

## RESEARCH ARTICLE

# The adverse effect of modifiable dementia risk factors on cognition amplifies across the adult lifespan

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## Abstract

**Background:** Reversible lifestyle behaviors (modifiable risk factors) can reduce dementia risk by 40%, but their prevalence and association with cognition throughout the adult lifespan is less well understood.

**Methods:** The associations between the number of modifiable risk factors for dementia (low education, hypertension, hearing loss, traumatic brain injury, alcohol or substance abuse, diabetes, smoking, and depression) and cognition were examined in an online sample ( $N = 22,117$ , ages 18–89).

**Findings:** