 2022; Corley et al., 2019; Dugué et al., 2018; Elliott et al., 2021; Linli et al., 2022; Lu et al., 2019; Ning et al., 2020; O'Shea et

al., 2022; Wendell et al., 2014; Whitsel et al., 2022). Accelerated aging may include compromised health systems, such as cardiovascular and pulmonary functioning, and neurological health, including functional and anatomical structure integrity. Thus, given the known impact of smoking on physical health, which can take years to develop, dependent on the use history and heaviness of smoking (Eagan et al., 2002; Gao et al., 2017), many researchers focus their attention on exploring associations in older adults when morbidity and mortality concerns mount. Assessing adult smoking behavior will vary, but prior work often includes measures of smoking status or overall exposure (i.e., pack years). Even though few studies directly examine earlier life smoking risk on later life cognition, many smoking measures will capture historical use, including during adolescence. Indeed, persistent smokers tend to start before adulthood, and the earlier an individual starts smoking, the likelihood of long-term continuation increases (Huggett et al., 2019; Rose et al., 2009) while the likelihood of quitting decreases (Belsky et al., 2013; Rose et al., 2009). Thus, studies of middle-aged and older adults (Bahorik et al., 2021; Conti et al., 2019; Durazzo et al., 2010; Hill et al., 2003; Nadar et al., 2021; Nooyens et al., 2008; Starr et al., 2007; Swan & Lessov-Schlaggar, 2007) have observed that continued smoking across the lifespan may be detrimental to cognitive health via impacted physical health pathways that accelerate aging (Bourassa et al., 2022; Finch, 2018; Swan & Lessov-Schlaggar, 2007; Whitsel et al., 2022).

Theories underlying smoking-cognition associations in later life have focused on processes of accelerated aging (Anstey et al., 2007; Durazzo et al., 2010; Swan & Lessov-Schlaggar, 2007). However, the timing of engagement in persistent smoking may

have differential effects on the course of cognitive development. For example, if individuals start smoking before adulthood, adolescent smoking may have more pronounced effects on cognitive development than starting at later ages, such as worse cognitive performance, dampen cognitive growth, or worse cognitive decline for age-sensitive abilities. This proposed pattern refers to the developmental sensitivity hypothesis, which suggests there are age-dependent smoking effects on cognitive development (c.f., Morin et al., 2019). In contrast, the neurotoxicity model does not presume a specific sensitive window for smoking to influence cognition but rather suggests smokers experience worse cognitive performance through neurological impairments that persist across time (c.f., Morin et al., 2019). Alternatively, the neuroplasticity model suggests that individuals can escape the lasting impacts of smoking by reducing their consumption or quitting. In other words, the brain can recover from the pernicious effects of smoking. Although past work has explored the impact of persistent smoking and possibly recovery for former smokers, few studies have explored the emergence of smoking effects on cognition in the first half of the lifespan. Further, past work has commonly used pack years to index dosage exposure. Pack years, although useful, does complicate interpretation given this measure combines smoking duration and consumption and can't elucidate whether the influence of smoking on cognition is stronger for heavier or longer use. In addition, adolescent smoking behavior is a salient time to consider when understanding the development of smoking behavior (Huggett et al., 2019; Rose et al., 2009). Moreover, when examining smoking consumption trajectories from adolescence to adulthood, individuals that become persistent smokers

tend to increase their consumption into adulthood (Dutra et al., 2017; Fuemmeler et al., 2013). Thus, this dissertation explored the impacts of smoking consumption on cognition across time in a sample starting just prior to adolescence and up to midlife.

Even though persistent smoking is detrimental to one's health, there are contextual factors that may influence when and how much an individual smokes. Smoking behavior development, like the development of many other behaviors, can be responsive to the environment and ecology surrounding an individual (Bronfenbrenner, 2005; Bronfenbrenner & Ceci, 1994; Knopik et al., 2017). Following the bioecological model of nested environmental influences (Bronfenbrenner, 2005; Bronfenbrenner & Ceci, 1994), more attention has been paid to proximal influences such as smoking exposure via parents and peers, as well as the individual's immediate environmental conditions, including household income and schooling (Rose et al., 2009). However, more distal environmental influences, such as tobacco control policies, can also be an important ecological feature to consider. Indeed, disparities in smoking prevalence across the United States exist (Boardman, 2009; Drope et al., 2018; Shmulewitz et al., 2016; Studlar, 2002). Moreover, decreases in smoking-related morbidity and mortality within the USA and beyond (Bradley et al., 2016; Gebreab et al., 2015; Jemal et al., 2003; Levy et al., 2013; Meyers et al., 2009), are partially explained by the changing attitudes surrounding tobacco but also active legislative action aimed at reducing tobacco use prevalence (Gao et al., 2022; Kendler et al., 2000; Lee et al., 2020; Levy et al., 2013; Pampel, 2010). Thus, this dissertation explored if smoking-cognition associations were influenced by state-level tobacco control policy, independent of more proximal

influences such as an individual's educational attainment. We expected that smoking behavior would be responsive to the surrounding tobacco control policy environment where more permissive states would magnify the detrimental effects of smoking on cognition, while states with greater control may reduce the impacts of smoking by delaying onset, decreasing frequency, and increasing the likelihood to quit.

Summary of General Findings

Study 1

In Study 1, smoking behavior was examined to determine if smoking was associated with cognition before midlife in a cross-sectional approach using data from the CATSLife1 study. We evaluated associations on seven cognitive tasks representing the cognitive domains of episodic memory, working memory, processing speed, spatial ability, and verbal ability. Smoking behaviors included two status smoking measures (current and ever) and dosage-dependent measures (pack years). Possible confounding was examined by adding common factors shared between smoking and cognition subsequently into analyses, starting with cardiovascular health, educational attainment, and tobacco control policies. Next, we tested to see if the state-level tobacco control score moderated the effects of smoking on cognition. Lastly, we completed sensitivity analyses on a subsample to evaluate if year 12 IQ influenced results, i.e., if it pointed to a selection effect of IQ prior to smoking onset. All analytical models were mixed-effects models, and covariates included age, sex, adoption status, study project, race, and ethnicity.

Results from Study 1 included observations that smoking behavior was associated with lower cognitive performance across the board, apart from Digit Span, a working

memory task. Based on model fit, smoking behavior(s) significantly associated with cognition included current smoking or pack years that varied between tasks. Moreover, the magnitude of effect differed between smoking behavior measures, with the largest effects found for current smoking. Current smoking combined with dosage effects as indexed by pack years suggested unique contributions for all tasks except for Picture Memory which was solely associated with pack years. Cardiovascular health did not account for smoking-cognitive effects. However, educational attainment attenuated nearly all results, excluding Picture Memory. Educational attainment fully attenuated smoking effects for Names and Faces and Vocabulary. Partial attenuation was found for the other cognitive tasks, with regression coefficients dropping in size from 12% to 26%. Study 1 also evaluated if tobacco control at the state level impacted results; we found no evidence to suggest that tobacco control score (TCS) was related to cognitive performance or moderated smoking-cognitive associations. Lastly, smoking-cognitive findings were not due to selection differences arising from early life intellectual ability level.

Study 2

Study 2 explored how smoking behavior influences cognitive development and later aging. We used data from CATSLife1, which includes two archival longitudinal projects of twins, siblings and adoptees, to track cognitive development from early adolescence to midlife. Two measures of smoking consumption (i.e., number of cigarettes smoked) were used to examine adolescent smoking and change in adulthood smoking since adolescence. More specially, change in adulthood smoking was a

difference score between CATSLife1 and year 16 smoking consumption. Associations between smoking and cognition were assessed using mixed effects growth models fitted to the cognitive data, with (a) smoking consumption at year 16 and (b) the smoking consumption difference score. Smoking consumption measures were entered as time-invariant predictors of average cognitive performance at age 16 and age-associated change. All models adjusted for fixed effects of sex, study project, adoption status, race, and ethnicity. Parental years of education were added to models to examine attenuation patterns between smoking and cognition.

Results from Study 2 results showed limited evidence of smoking after age 16 or increases in smoking consumption to impact cognitive trajectories, indicating smoking effects emerged prior to adulthood. We found that higher smoking consumption at year 16 was associated with lower average performance, and the effect was twice the size of the smoking difference score. Adolescent smoking was significant on average performance at age 16 for all cognitive tasks, except for Names and Faces, an episodic memory binding task. When examining differential growth rates, we found adolescent smoking moderated the rate of cognitive growth for Names and Faces and Digit Symbol. Age-curve results indicated that a more rapid decline was associated with greater levels of adolescent smoking for Names and Faces. For Digit Symbol, age curves suggested reduced growth at greater levels of adolescent and adulthood smoking gains. Moreover, the smoking difference score was significant on average cognitive performance at age 16, two tasks, Colorado Perceptual Speed and Block Design, albeit the effects were modest but suggested that lower age 16 performance may be associated with gains in smoking in

adulthood. In addition, smoking-cognitive associations were not explained by parental education except for Digit Span, indicating confounding with a common vulnerability for this trait domain. Results from Study 2 indicated adolescent smoking, and to a lesser extent adulthood smoking, have a small negative effect on cognitive performance and change from adolescence up to midlife.

Age-curve patterns differed from expected patterns given the cognitive aging literature on trajectories for working memory, processing speed, and spatial ability (Baltes, 1997; Hartshorne & Germine, 2015; Horn & Cattell, 1967; Li et al., 2004; McArdle et al., 2002; Salthouse, 2009; Tucker-Drob, 2019). Specific cognitive measures retested were Digit Span, Colorado Perceptual Speed, Digit Symbol, and Block Design. Therefore, we completed sensitivity analyses with only the Colorado Adoption Project (CAP; Plomin & DeFries, 1983), which included more measurement waves in young adulthood and with greater representation of ages 30 to 40 compared to LTS. We generally replicated age patterns observed in the literature with the CAP-only analyses, yet with generally similar patterns of results with smoking consumption as in the original analyses. For Digit Symbol, we did not find slope interactions with smoking consumption attributable to low slope heterogeneity at older ages.

Implications

Tobacco use has been declining since the start of the 20th century when prevalence was highest (Pampel, 2010), but tobacco use is not rare. Across the globe, the World Health Organization (WHO) projects that about 17.3% or over a billion individuals over the age of 14 will be smoking by 2025 (World Health Organization,

2019). In the United States, about 15% or 34.3 million US adults were estimated to be currently smoking in 2017 (Centers for Disease Control and Prevention, 2018; Jamal et al., 2018). Smoking remains a health and economic burden, with smokers having 10 years lower life expectancy and economic costs exceeding $300 billion per year (U.S. Department of Health and Human Services, 2014). Smoking has a detrimental impact on physical health (Centers for Disease Control and Prevention, 2018; Finch, 2018; Royal College of Physicians of London: Tobacco Advisory Group, 2000; U.S. Department of Health and Human Services, 2014; World Health Organization, 2019). Indeed, smoking has been identified as a modifiable health risk for Alzheimer's disease and related dementias (ADRD) (Livingston et al., 2020). Moreover, the smoking-ADRD risk is noted as amenable to reduction even in later life for individuals that quit (Livingston et al., 2020). However, the risk window for smoking exposure is wide in regard to brain and cognitive health (Bourassa et al., 2022; Galanis et al., 1997; Karama et al., 2015; Mons et al., 2013; Whitsel et al., 2022). In other words, the accumulated harm from persistent use on neurological and cognitive health is evident by midlife, suggesting the underpinnings of effects emerge earlier in life.

There is well-developed literature devoted to examining smoking behavior effects on cognitive functioning and change, but research is predominately done with older adults (Anstey et al., 2007; Conti et al., 2019; Durazzo et al., 2010; Peters et al., 2008; Swan & Lessov-Schlaggar, 2007). Thus, theorized mechanisms have centered on aspects of biological aging via worsening physical health in cardiovascular and pulmonary systems, as well as neurological integrity (Bourassa et al., 2022; Corley et al., 2019;

Dugué et al., 2018; Elliott et al., 2021; Linli et al., 2022; Lu et al., 2019; Ning et al., 2020; O'Shea et al., 2022; Wendell et al., 2014; Whitsel et al., 2022). What remains unknown, however, from prior work is whether earlier life associations would follow a similar theorized path that continuous and concurrent smoking accelerates the aging process that impacts cognitive functioning and decline. Alternatively, early life smoking is postulated to be a neurotoxic effect on cognition at younger ages that disrupt maturation processes which could persist across time (c.f., Dwyer et al., 2009; Goriounova & Mansvelder, 2012; Mooney-Leber & Gould, 2018; Poorthuis et al., 2009; Thorpe et al., 2020; Zeid et al., 2018). Hence, research to disentangle the timing of smoking's influence on cognition is essential to undertake.

This dissertation makes several contributions to the current literature. First, this dissertation included the first study to consider the tobacco control environment individuals are embedded in and its possible contribution to smoking-cognition associations. We did not find evidence to suggest variation in tobacco control across states alters associations in adulthood prior to midlife; nonetheless, the practice of including measures on policy climate can be informative. Understanding the role environment in shaping health behaviors can inform research on social determinants of health, which may also reveal regional disparities (Couillard et al., 2021; Harris et al., 2016; Lochner et al., 2001; Mensah et al., 2005; Singh et al., 2017). A second major contribution of this dissertation was identifying the influence of adolescent smoking on cognitive trajectories. Study 2 within the dissertation was the first study, to our knowledge, to test how adolescent smoking consumption and change in adulthood

consumption influence cognition from early adolescence to the cusp of midlife. Prior research, mostly observational with few prospective examples, had not lent a clear picture of the effect of smoking on cognition (Castellanos-Ryan et al., 2017; Fried et al., 2006; Jacobsen et al., 2005; Mahedy et al., 2018; Mahedy et al., 2021). This dissertation work helps clarify the early associations which may be suggestive of a neurotoxic effect on the maturing brain (Dwyer et al., 2009; Goriounova & Mansvelder, 2012; Mooney-Leber & Gould, 2018; Thorpe et al., 2020). Moreover, we found evidence, albeit small effects of gains in smoking consumption by adulthood to also impact cognition across time. In particular, the associations we found were with age-sensitive tasks. Thus, this early evidence may also indicate the cumulative impact of smoking on age processes linked with cognitive functioning (Corley et al., 2019; O'Shea et al., 2022; Wendell et al., 2014).

Overall, this dissertation added important contributions to the extant literature. In the following sections, we take a closer look at the implications of the specific smoking behaviors associations examined in Study 1 and Study 2. Next, we will explore what parental and self-attained education may suggest between the two studies. Lastly, we will discuss the adolescent smoking implications for future policy endeavors.

Distal and Proximal Impacts of Smoking on Cognition

Comparing the results of the two studies, we found some notable differences between specific smoking behaviors. In particular, our findings from Study 2 are a little surprising given the effect of current smoking in Study 1. Study 1 incorporated multiple measures of smoking behavior, including a dosage-dependent measure of pack years and ever smoking. Interestingly, when examining the smoking effect after controlling for

educational attainment, results from Study 1 suggest that more proximal effects are more strongly related to worse cognitive performance before midlife than dosage or a history of ever smoking. The cognitive aging literature tends to find a similar pattern with current smoking compared to former smokers (Amini et al., 2021; Collins et al., 2009; Lo et al., 2014; Nooyens et al., 2008; Sabia et al., 2012; Vermeulen et al., 2018; Weiser et al., 2010; Whalley et al., 2005).

Prior work within the smoking-cognitive literature tends to be studied with older adults, and it's difficult to parse from earlier work whether selection differences influence the findings for current smoking due to attrition biases in older samples (Hernán et al., 2008; Weuve et al., 2012) or earlier life differences (Daly & Egan, 2017; Jacobsen et al., 2005; Johnson et al., 2009). For example, the similarity between never-smokers and long-term quitters may represent brighter individuals tending to start smoking later (Jacobsen et al., 2005; Johnson et al., 2009) or are more likely to quit (Daly & Egan, 2017). Indeed, ever smoking included individuals who currently smoke and former smokers, but it does not distinguish when individuals started smoking or quit. Moreover, ever smokers might include individuals who experimented with smoking but quit fairly quickly in adulthood and never reached consumption rates and length of use as current smokers. Thus, current smokers by the time of CATSLife1 may have been early initiators, which would overlap with many individuals that were adolescent smokers as identified in Study 2.

Our findings from Study 2 help clarify the proximal and distal associations between smoking and cognition because we can specify a certain time when individuals were smoking during adolescence and trace backward how starting smoking after age 16

or gains in smoking consumption influence longitudinal cognitive trends. Examining these specific features of smoking behavior is unavailable when only exploring a status measure or including pack years which is the multiplicative of duration and consumption. Based on findings from Study 2, we can therefore identify cognitive abilities that suggest patterns of preserved differentiation, or maintained deficits across time that occur before adulthood (Salthouse, 2006; Tucker-Drob, 2019). If we had only examined the cross-sectional associations of smoking on cognition that were conducted in Study 1, we would not have uncovered the early and prolonged influence of adolescent smoking. Thus, our findings from Study 2 do not contradict findings from Study 1; rather, findings from Study 2 provide a more nuanced picture of the timing effects of smoking.

It is unclear with our work whether year 16 effects from Study 2 are recovery responsive, representing true neuroplasticity or if individuals who quit smoking show comparable performance to never smoking peers because they merely "catch up" rather than gain back their losses. To say it another way, former smokers may decelerate their cognitive decline, predicted by persistent smoking and worse health. Thus, enabling cognitive maintenance over some length of time that is equitable to performance levels for those who hadn't smoked. For example, cortical thinning attributed to smoking behavior indexed by pack years demonstrated some plasticity after cessation, but complete recovery was only achieved after 25 years (Karama et al., 2015). Similarly, after about 30 years after quitting, former smokers see similar levels of cognitive functioning more in line with never-smokers (Mons et al., 2013), with reduced risk for dementia after quitting for more than 9 years (Deal et al., 2020). Based on past work, it

remains uncertain whether recovery may be greatest for those that started smoking later in life and avoided the risker developmental period of adolescence. For example, even though some recovery was achievable after 30 years of cessation, we don't know when former smokers transitioned to persistent use and whether the age of onset moderated the recovery patterns observed (Mons et al., 2013). Thus, within the smoking-cognitive literature, it is uncertain if recovery exists for all at the same rate or if early onset leads to a pervasive, unyielding effect on cognitive functioning.

Our findings provide a glimpse into the long-reaching impact of cognitive functioning, but we cannot determine the effect of adolescent smoking on cognitive aging in totality. Follow-up research is warranted to explore how cessation may contribute to cognitive functioning based on smoking onset and the length of recovery necessary for different smoking usage patterns across time (Dutra et al., 2017; Fuemmeler et al., 2013). Even if selection differences contribute to who is more likely to become a former smoker, that is also correlated with cognition, nonetheless, there is a tacit understanding of the benefits of quitting. As this study and others have found, smoking behavior related-consequences have a long reach across the lifespan (Galanis et al., 1997; Karama et al., 2015; Mons et al., 2013; Whitsel et al., 2022), but recovery may be possible, and the earlier and longer an individual abstains the more likely those deficits may be minimized or ameliorated.

Attenuation of Smoking Behavior: Parental or Self-attained Education

Each study in the dissertation included a measure of educational attainment, either parental or self-attained, to account for possible selection differences between smokers

and non-smokers. Across the board, education was related to cognitive performance, as was expected (Lövdén et al., 2020; Ritchie & Tucker-Drob, 2018; Turrell et al., 2002). The main purpose of including education was to see the attenuation between smoking and cognition. Interestingly, self-attained education in Study 1 showed fairly consistent patterns of attenuation across tasks, but less evidence emerged for attenuation by parental educational attainment in Study 2. SES conditions in childhood, including parental education, have independent effects on later cognitive functioning outside self-attained education (Lövdén et al., 2020; Turrell et al., 2002). In addition, parental and self-attained education predict smoking outcomes (Corley et al., 2019; Pampel et al., 2014; Silventoinen et al., 2022). Although past work suggests the predictive role of parental and self-attained education on smoking outcomes, we found differential patterns between the two studies that may indicate different operating mechanisms.

Why might parental education not attenuate adolescent smoking-cognitive associations at the same level as self-attained education? Perhaps the answer lies in the timing effect of earlier life experiences influencing later adulthood outcomes (Elder Jr, 1998; Lövdén et al., 2020; Pampel et al., 2014). For example, Pampel et al. (2014) examined smoking trajectories from age 11 to 34 in the national longitudinal ADD Health sample and found that the effect of parental education on smoking trajectories was small during adolescence, but parental education influenced greater disparities by adulthood. Further, self-attained educational attainment and the adoption of adult roles within a normative age were also associated with adulthood smoking. These finds support the life course theory (Pampel et al., 2014). The life course theory suggests development

is inextricably connected to our social convoy, which can provide some coherence across the life course (Elder Jr, 1998). Moreover, the experiences that come with parents with higher education can provide earlier life advantages, such as attending better school districts that accumulate over time to benefit later transitory periods, including assuming adult roles (Elder Jr, 1998). With this explanation in mind, our findings that parental education does not attenuate the smoking-cognitive relationship may indicate the effects of parental education has a larger influence on smoking as individuals exit adolescence.

There may be another explanation for why self-attained education demonstrated more attenuation on the smoking-cognitive associations than parental education. Self-attained education may be a better measure to capture a common vulnerability to low education and the risk of smoking (Gage et al., 2022). Specifically, smoking and education may have origins in shared genetic risk indicating some pleiotropy (Wedow et al., 2018). Pleiotropy is the case where the same genetic variant(s) influence two traits, in this case, smoking behavior and educational attainment (Knopik et al., 2017). Indeed, years of education is highly genetically correlated with smoking initiation and cigarettes per day (Liu et al., 2019). The shared genetic effects between smoking and education may also influence an individual's selection of certain environments, such as education. Environments are not randomly distributed and can be correlated based on the individual's genetic propensity (Knopik et al., 2017). The process by which individuals seek environments that foster their underlying genetic propensity is known as active gene-environment correlation or niche-picking. Indeed, it is proposed that niche-picking becomes stronger as individuals leave the parental home and assume a more active role in

their development (Bergen et al., 2007; Reynolds et al., 2014). Thus, self-attained education would better represent the product of shared genetic influences between smoking and education and the process of niche picking.

The shared influence between smoking and education is a complex pattern to disentangle. This dissertation cannot determine the underlying causes of attenuation pattern differences. However, we have highlighted some possible mechanisms at play. It remains for future research to explore how both parental and self-attained education may mutually or independently impact smoking influence on cognitive development.

Clues from the Broader Environmental Context of Tobacco Control

Only Study 1 included the TCS measure, which examined concurrent tobacco policies with cognitive functioning. We did not find evidence that TCS was associated with cognitive performance or that the smoking-cognitive effects varied by TCS. However, the lack of findings may be related to timing, as the policy scoring was concurrent with cognitive assessment. In other words, to better capture whether TCS moderates the smoking effects, there should be a time lag to capture potential changes in smoking prevalence that may alter cognitive performance. For example, TCS could be created before participants reach adolescence, a period when smoking initiation commonly occurs (Dutra et al., 2017; Fuemmeler et al., 2013; Huggett et al., 2019). Moreover, adolescence may mark a particularly vulnerable window for cognitive development given the growth and maturational processes underway that can be sensitive to chronic nicotine exposure (Dwyer et al., 2009; Goriounova & Mansvelder, 2012; Mooney-Leber & Gould, 2018; Thorpe et al., 2020).

As Study 2 demonstrated, adolescent smoking was associated with worse average cognitive performance at age 16 for nearly all tasks, except for Digit Span, which persisted up to midlife. On average, about 15% of the sample smoked by year 16, and participants started regularly smoking at approximately 13.5 years old, a few years prior to the year 16 assessment. Even though individuals were smoking for a couple of years before the age of 16, it's uncertain, based on our work, how many individuals progressed to persistent use. Although, the transition to problem use, or persistent use, is seen to have a longer latency the younger an individual initiates smoking which may be partly due to accessibility issues (Huggett et al., 2019). However, minimum ages and enforcement differed between project cohorts of CAP and Longitudinal Twin Study (LTS; Rhea et al., 2013) when participants were approaching adolescents.

It was not until the Synar Amendment in the Alcohol, Drug Abuse, and Mental Health Administration Act of 1991 that established the federal minimum age of 18 years to purchase tobacco products (Studlar, 2002). Before the amendment, states were free to establish their own legal tender age and by 1939 all states had adopted a minimum of 16 years (Apollonio & Glantz, 2016; Studlar, 2002). However, most laws restricting tobacco access by age were not successfully enforced (Forster & Wolfson, 1998; Studlar, 2002), including in Colorado, where most study subjects were born (Centers for Disease Control and Prevention, 1990). Studies of enforcement in Colorado found that over 60% of attempts from minors to purchase tobacco were successful across vendors and vending machines. Moreover, due to tobacco industry interference, Colorado's legal age was repealed (Apollonio & Glantz, 2016). In 1912, Colorado enacted an age limit of 16,

which remained until 1972, when it was repealed, and a new higher minimum age of 18 wasn't adopted until 1987 (Tobacco Merchants Association, 1993).

The Synar Amendment not only set a new federal minimum age of 18 years in 1991 but also included enforcement provisions to punish vendors that sold to minors (Studlar, 2002). Given the shifts in the legal tender age for cigarettes, access to cigarettes would have varied between study projects during participants' formative years. For instance, as the older CAP cohort reached age 12, the majority of the sample would have experienced a time without a set age limit in Colorado and before enforcement measures were made, further restricting access. In contrast, the younger LTS cohort would have lived in an environment with greater restrictions as they approached adolescence. Indeed, as seen in Appendix 2 for Table A2.2, the older CAP project participants tended to smoke two more cigarettes at age 16 than the LTS project participants for those that reported smoking at least one cigarette in the last month. Hence, future work could employ TCS at an earlier time that may impact the uptake of smoking and include scoring dimensions on minimum age limits for tobacco products. Moreover, the preadolescent TCS could be included to examine if TCS alters smoking behavior's influence on cognitive trajectories.

Future Directions

Cognitive Functioning Measurement

This dissertation examined smoking-cognitive associations across a variety of specific abilities, thus providing a more nuanced overview of the differing sensitivities between tasks and time. We view this approach as a strength of the dissertation but acknowledge there are other cognitive measures we could have examined, such as a

general factor of intelligence or higher-order domain measures such as executive functioning. In addition, examining individual cognitive abilities does not examine the positive manifold of intelligence or how that structure may vary with smoking behavior and across time (Horn & Blankson, 2005; Spearman, 1904). For example, the prominent processing speed theory in cognitive aging suggests that losses in processing speed declines may mediate cognitive decline in other cognitive abilities (Salthouse, 1996). This theory is supported by prior work, which found processing speed losses were coupled with losses in memory and spatial functioning across middle age (Finkel et al., 2007). Although the processing speed theory is persuasive, it is not a definitive answer to cognitive aging. Indeed, researchers have contested that cognitive features mixed within processing speed measures, not processing speed itself, are the main driver (Horn & Blankson, 2005). Horn and Blankson (2005) suggested in their chapter that declines in age-sensitive cognitive abilities relate to focusing and maintaining attention which the authors further noted appears to be related to apprehension, as suggested initially by Spearman. Thus, the underlying mechanism contributing to cognitive decline as suggested by the processing speed theory is still under debate (Horn & Blankson, 2005).

Cognitive decline may also be determined by a general factor of cognitive aging (Tucker-Drob et al., 2019). A meta-analysis of longitudinal studies of cognitive aging found shared covariance across trajectories for several cognitive abilities. Thus, age-based coupling of processing speed, episodic memory, and visuospatial ability demonstrated within-person shared losses across these age-sensitive cognitive abilities, perhaps indicating a general factor. This dissertation does not contribute support to a

certain mechanism, but we only highlight the complexity at the center of aging and cognitive health. It remains for future work to explore the dynamics of cognitive aging to provide a more nuanced picture of whether the smoking-associated risk is shared for the same person across abilities or if individual differences influence certain abilities more for some but not others. Elucidating potential cognitive clusters at risk for smoking behavior and other health behaviors may reveal differences in underlying vulnerabilities and/or compensatory mechanisms in action.

Smoking Behavior Comorbidities

This dissertation focused on elucidating earlier life cigarette use and its influence on cognitive functioning and development. We chose to examine one substance use behavior exclusively (i.e., smoking behavior via cigarette use) to better articulate the associations between smoking and cognition, especially since the extant literature in younger adults commonly includes tobacco use as a covariate (Castellanos-Ryan et al., 2017; Mahedy et al., 2018; Meier et al., 2012; Meier et al., 2022). With that being said, smoking behavior represents one type of behavior within a larger hierarchical structure of externalizing behaviors and hence other substance use behaviors (Hicks et al., 2021; Keyes et al., 2007; Krueger et al., 2002; Krueger et al., 2021). Smoking behavior is not entirely isolated from other substance use, other psychopathological traits (De Leon & Diaz, 2005; Grant et al., 2004; Thorpe et al., 2020), or health behaviors (Johnson et al., 2011; Ross et al., 2022). Tobacco use, and more specifically nicotine dependency, tend to be comorbid with several other mental conditions and disorders, namely schizophrenia, ADHD, alcohol use disorders, and anxiety (De Leon & Diaz, 2005; Grant et al., 2004;

Thorpe et al., 2020). Thus, future research should explore the cooccurrence of other psychopathological traits not examined in this study. Disentangling the complex development of tobacco smoking and the cooccurrence of polysubstance will help shed light on how cognitive and substance use behavior codevelop. Additionally, there may be polysubstance use that additively contributes to the pernicious effects (Cardenas et al., 2020; Glass et al., 2009; Logtenberg et al., 2021; Ning et al., 2020), diminish deleterious effects (Jung et al., 2022; Schuster et al., 2015) or interact on independent subsystems related to a specific substance (Valjent et al., 2002). For example, a young adult study found tobacco use attenuated the negative associations of marijuana use on episodic memory after controlling for alcohol and other sociodemographics (Schuster et al., 2015). Further, the attenuation patterns were not explained by the differences in tobacco users' IQ, education, mental health, or other substance use behaviors. The authors speculated that the effect from constituent tobacco might weaken the cannabis negative influence by the proliferation of nAChRs via nicotine in shared neural regions that are known to be negatively impacted by THC. Therefore, tobacco use may act as a compensatory mechanism for the pernicious effects implicated by biochemical process effects derived from THC. This postulation may be true for more recent smokers, given the enhanced effects of nicotine, but based on our findings, it is unlikely for persistent use. Hence, further work on polysubstance is needed.

Tobacco Control Policy

The TCS measure is a multi-policy domain metric that could be compared to other country control policies via subdomain scores in Tobacco Control Scale (Joossens

et al., 2019; Joossens & Raw, 2006). Since not all aspects of the dissertation TCS parallel the international Tobacco Control Scale, more work could be done with public health policy experts to fully align the TCS with the Tobacco Control Scale. Efforts to incorporate the TCS with the Tobacco Control Scale will allow future comparative work of smoking-cognitive associations across countries. The TCS we developed for this dissertation serves as a proxy to examine tobacco control efforts across states, but just as the Tobacco Control Scale needs to be formally validated (Feliu et al., 2020), so does the TCS measure in our work. In addition, the TCS is not a comprehensive metric for all aspects of tobacco control across time. Take, for instance, policies related to the minimum age for tobacco. Policy scoring for minimum age cutoffs was not incorporated into the original Tobacco Control Scale and thus was not included in the dissertation TCS measure, especially since the federal minimum age has been 18 since 1992 and only recently changed to 21 in 2019.

This dissertation developed the TCS to evaluate how environments that vary based on public health policy aimed at tobacco use may influence smoking and cognitive health. For the reasons outlined above, more work is warranted. State-level tobacco control represents one domain of public health and examining multiple levels between the broader ecological policy landscape of local municipalities and individual-level factors will further articulate the relationship between policy context and the smoking-cognitive health effects (Gebreab et al., 2015). The TCS is a promising tool for further research endeavors to examine distal environmental processes that may be operating in the background to influence health outcomes, including cognition.

Conclusion

As this dissertation indicates, the influence of smoking behavior on cognition emerges early in the lifespan. Research thus far has focused on the impact of smoking behavior on cognition in older adults (Anstey et al., 2007; Conti et al., 2019; Durazzo et al., 2010; Swan & Lessov-Schlaggar, 2007). This dissertation elucidates the timing effects of smoking on cognitive performance and trajectories. The collective findings from this dissertation contribute to the literature in fundamental ways that relate to formative developmental windows of risk on cognitive development and decline, which to date have been understudied, but further work remains. Cognitive dysfunction and impairment are not inevitable, and aging processes are not centered only in later life (Barnett et al., 2013; Bourassa et al., 2022). Smoking behavior is a pernicious yet modifiable health risk to cognition. The earlier we focus on making sustainable changes, the sooner we help alleviate the future harm smoking may impose on cognitive health.

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Appendices

Appendix 1. State-Level Scoring for the Tobacco Control Score and Sensitivity Analysis with Year 12 IQ (Study 1)

Appendix 2. Supplemental Tables and Figures (Study 2)

Appendix 1. State-Level Scoring for the Tobacco Control Score and Sensitivity Analysis with Year 12 IQ (Study 1)

Supplemental Methods

State-Level Tobacco Control Score

A tobacco control score (TCS) was created across states in the USA to index level of smoking intervention policies within the USA across each state by the year 2018. Only 3 states are not represented as no CATSLife1 participants reside in those states: Vermont, Missouri, and Alabama. Utilizing the Framework of Convention on Tobacco Control (FCTC) developed by the World Health Organization, policy specific legislation was scored by state according to the 2019 version of Tobacco Control Scale (Joossens et al., 2019; Joossens & Raw, 2006) within domains of cigarette pack pricing, restricted/banned on workplace and public smoking, restricted/banned cigarette advertising, and health warning labels on cigarette products. Domains not included within the within the study TCS due to lack of accessible information necessary to score were health insurance coverage aimed at supporting cessation/treatment programs, interstate illicit tobacco trade, spending on public information campaigns, legislation on preventing tobacco industry lobbying interference, and ratifying to the WHO FCTC future recommendations. These policy domains, although important when considering policies focused on decreasing initiation rates (e.g., public campaigns) or increasing cessation (e.g., insurance) were less publicly available and experts would be required to examine insurance and public campaign spending across states to ensure proper adherence to the tobacco control scale.

For the policies domains used in the study TCS, the point coverage break out from the original scale are: Price (30 points), smoke-free (22 points), advertising bans (13

points), and warning labels (10 points); Total (75 points). We preserved the point assignments by domain given the point weights were assigned via expert panels (Joossens & Raw, 2006). We scored each category within specific policy domain across states. For instance, price was a fixed score dependent on whether the average cost of cigarette pack reached €10, the benchmark of balancing the purchasing power of an individual within a country and lack of affordability for purchasing cigarettes. To align with the 2019 version of the Tobacco Control Scale, we first found the average cost of cigarette packs per state by 2018 (Orzechowski & Walker, 2019). States varied in price from the highest in New York at $10.3 to Missouri at $4.96 (*M*=6.92, *SD*=1.46).

Next to scale the cost of the cigarette price to purchasing power within the state we found the regional price parities (RPP) per state which is expressed as the percentage relative to the national price level on all items (e.g., goods, services, rent) (Figueroa & Aversa, 2019). Next, we then multiplied the cost of a cigarette pack to the RPP. Lastly, to align with the Tobacco Control Scale we divided the cost of the cigarette pack by $11.80 (the equivalent to €10 in 2018) and multiplied the quotient by 30 points. Thus, if a state RPP relative cigarette cost was $11.80 then that state would receive the full 30 points.

The remaining policy domains were scored per category, please see (Joossens et al., 2019) to review the categories available per domain section. Please see Appendix 1 for Tables A1.1-A1.3 to review the state-level scoring per policy domain. Once all the domain policy scores were found, we totaled all domains with a possible score ranging from 0 to 75 with higher scores indicating greater levels of tobacco control. To calibrate the scale to the original Tobacco Control Scale that ranged to 100, a percent was

calculated representing compliance for the represented domains (e.g., out of a maximum 75 points). In other words, a score of 30 would mean about 30% compliance to the Tobacco Control Scale.

Table A1.1. Smoke Free Work and Other Public Places by State.

State	Workplaces excluding cafes and restaurants	Cafes and restaurants	Public transport	Private cars	Complete ban in educational, health, government and cultural places
AK [1-3]	2	2	0	0	0
AR [4; 5]	4	4	2	1	1
AZ [6; 7]	10	8	2	0	1
CA [8-11]	10	8	0	1	1
CO [12-16]	6	8	2	0	1
CT [17; 18]	6	8	0	0	1
DC [19; 20]	10	6	2	0	1
DE [21]	10	8	2	0	1
FL [17; 22; 23]	10	4	2	0	1
GA [17]	2	2	0	0	1
HI [24]	10	8	2	0	1
IA [25; 26]	8	8	2	0	1
ID [17; 27]	8	4	0	0	1
IL [28; 29]	10	8	2	0	1
IN [17; 30]	4	4	0	0	1
KS [31; 32]	10	8	2	0	1
KY [17]	0	0	0	0	0
LA [33-35]	8	4	2	1	1
MA [36; 37]	10	8	2	0	1
MD [38; 39]	10	6	2	0	1
ME [33; 40; 41]	10	8	2	1	1
MI [17; 32; 42]	10	8	2	0	1
MN [17; 43]	10	8	2	0	1
MO [17; 44]	4	4	2	0	0
MT [17; 45; 46]	10	8	2	0	1
NC [47]	0	8	0	0	0
ND [48; 49]	10	8	2	0	1
NE [50; 51]	10	8	2	0	1
NH [52]	6	8	2	0	1
NJ [32; 53; 54]	10	8	2	0	1
NM [55]	8	8	2	0	1
NV [17; 56]	10	4	0	0	1
NY [23; 57]	10	8	2	0	1
OH [58]	6	8	2	0	1
OK [59-61]	6	4	2	0	0

State	Workplaces excluding cafes and restaurants	Cafes and restaurants	Public transport	Private cars	Complete ban in educational, health, government and cultural places
OR [62-65]	10	8	2	1	1
PA [17; 66]	4	6	2	0	1
RI [17]	10	8	2	0	1
SC [67; 68]	0	0	2	0	0
SD [17; 69-71]	10	6	2	0	1
TN [72]	2	2	2	0	1
TX [17]	0	0	0	0	0
UT [33; 73; 74]	10	8	2	1	1
VA [75; 76]	2	6	2	1	0
WA [15; 77; 78]	10	8	2	0	1
WI [79]	10	8	2	0	1
WV [17]	0	0	0	0	0
WY [17]	0	0	0	0	0

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Table A1.2. Federal Scoring Comprehensive Bans on Advertising and Promotion.

State	Complete ban on tobacco advertising on television and radio	Ban on cinema advertising	Complete ban on outdoor advertising (e.g. posters)	Complete ban on advertising in print media (e.g. newspapers and magazines)	Ban on display of tobacco products at the point of sale	Ban on sponsorship	Ban on point of sale advertising	Ban on internet advertising	Complete ban on indirect advertising (e.g. cigarette branded clothes, watches, etc)
USA [1-3]	2	0	2	0	0	0	0	0	0

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Table A1.3. Federal Scoring for Warning Label on Cigarette Packages.

State	Plain packaging*	Percentage of size of the warnings is 50% or less of packet	Does the warning include a picture for cigarettes?	Does the warning include a picture for cigarettes or rolled cigarettes?
USA[1]	0	1	0	0

Note. *The removal of trademarks, logos, colors and graphics, except for the government health warning, and brand name presented in a standardized typeface.

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Table A1.4. Multilevel Models with Year 12 IQ by Cognitive Measure with Random Effects for Siblings.

Model (M) parameters		PM	NF	CPS	DSy	BD	V
Intercept	b1	**51.18**	**51.4**	**51.75**	**52.21**	**49.00**	**49.03**
	se	1.73	1.73	1.64	1.59	1.40	1.36
Age	b2	0.30	0.16	-0.20	-0.07	-0.27	**0.42**
	se	0.19	0.19	0.18	0.17	0.15	0.15
Sex	b3	**-3.71**	**-3.81**	**-1.35**	**-3.94**	**2.69**	-0.42
	se	0.69	0.69	0.65	0.63	0.54	0.54
Adopted	b4	0.13	-1.63	-1.69	-0.98	-1.40	**-2.12**
	se	1.04	1.07	1.02	1.00	0.91	0.82
Non-	b5	-2.60	-0.06	1.03	1.92	0.09	1.16
Hispanic	se	1.79	1.73	1.64	1.58	1.36	1.41
White	b6	2.99	0.57	-1.20	-1.19	0.34	-0.24
	se	1.70	1.65	1.55	1.51	1.32	1.33
Project	b7	2.42	1.79	0.20	0.69	0.26	2.34
	se	1.62	1.67	1.56	1.53	1.36	1.27
Year 12 IQ	b8	**0.12**	**0.25**	**0.37**	**0.35**	**0.46**	**0.40**
	se	0.04	0.04	0.04	0.04	0.04	0.03
Year 12	b9	-0.04	-0.03	-0.04	-0.05	-0.03	**0.08**
IQxProj	se	0.06	0.06	0.05	0.05	0.05	0.04
Current	b10		-1.38	**-1.78**	**-1.90**	**-3.62**	-0.50
	se		0.96	0.89	0.88	0.70	0.76
PKYRS	b11	**-1.01**	-0.64	**-1.17**	**-1.43**		**-0.87**
(log)	se	0.35	0.39	0.36	0.36		0.30
σ2BW: AD		0	0	0	0	0	0
σ2BW: Con		0	0	3.87	5.97	5.17	0
σ2BW: DZ		0.64	28.89	15.57	20.18	21.86	6.26
σ2BW: MZ		29	30.9	26.59	23.5	7.38	19.54
σ2WI: AD		30.25	40.92	46.48	36.69	30.44	34.77
σ2WI: Con		91.54	84.82	83.9	71.83	61.84	59.29
σ2WI: DZ		72.3	62.45	53.77	53	35.16	34.76
σ2WI: MZ		85.63	54.78	52.76	51.25	46.2	35.41
Model Fit							
N (Individuals)		922	911	922	919	919	919
N (Sibships)		593	588	593	590	590	590
-2ll		6668.1	6678.9	6531.6	6482.1	6295.2	6218.1
AIC		6702.1	6714.9	6569.6	6520.1	6331.2	6254.1

Note. PM=Picture Memory; NF=Names & Faces; DSpa=Digit Span; CPS=Colorado Perceptual Speed; DS= Digit Symbol; BD=Block Design; V=Vocabulary; Adjusted for Age (centered at *M*=33.28), Sex (female=0, male=1), Adopted = adopted status (non-

adopted=0, adopted=1), Non-Hispanic ethnicity (0=Hispanic, 1=Non-Hispanic), Project (CAP=0, LTS=1), and race (0=non-White, 1=White), MAP=mean arterial pressure (centered at *M*=85.21); CVD=count of cardiovascular conditions; EDU_{yrs}= ISCED years of education (centered at the median of 16 yrs); Random effects: σ2BW=between siblings and σ2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins; Bolded parameters are significant $p < .05$

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Appendix 2. Supplemental Tables and Figures (Study 2)

Table A2.1. Summary of Available Longitudinal Cognitive Data by Project.

Assessment	CAP		LTS	
Wave Count	***N***	**%**	***N***	**%**
1	6	1.1	5	0.7
2	133	23.6	70	10.4
3	13	2.3	107	15.9
4	48	8.5	491	73.0
5	160	28.4	--	--
6	203	36.1	--	--

Note. Project N and percentages are provided are based on individual cognitive wave availability in the analytic sample (N=1,236). The majority of CAP (73.0%) and LTS (88.9%) participants had cognitive data available for at least half of the available time points within each project. Grayed-outs indicate waves not assessed for the project.

Table A2.2. Descriptives of Smoking Measures across Project.

Project Measure	*N*	*M*	*SD*	Min	Max	Skew	Smoking ≥ 1 Cigarette at 16 *M*	Smoking ≥ 1 Cigarette at 16 *SD*
CAP								
Cigs16	563	1.9	5.9	0.0	40.0	3.5	9.7	9.9
SmkDiff		2.9	8.3	-35.0	60.0	1.1	0.5	11.9
LTS								
Cigs16	673	0.9	3.9	0.0	40.0	5.8	7.5	8.8
SmkDiff		1.8	5.5	-25.0	37.0	2.2	1.9	9.9

Note. CAP=Colorado Adoption Project; LTS=Longitudinal Twin Study. Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=Difference in the number of cigarettes smoked from CATSLife1 (i.e., CATSLife) and year 16.

Table A2.3. Conditional Growth Model Random Effects: Picture Memory (PM) from year 12 to CATSLife1.

		Model 1	Model 4
Residual σ^2		62.19	62.19
Intercept	σ^2BW_{AD}	0.00	0.00
	σ^2BW_{Con}	8.93	8.89
	σ^2BW_{DZ}	22.40	22.41
	σ^2BW_{MZ}	25.74	25.66
	σ^2WI_{AD}	41.67	41.66
	σ^2WI_{Con}	22.15	22.10
	σ^2WI_{DZ}	24.54	24.54
	σ^2WI_{MZ}	7.95	7.95

Note. Random effects are not estimated on the bilinear terms, thus Model 2 & 3 with smoking behavior interaction on the slope is not shown. Model 1 refers to adding smoking behavior on the intercept; Model 4 refers to the model with smoking behavior on the intercept and entering parental education.
Adjusted for sex, project, adoption status, ethnicity, and race.
Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins.
Total N of persons=710; Total N of Observations=4923

Table A2.4. Conditional Growth Model Random Effects: Names and Faces (NF) from year 12 to CATSLife1.

		Model 1	Model 2	Model 3	Model 4
Residual σ^2		38.71	38.71	38.71	38.72
Intercept	σ^2BW_{AD}	13.34	13.41	14.05	13.41
	σ^2BW_{Con}	20.20	20.25	20.48	20.48
	σ^2BW_{DZ}	18.66	18.79	19.10	18.78
	σ^2BW_{MZ}	53.20	53.52	53.93	52.64
	σ^2WI_{AD}	39.53	39.56	39.74	40.41
	σ^2WI_{Con}	42.85	42.87	42.77	42.58
	σ^2WI_{DZ}	33.17	33.13	32.97	32.94
	σ^2WI_{MZ}	8.17	8.07	8.10	8.10
COV Intercept & Spline1	σ^2BW_{AD}	14.75	14.96	14.76	13.35
	σ^2BW_{Con}	-0.91	-0.94	-0.97	-0.94
	σ^2BW_{DZ}	15.59	15.77	16.02	15.57
	σ^2BW_{MZ}	31.44	31.60	31.78	31.83
	σ^2WI_{AD}	17.25	17.19	17.62	18.69
	σ^2WI_{Con}	27.86	27.82	27.52	27.44
	σ^2WI_{DZ}	15.31	15.30	15.16	15.15
	σ^2WI_{MZ}	7.65	7.61	7.91	7.92
Spline1	σ^2BW_{AD}	0.00	0.00	0.00	0.00
	σ^2BW_{Con}	0.00	0.00	0.00	0.00
	σ^2BW_{DZ}	9.75	10.02	10.34	9.70
	σ^2BW_{MZ}	21.13	21.14	21.27	21.02
	σ^2WI_{AD}	35.92	35.89	35.74	35.18
	σ^2WI_{Con}	0.00	0.00	0.00	0.00
	σ^2WI_{DZ}	0.00	0.00	0.00	0.00
	σ^2WI_{MZ}	0.00	0.00	0.00	0.00
COV Intercept & Spline2	σ^2BW_{AD}	-0.90	-1.01	-1.13	-1.05
	σ^2BW_{Con}	1.02	0.97	0.92	0.92
	σ^2BW_{DZ}	0.76	0.67	0.79	0.77
	σ^2BW_{MZ}	-1.95	-2.16	-2.23	-2.30
	σ^2WI_{AD}	1.53	1.55	1.56	1.50
	σ^2WI_{Con}	-1.78	-1.72	-1.68	-1.68
	σ^2WI_{DZ}	-2.07	-1.98	-1.97	-1.94
	σ^2WI_{MZ}	0.99	1.05	1.01	1.01

		Model 1	Model 2	Model 3	Model 4
COV Spline1 & Spline2	σ^2BW_{AD}	-1.64	-1.81	-1.82	-1.69
	σ^2BW_{Con}	3.03	2.97	2.98	2.99
	σ^2BW_{DZ}	-1.29	-1.43	-1.47	-1.42
	σ^2BW_{MZ}	-4.15	-4.37	-4.43	-4.35
	σ^2WI_{AD}	6.43	6.41	6.39	6.30
	σ^2WI_{Con}	0.26	0.37	0.40	0.40
	σ^2WI_{DZ}	-1.24	-1.18	-1.19	-1.18
	σ^2WI_{MZ}	2.63	2.65	2.63	2.63
Spline2	σ^2BW_{AD}	0.10	0.16	0.18	0.18
	σ^2BW_{Con}	0.03	0.07	0.07	0.07
	σ^2BW_{DZ}	0.00	0.00	0.00	0.00
	σ^2BW_{MZ}	0.80	0.84	0.85	0.84
	σ^2WI_{AD}	0.14	0.10	0.10	0.09
	σ^2WI_{Con}	0.74	0.68	0.68	0.68
	σ^2WI_{DZ}	0.80	0.70	0.69	0.68
	σ^2WI_{MZ}	0.00	0.00	0.00	0.00

Note. Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and 2nd slope; Model 3 refers to only including smoking behavior on the 2nd slope; Model 4 refers to the model with smoking behavior on the 2nd slope and entering parental education.
Adjusted for sex, project, adoption status, ethnicity, and race.
Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins.
Total N of persons=710; Total N of Observations=4926

Table A2.5. Conditional Growth Model Random Effects: Digit Span (Dspa) from year 16 to CATSLife1.

		Model 1	Model 2	Model 3	Model 4
Residual σ^2		35.91	35.95	35.97	35.91
Intercept	σ^2BW_{AD}	0.00	0.00	0.00	0.00
	σ^2BW_{Con}	25.85	25.97	26.07	26.13
	σ^2BW_{DZ}	34.48	34.47	34.19	33.67
	σ^2BW_{MZ}	57.62	57.69	58.33	56.64
	σ^2WI_{AD}	66.81	66.87	67.60	67.40
	σ^2WI_{Con}	42.87	42.71	43.07	42.81
	σ^2WI_{DZ}	18.03	18.06	17.65	18.08
	σ^2WI_{MZ}	4.83	4.70	5.31	4.78
COV Intercept & Slope	σ^2BW_{AD}	1.39	1.34	1.34	1.48
	σ^2BW_{Con}	2.47	2.42	2.36	2.49
	σ^2BW_{DZ}	-2.29	-2.29	-2.34	-2.14
	σ^2BW_{MZ}	1.09	1.06	1.15	0.98
	σ^2WI_{AD}	-0.42	-0.37	-0.47	-0.50
	σ^2WI_{Con}	-1.59	-1.52	-1.56	-1.62
	σ^2WI_{DZ}	9.50	9.49	9.42	9.49
	σ^2WI_{MZ}	1.80	1.84	1.84	1.80
Slope	σ^2BW_{AD}	0.00	0.00	0.00	0.00
	σ^2BW_{Con}	0.00	0.00	0.00	0.00
	σ^2BW_{DZ}	0.46	0.47	0.47	0.44
	σ^2BW_{MZ}	0.56	0.57	0.54	0.57
	σ^2WI_{AD}	0.06	0.02	0.04	0.05
	σ^2WI_{Con}	0.13	0.12	0.13	0.13
	σ^2WI_{DZ}	0.11	0.11	0.11	0.11
	σ^2WI_{MZ}	1.57	1.56	1.56	1.57

Note. Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and slope; Model 3 refers to only including smoking behavior on the slope; Model 4 refers to the model with smoking behavior on the intercept and entering parental education.
Adjusted for sex, project, adoption status, ethnicity, and race.
Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins.
Total N of persons=710; Total N of Observations=2994

Table A2.6. Conditional Growth Model Random Effects: Colorado Perceptual Speed (CPS) from year 12 to CATSLife1.

		Model 1	Model 2	Model 3	Model 4
Residual σ^2		26.60	26.61	26.61	26.60
Intercept	σ^2BW_{AD}	22.58	22.77	24.58	23.59
	σ^2BW_{Con}	4.49	4.60	5.58	4.52
	σ^2BW_{DZ}	23.77	23.78	24.24	24.09
	σ^2BW_{MZ}	45.24	45.32	47.10	42.54
	σ^2WI_{AD}	42.38	42.37	45.08	42.50
	σ^2WI_{Con}	54.11	53.87	52.70	53.63
	σ^2WI_{DZ}	28.09	28.07	28.19	27.98
	σ^2WI_{MZ}	5.70	5.70	5.73	5.69
COV Intercept & Spline2	σ^2BW_{AD}	-1.66	-1.74	-2.02	-1.57
	σ^2BW_{Con}	1.31	1.26	1.24	1.25
	σ^2BW_{DZ}	1.51	1.51	1.62	1.46
	σ^2BW_{MZ}	1.48	1.42	1.81	1.43
	σ^2WI_{AD}	2.91	2.82	2.80	2.90
	σ^2WI_{Con}	0.04	0.21	0.22	0.11
	σ^2WI_{DZ}	1.55	1.58	1.51	1.56
	σ^2WI_{MZ}	1.14	1.17	0.93	1.13
Spline2	σ^2BW_{AD}	0.00	0.00	0.00	0.00
	σ^2BW_{Con}	0.00	0.00	0.00	0.00
	σ^2BW_{DZ}	0.69	0.66	0.65	0.69
	σ^2BW_{MZ}	0.40	0.31	0.29	0.40
	σ^2WI_{AD}	1.49	1.51	1.52	1.48
	σ^2WI_{Con}	0.78	0.76	0.76	0.78
	σ^2WI_{DZ}	0.00	0.00	0.00	0.00
	σ^2WI_{MZ}	0.00	0.00	0.00	0.00

Note. Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and 2nd slope; Model 3 refers to only including smoking behavior on the 2nd slope; Model 4 refers to the model with smoking behavior on the intercept and entering parental education.
Adjusted for sex, project, adoption status, ethnicity, and race.
Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins.
Total N of persons=710; Total N of Observations=4943

Table A2.7. Conditional Growth Model Random Effects: Digit Symbol (DSy) from year 16 to CATSLife1.

		Model 1	Model 2	Model 3	Model 4
Residual σ^2		26.51	26.43	26.49	26.42
Intercept	σ^2BW_{AD}	4.91	5.21	4.40	5.06
	σ^2BW_{Con}	13.12	14.05	15.19	13.41
	σ^2BW_{DZ}	23.10	23.49	24.44	23.12
	σ^2BW_{MZ}	60.64	61.47	63.89	57.91
	σ^2WI_{AD}	53.40	53.65	57.48	54.94
	σ^2WI_{Con}	44.71	43.28	41.44	42.89
	σ^2WI_{DZ}	32.89	32.99	33.43	32.87
	σ^2WI_{MZ}	7.77	7.52	7.14	7.45
COV Intercept & Slope	σ^2BW_{AD}	-0.02	-0.01	0.03	0.26
	σ^2BW_{Con}	0.92	0.71	0.62	0.66
	σ^2BW_{DZ}	0.86	0.73	0.82	0.73
	σ^2BW_{MZ}	-0.07	-0.28	-0.09	-0.37
	σ^2WI_{AD}	0.15	0.01	-0.37	-0.13
	σ^2WI_{Con}	-0.66	-0.20	-0.07	-0.25
	σ^2WI_{DZ}	1.15	1.12	0.92	1.10
	σ^2WI_{MZ}	0.42	0.51	0.50	0.52
Slope	σ^2BW_{AD}	0.00	0.00	0.00	0.00
	σ^2BW_{Con}	0.23	0.20	0.18	0.19
	σ^2BW_{DZ}	1.21	1.21	1.20	1.22
	σ^2BW_{MZ}	0.68	0.61	0.55	0.61
	σ^2WI_{AD}	0.63	0.64	0.66	0.64
	σ^2WI_{Con}	0.30	0.27	0.29	0.28
	σ^2WI_{DZ}	0.00	0.00	0.00	0.00
	σ^2WI_{MZ}	0.00	0.00	0.00	0.00

Note. Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and slope; Model 3 refers to only including smoking behavior on the slope; Model 4 refers to the model with smoking behavior on the intercept and slope and entering parental education.
Adjusted for sex, project, adoption status, ethnicity, and race.
Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins.
Total N of persons=710; Total N of Observations=2991

Table A2.8. Conditional Growth Model Random Effects: Block Design (BD) from year 12 to CATSLife1.

		Model 1	Model 4
Residual σ^2		26.61	26.61
Intercept	σ^2BW_{AD}	20.54	20.14
	σ^2BW_{Con}	19.88	20.38
	σ^2BW_{DZ}	30.94	30.22
	σ^2BW_{MZ}	53.06	49.89
	σ^2WI_{AD}	49.53	50.15
	σ^2WI_{Con}	28.34	28.34
	σ^2WI_{DZ}	34.35	34.36
	σ^2WI_{MZ}	5.88	5.91

Note. Random effects are not estimated on the linear term, thus Model 2 & 3 with smoking behavior interaction on the slope is not shown. Model 1 refers to adding smoking behavior on the intercept; Model 4 refers to the model with smoking behavior on the intercept and entering parental education.
Adjusted for sex, project, adoption status, ethnicity, and race.
Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins.
Total N of persons=710; Total N of Observations=3977

Table A2.9. Conditional Growth Model Random Effects: Vocabulary (V) from year 12 to CATSLife1.

		Model 1	Model 4
Residual σ^2		24.68	24.66
Intercept	$\sigma^2 BW_{AD}$	6.99	9.19
	$\sigma^2 BW_{Con}$	14.49	13.10
	$\sigma^2 BW_{DZ}$	39.18	31.43
	$\sigma^2 BW_{MZ}$	50.25	41.67
	$\sigma^2 WI_{AD}$	40.37	40.35
	$\sigma^2 WI_{Con}$	17.21	17.52
	$\sigma^2 WI_{DZ}$	15.89	15.76
	$\sigma^2 WI_{MZ}$	0.00	0.00

Note. Random effects are not estimated on the linear term, thus Model 2 & 3 with smoking behavior interaction on the slope is not shown. Model 1 refers to adding smoking behavior on the intercept; Model 4 refers to the model with smoking behavior on the intercept and entering parental education.
Adjusted for sex, project, adoption status, ethnicity, and race.
Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings, Con=control family siblings, DZ=dizygotic twins, and MZ=monozygotic twins.
Total N of persons=710; Total N of Observations=4868

Table A2.10. CAP-Only Model Fit Statistics for Unconditional Spline models with different Knot Points.

Spline Model Knot Points		Age 16	Age 21	Age 30	Age 16 & Age 30	Age 21 & Age 30
Dspa[a]						
	K	--	16[b]	16 [b]	--	--
	-2lnL	--	11680.3	11760.7	--	--
	AIC	--	11712.3	11792.7	--	--
CPS						
	K	28	28	28	29[c]	29[c]
	-2lnL	17084.9	17146.8	17672.2	16861.9	17122.6
	AIC	17140.9	17202.8	17728.2	16919.9	17180.6
DSy[a]						
	K	--	28	16 [b]	--	--
	-2lnL	--	11484.7	11518.7	--	--
	AIC	--	11540.7	11550.7	--	--
BD						
	K	28	28	28	45	29[c]
	-2lnL	13755.9	13730.2	13764.2	13706.4	13721.2
	AIC	13811.9	13786.2	13820.2	13796.4	13827.2

Note.
Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, and BD=Block Design; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; df = degrees of freedom. Best fitting models based on lowest AIC are highlighted as green.
Total N of persons=351; Total N of Observations=1679-2517
[a]Cognitive Measures earliest wave is 16.
[b]Model couldn't converge with random effects simultaneously modeled on splines 1 and 2; Spline1 dropped.
[c]Model couldn't converge with random effects simultaneously modeled on splines 1, 2, and 3; spline 3 dropped.

Table A2.11. CAP-Only Model Fit Statistics for Unconditional Growth Curves.

	K	-2lnL	AIC	Model (M) Comparison	$\Delta\chi^2$	df	*p*
Dspa (centered at age 21)							
M0: Means only	5	12035.7	12045.7				
M1: Linear	15	11844.7	11874.7	M0-M1	191	10	**<.0001**
M2: Quadratic	16[a]	11717.1	11749.1	M1-M2	127.6	1	**<.0001**
M3: Spline at 21 years	--[b]	--	--	--	--	--	--
M3a: Spline- no random effects on 2nd slope	16	11677.7	11709.7	M1-M2a	167.0	1	**<.0001**
M3b: Spline- no random effects on 1st slope	16	11680.3	11712.3	M1-M2b	164.4	1	**<.0001**
M3c: Spline- no random effects on any slopes	8	11693.5	11709.5	M2c-M2a	13.2	8	.105
CPS (centered at age 16)							
M0: Means only	6	19213.7	19225.7				
M1: Linear	15	18402.3	18432.3	M0-M1	811.4	9	**<.0001**
M2: Quadratic	28	17213.4	17269.4	M1-M2	1188.9	13	**<.0001**
M3: Spline at 16 and 30 years	--[b]	--	--	--	--	--	--
M3a: Spline- no random effects on 3rd slope	29	16861.9	16919.9	M1-M3	1540.4	14	**<.0001**
M3b: Spline- no random effects on 2nd & 3rd slope	17	16936.7	16970.7	M3b-M3a	74.8	12	**<.0001**
M3c: Spline- no random effects on any slope	9	17028.8	17046.8	M3c-M3b	92.1	8	**<.0001**

	K	-2lnL	AIC	Model (M) Comparison	$\Delta\chi^2$	df	*p*
DSy (centered at age 21)							
M0: Means only	6	11644.5	11656.5				
M1: Linear	15	11586.0	11616.0	M0-M1	58.5	17	**<.0001**
M2: Quadratic	28	11472.3	11528.3	M1-M2	113.7	17	**<.0001**
M2a: no random effects on quadratic slope	16	11487.4	11519.4	M2a-M2	15.1	12	.236
M2b: no random effects on any slope	8	11498.5	11514.5	M2b-M2a	11.1	8	.196
M3: Spline at 21 years	28	11484.7	11540.7	M1-M3	101.3	17	**<.0001**
BD (centered at age 21)							
M0: Means only	6	13929.0	13941.0				
M1: Linear	15	13852.6	13882.6	M0-M1	76.4	17	**<.0001**
M2: Quadratic	28	13733.2	13789.2	M1-M2	119.4	17	**<.0001**
M3: Spline at 21 years	28	13730.2	13786.2	M1-M3	122.4	13	**<.0001**
M3a: Spline- no random effects on 2nd slope	16	13741.0	13769.0	M3a-M3	10.8	12	.546
M3b: Spline- no random effects on slopes	8	13760.3	13772.3	M3b-M3a	19.3	8	**.013**

Note. Dspa=Digit Span; CPS=Colorado Perceptual Speed; DSy=Digit Symbol; BD=Block Design; M0=means only; M1=linear model; M2=quadratic model; M3=spline with noted knot points; M2a-M2b=quadratic model with no random effects on noted slope; M3a-M3c=spline model with no random effects on noted slope; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; df = degrees of freedom. Best fitting models are highlighted as green. Bolded parameters are significant $p < .05$. Total N of persons=351; Total N of Observations=1679-2517.
[a]Model couldn't converge with random effects simultaneously modeled on linear and quadratic terms; quadratic term dropped.
[b]Model couldn't converge with random effects simultaneously modeled on splines 1 and 2.

Table A2.12. CAP-Only Fixed Effects for Best Fitting Unconditional Growth Model across Cognitive Measures.

		Dspa	CPS	DSy	BD
Spline (S) or Quadratic (Q)		S at 21 B (SE)	S at 16 & 30 B (SE)	Q at 21 B (SE)	S at 21 B (SE)
Performance centered age		**56.72** (0.51)	**51.73** (0.44)	**54.12** (0.43)	**53.08** (.44)
Spline1/Linear		**6.36** (0.41)	**20.33** (0.47)	**2.24** (0.18)	**2.34** (0.22)
Spline2/Quadratic		0.09 (0.11)	**3.00** (0.16)	**-0.63** (0.06)	**-0.22** (0.09)
Spline3			**-2.68** (0.25)		
Random Effects					
Residual σ^2		28.29	25.14	28.01	21.78
Intercept	σ^2BW_{AD}	8.48	33.44	7.33	24.03
	σ^2BW_{Con}	43.67	3.62	21.22	23.45
	σ^2WI_{AD}	73.32	59.54	61.93	58.15
	σ^2WI_{Con}	37.69	66.38	43.89	31.18
COV Intercept & Spline1 /Linear	σ^2BW_{AD}	7.99	20.03		-0.28
	σ^2BW_{Con}	11.99	-8.22		1.11
	σ^2WI_{AD}	2.37	25.74		3.32
	σ^2WI_{Con}	-2.76	30.69		1.63
Spline1	σ^2BW_{AD}	4.36	24.31		0.00
	σ^2BW_{Con}	0.00	0.42		0.00
	σ^2WI_{AD}	0.00	0.00		3.39
	σ^2WI_{Con}	9.64	0.00		5.02
COV Intercept & Spline2	σ^2BW_{AD}		-5.76		
	σ^2BW_{Con}		2.47		
	σ^2WI_{AD}		2.22		
	σ^2WI_{Con}		-1.73		
COV Spline1 & Spline2	σ^2BW_{AD}		-7.54		
	σ^2BW_{Con}		2.78		
	σ^2WI_{AD}		6.37		
	σ^2WI_{Con}		1.43		
Spline2	σ^2BW_{AD}		1.17		
	σ^2BW_{Con}		0.00		
	σ^2WI_{AD}		2.19		
	σ^2WI_{Con}		0.53		

Note. Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, and BD=Block Design. Random effects: σ^2BW=between siblings and σ^2WI=within siblings; subscript notes sibling type: AD=adoptive family siblings and Con=control family siblings. Bolded parameters are significant $p < .05$. Total N of persons=351; Total N of Observations=1679-2517

Table A2.13. CAP-Only Conditional Growth Model Fixed Effects: Colorado Perceptual Speed (CPS) from year 12 to CATSLife1.

	Model 1		Model 2		Model 3		Model 4	
	B	SE	B	SE	B	SE	B	SE
Performance at age 16	**52.78**	0.65	**52.75**	0.65	**52.28**	0.64	**52.71**	0.68
Sex	-1.44	0.79	-1.45	0.79	-1.69	0.80	-1.44	0.79
Adopted	-1.71	0.90	-1.74	0.90	**-2.01**	0.91	-1.71	0.90
Hispanic	-2.25	3.03	-2.29	3.03	-2.46	3.08	-2.17	3.03
Non-white	-0.88	2.34	-0.85	2.34	-0.67	2.38	-0.91	2.34
PEdu							0.08	0.20
Cigs16	**-0.19**	0.07	**-0.17**	0.07			**-0.19**	0.07
SmkDiff	**-0.13**	0.04	**-0.12**	0.05			**-0.13**	0.04
Spline1 (12-16 years)	**20.95**	0.71	**20.95**	0.71	**20.97**	0.71	**20.89**	0.74
Sex	1.19	0.90	1.22	0.90	1.27	0.90	1.20	0.90
Adopted	**-2.97**	0.98	**-2.99**	0.98	**-3.03**	0.98	**-2.96**	0.98
Hispanic	-4.68	3.41	-4.68	3.41	-4.60	3.40	-4.60	3.42
Non-white	0.53	2.46	0.55	2.46	0.49	2.45	0.51	2.46
PEdu							0.07	0.22
Spline2 (16-30 years)	**2.84**	0.21	**2.89**	0.21	**2.91**	0.21	**2.86**	0.21
Sex	**0.45**	0.22	**0.46**	0.22	**0.47**	0.22	**0.44**	0.22
Adopted	-0.18	0.25	-0.15	0.25	-0.13	0.25	-0.18	0.25
Hispanic	-0.05	0.88	-0.001	0.88	-0.01	0.88	-0.08	0.88
Non-white	0.84	0.69	0.82	0.69	0.82	0.69	0.85	0.69
PEdu							-0.02	0.05
Cigs16			-0.03	0.02	-0.04	0.02		
SmkDiff			-0.01	0.01	-0.01	0.01		
Spline3 (age 30+ years)	**-2.70**	0.24	**-2.70**	0.24	**-2.70**	0.24	**-2.70**	0.24
Goodness-of-fit								
K	31		33		31		34	
-2lnL	16812.4		16810.7		16819.8		16819.8	
AIC	16874.4		16876.7		16881.8		16887.8	
Model Comparison	M0-M1		M1-M2		M0-M3		M1-M4	
$\Delta\chi 2$	10.6		1.7		3.2		7.4	
df	2		2		2		3	
p	**.005**		.427		.202		.060	

Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Model 1 refers to adding smoking behavior on the intercept; Model 2 refers to adding smoking behavior on the intercept and 2nd slope; Model 3 refers to only including smoking behavior on the 2nd slope; Model 4 refers to the model with smoking behavior on the 2nd slope and entering parental education; K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=351; Total N of Observations=2073

Table A2.14. CAP-Only Conditional Growth Model Fixed Effects: Digit Symbol (DSy) from year 16 to CATSLife1.

	Model 1		Model 4	
	B	SE	B	SE
Performance at age 21	**57.15**	0.64	**56.94**	0.66
Sex	**-3.82**	0.72	**-3.81**	0.72
Adopted	-0.96	0.78	-0.99	0.78
Hispanic	1.68	2.11	1.55	2.11
Non-white	-2.89	2.68	-2.58	2.69
PEdu			0.25	0.18
Cigs16	**-0.26**	0.07	**-0.25**	0.07
SmkDiff	-0.09	0.05	-0.09	0.05
Linear	**2.24**	0.18	**2.24**	0.18
Quadratic	**-0.63**	0.06	**-0.63**	0.06
Goodness-of-fit				
K	14		15	
-2lnL	11450.9		11449.0	
AIC	11478.9		11479.0	
Model Comparison	M0-M1		M1-M4	
$\Delta\chi 2$	13.9		1.9	
df	2		1	
p	**.001**		.168	

Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Model 1 refers to adding smoking behavior on the intercept; Random effects are not estimated on the linear or quadratic terms, thus Model 2 & 3 with smoking behavior interaction on the slope is not shown. Model 1 refers to adding smoking behavior on the intercept; Model 4 refers to the model with smoking behavior on the intercept and entering parental education; Bolded parameters are significant $p < .05$; Total N of persons=351; Total N of Observations=1679

Table A2.15. CAP-Only Conditional Growth Model Fixed Effects: Block Design (BD) from year 12 to CATSLife1.

	Model 1		Model 4	
	B	SE	B	SE
Performance at age 21	**52.79**	0.63	**52.61**	0.65
Sex	**3.65**	0.69	**3.66**	0.69
Adopted	**-2.23**	0.81	**-2.25**	0.81
Hispanic	-0.51	2.13	-0.55	2.13
Non-white	-1.69	2.74	-1.59	2.74
PEdu			0.24	0.20
Cigs16	**-0.22**	0.07	**-0.22**	0.07
SmkDiff	-0.08	0.04	-0.08	0.04
Spline1	**2.52**	0.32	**2.39**	0.33
Sex	0.36	0.36	0.39	0.36
Adopted	**-0.95**	0.37	**-0.96**	0.37
Hispanic	0.18	0.98	0.14	0.98
Non-white	1.43	1.29	1.48	1.29
PEdu			0.17	0.09
Spline2	**-0.22**	0.09	**-0.19**	0.09
Goodness-of-fit				
K	22		23	
-2lnL	13686.1		13681.4	
AIC	13730.1		13727.4	
Model Comparison	M0-M1		M1-M4	
$\Delta\chi 2$	10.9		4.7	
df	2		1	
p	.004		.030	

Note. PEdu=Parental Education, Cigs16=Number of cigarettes reported smoking at age 16, SmkDiff=consumption difference from CATSLife1 from year16 consumption; Adjusted for sex (0=F, 1=M), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-hispanic, 1=Hispanic), and race (0=White, 1=Non-White); Random effects are not estimated on the 2nd spline term, thus Model 2 & 3 with smoking behavior interaction on the 2nd slope is not shown. Model 1 refers to adding smoking behavior on the intercept; Model 4 refers to the model with smoking behavior on the intercept and entering parental education; Bolded parameters are significant $p < .05$; Total N of persons=351; Total N of Observations=2073

Table A2.16. Sensitivity Analysis with Square-root Adjusted Smoking Measures: Fixed Effects for Best Fitting Conditional Growth Models across Cognitive Measures.

	PM		NF		Dspa		CPS		DSy		BD		V	
	Spline		Spline		Linear		Spline		Linear		Linear		Linear	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Performance at age 16	**51.24**	0.40	**52.58**	0.44	**51.42**	**0.49**	**52.43**	0.41	**54.27**	0.46	**50.16**	0.42	**54.09**	0.35
Sex	**-2.54**	0.46	**-4.28**	0.56	0.46	0.61	**-2.40**	0.51	**-5.33**	0.57	**2.85**	0.51	0.81	0.44
Adopted	0.23	0.66	-0.97	0.83	**-2.03**	**0.90**	-1.07	0.78	-0.63	0.82	**-1.68**	0.78	**-2.00**	0.66
Non-Hispanic	0.63	1.21	-2.20	1.45	-1.75	1.57	0.79	1.27	0.98	74.00	0.33	1.33	-1.24	1.13
White	-1.63	1.11	0.26	1.32	-0.36	1.43	-0.68	1.15	0.19	1.32	-1.74	1.18	0.18	0.96
Project	**-1.67**	0.54	**-1.64**	0.70	**-3.23**	**0.75**	**-1.85**	0.61	**-2.67**	0.68	0.17	0.62	**-1.23**	0.53
PEdu	0.07	0.11	**0.28**	0.13	0.26	0.14	**0.33**	0.12	**0.44**	0.13	**0.37**	0.12	**0.89**	0.11
Cigs16sq	**-0.82**	0.20			**-0.52**	**0.24**	**-0.71**	0.21	**-0.85**	0.24	**-0.79**	0.21	**-0.46**	0.17
Smk_gainsq	-0.11	0.15			0.29	0.18	**-0.49**	0.15	-0.34	0.18	**-0.40**	0.15	-0.10	0.12
Spline1	**7.76**	0.46	**15.93**	0.56			**20.45**	0.31						
Sex			**-2.30**	0.74										
Adopted			-2.04	1.18										
Non-Hispanic			**-4.81**	1.88										
White			1.31	1.78										
Project			**-1.76**	0.89										
PEdu			0.04	0.17										

	PM		NF		Dspa		CPS		DSy		BD		V	
	Spline		Spline		Linear		Spline		Linear		Linear		Linear	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Spline2 or Linear	**-1.14**	0.08	**-0.36**	**0.12**	**1.25**	**0.11**	**1.04**	0.09	**1.19**	0.11	**0.76**	0.05	**1.90**	0.05
Sex			**0.33**	**0.14**	0.13	0.14	**0.38**	0.12	**0.43**	0.13				
Adopted			-0.09	0.18	-0.01	0.17	-0.29	0.16	-0.01	0.17				
Non-Hispanic			0.77	0.42	-0.23	0.43	-0.36	0.35	-0.67	0.39				
White			-0.30	0.37	0.23	0.38	0.29	0.31	0.03	0.35				
Project			-0.09	0.18	0.28	0.18	0.07	0.14	**1.34**	0.16				
PEdu			0.001	0.03	-0.01	0.03	-0.003	0.03	0.01	0.03				
Cigs16sq			**-0.13**	0.06					-0.10	0.06				
Smk_gainsq			-0.08	0.04					**-0.10**	0.04				
Goodness-of-fit														
K	20		72		41		42		43		19		19	
-2lnL	35715.1		34050.3		21267.1		33131.3		20596.4		26669.1		31564.0	
AIC	35755.1		34194.3		21349.1		33215.3		20682.4		26707.1		31602.0	

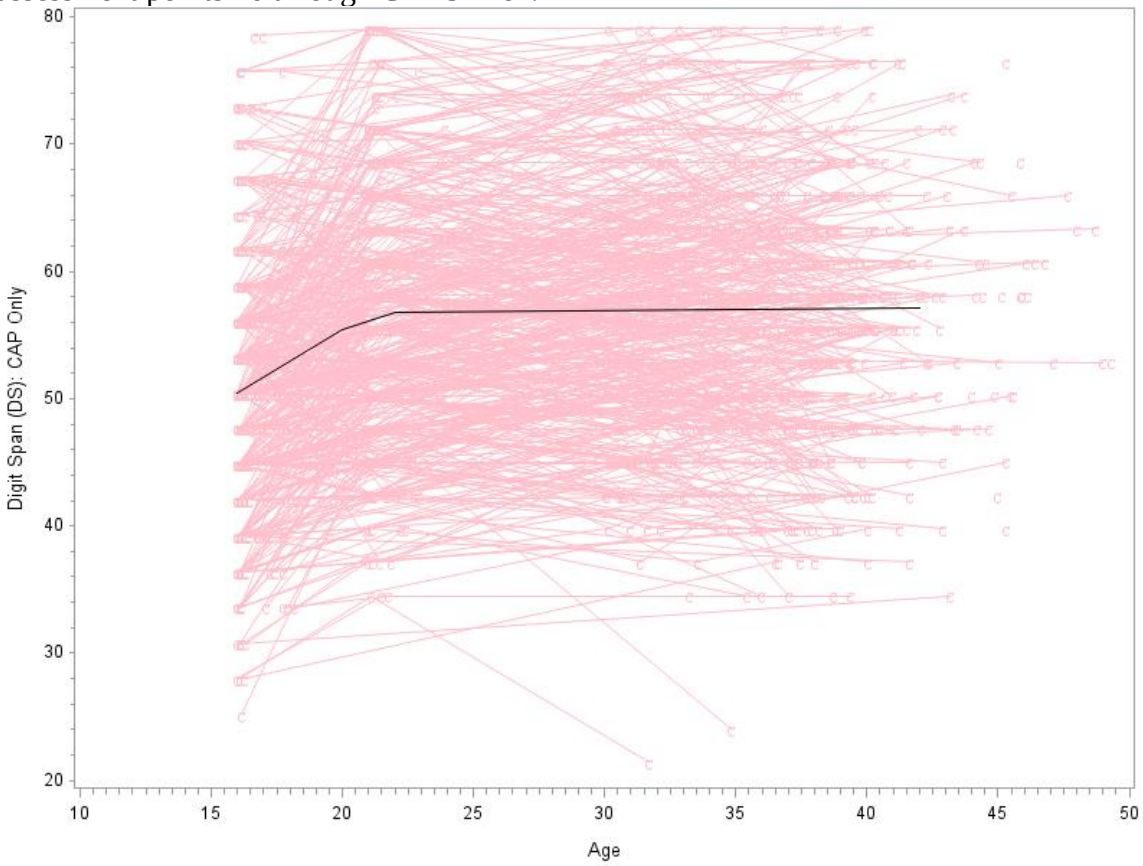
Note. PM=Picture Memory, NF=Names & Faces, Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, BD=Block Design, V=Vocabulary; PEdu=Parental Education, Cigs16sq=square-root transformation of Number of cigarettes reported smoking at age 16, Smk_gainsq=square-root transformation of smoking difference for only those that gain in consumption by CATSLife1; Adjusted for sex (0=F, 1=M), adoption status (0=Non-adopted, 1=Adopted), ethnicity (0=Non-Hispanic, 1=Hispanic), and race (0=White, 1=Non-White); K is the number of estimated parameters, including means and variances; AIC is equal to -2lnL+2*K; Bolded parameters are significant $p < .05$; Total N of persons=710; Total N of Observations=2991-4943

Table A2.17. Expected Intercept and Slope Fixed Effects for Square-root Adjusted and Original Smoking Measures

			Intercept		Slope	
		# Cigs	SQ	Orig	SQ	Orig
PM	Cigs16	9	**-2.47**	**-1.77**		
	Gains/Diff	10	-0.36	-0.51		
NF	Cigs16	9			**-0.40**	**-0.28**
	Gains/Diff	10			-0.25	-0.14
Dspa	Cigs16	9	**-1.56**	-1.02		
	Gains/Diff	10	0.92	0.44		
CPS	Cigs16	9	**-2.12**	**-1.82**		
	Gains/Diff	10	**-1.56**	**-1.11**		
DSy	Cigs16	9	**-2.55**	**-1.79**	-0.30	**-0.27**
	Gains/Diff	10	-1.07	-0.59	**-0.31**	**-0.26**
BD	Cigs16	9	**-2.37**	**-1.80**		
	Gains/Diff	10	**-1.27**	**-0.86**		
V	Cigs16	9	**-1.37**	**-1.12**		
	Gains/Diff	10	-0.31	-0.35		

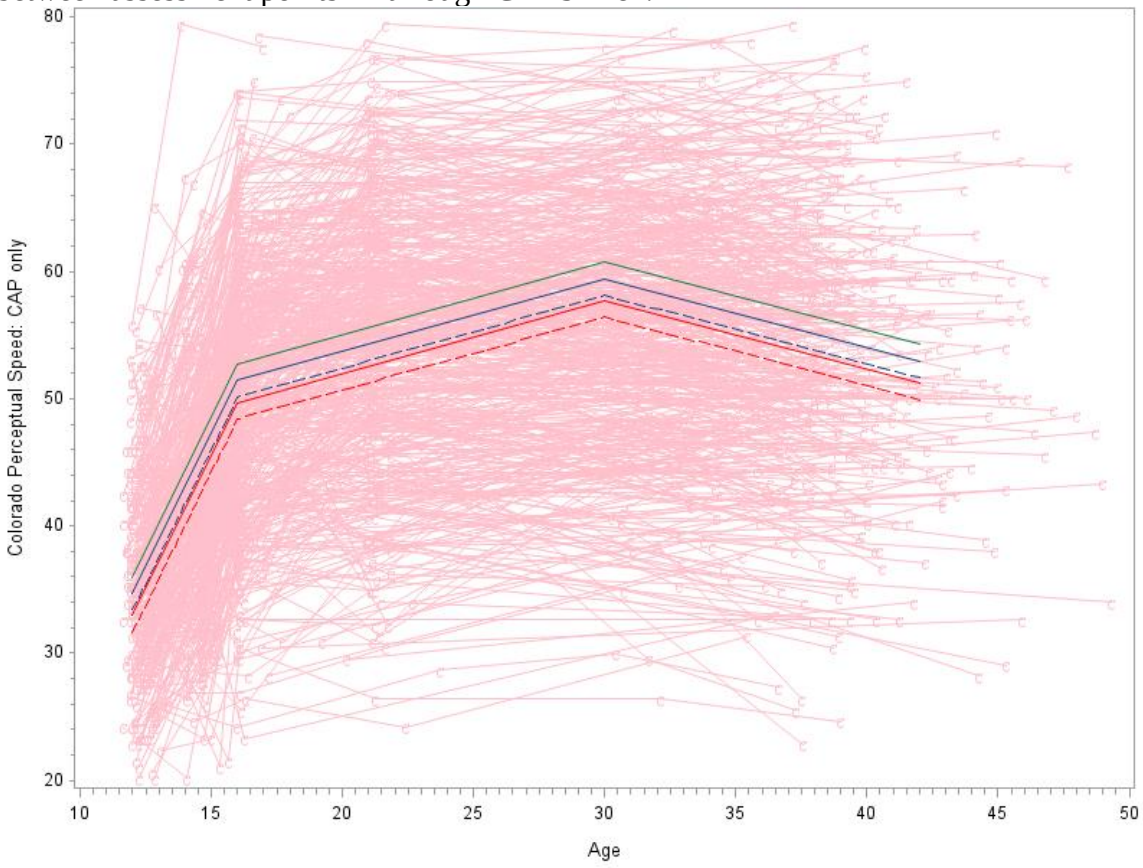
Note. Adjusted for sex, project, adoption status, ethnicity, race, and parental education. PM=Picture Memory, NF=Names & Faces, Dspa=Digit Span; CPS=Colorado Perceptual Speed, DSy=Digit Symbol, BD=Block Design, V=Vocabulary. SQ=square-root adjusted score, Orig=original smoking measures scale, Cigs16=Number of cigarettes reported smoking at age 16, Gains=Square root adjusted gains score in consumption by CATSLife1, Diff=Original smoking difference score.
Bolded parameters are significant $p < .05$

Figure A2.1. Trajectories of Digit Span (Dspa) for CAP-only participants between assessment points 16 through CATSLife1.



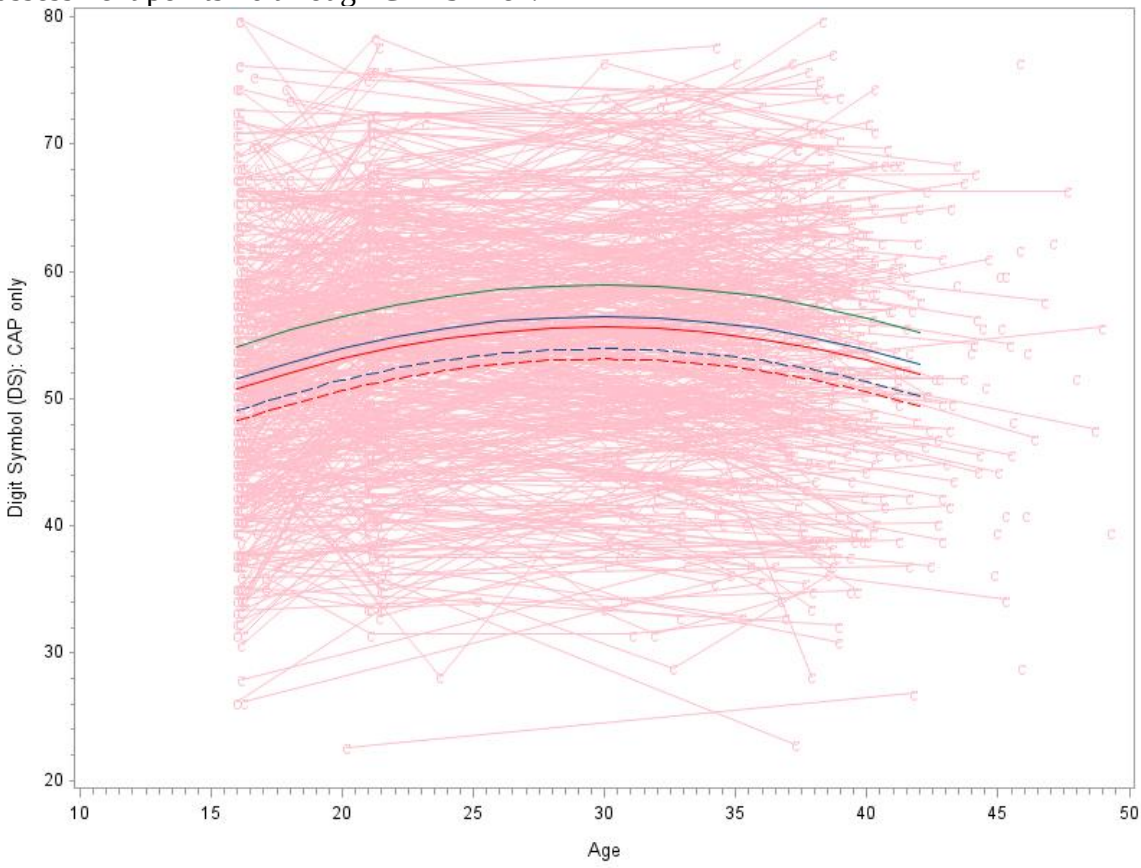
Note. Observed Digit Span *T*-scores across age.
Black solid line is the expected trajectory for the linear spline model with a knot at 21 years. Adjusted for sex, adoption status, ethnicity, race, and parental education.

Figure A2.2. Trajectories of Colorado Perceptual Speed (CPS) for CAP-only participants between assessment points 12 through CATSLife1.



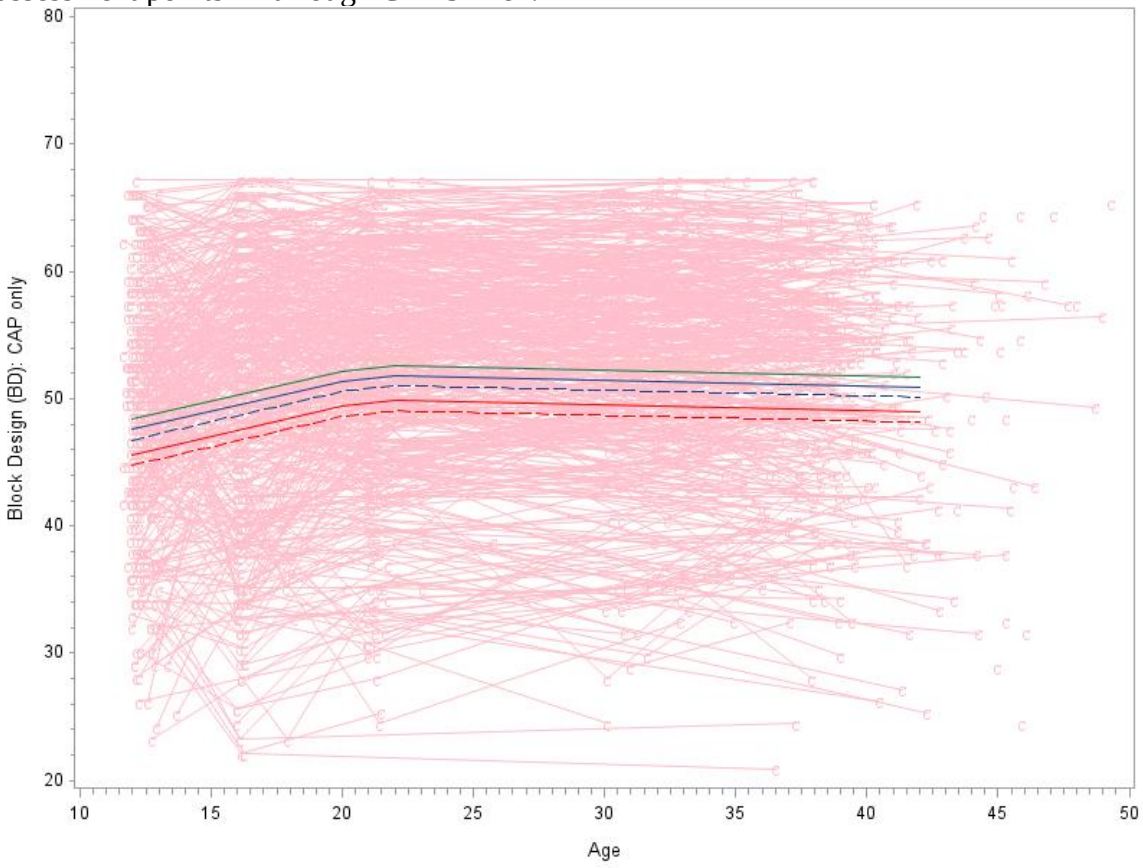
Note. Observed Colorado Perceptual Speed *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants.
Expected spline trajectories with knot points at 16 and 30 years, based on year 16 smoking consumption and gains in smoking by CATSLife1 are adjusted for sex, adoption status, ethnicity, race, and parental education. Green = non-smokers; Blue = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.

Figure A2.3. Trajectories of Digit Symbol (DSy) for CAP-only participants between assessment points 16 through CATSLife1.



Note. Observed Digit Symbol *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants.
Expected quadratic trajectories centered at age 21 years by year 16 smoking and gains in smoking by CATSLife1, adjusted for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and smoke ½ pack by CATSLife1; Blue dashed = year 16 non-smokers and smoke 1 pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and smoke ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and smoke 1 pack by CATSLife1.

Figure A2.4. Trajectories of Block Design (BD) for CAP-only participants between assessment points 12 through CATSLife1.



Note. Observed Block Design *T*-scores across age. Pink solid lines with the letter C depict the raw trajectories for CAP participants.
All plotted spline models with knot point at age 21 represent expected trajectories with year 16 smoking consumption and gains in smoking amount by CATSLife1, adjusting for sex, adoption status, ethnicity, race, and parental education: Green = non-smokers; Blue = year 16 non-smokers and gain ½ pack by CATSLife1; Blue dashed = year 16 non-smokers and gain a pack by CATSLife1; Red = smoke 9 cigarettes at year 16 and gain ½ pack by CATSLife1; Red dashed = smoke 9 cigarettes by year 16 and gain 1 pack by CATSLife1.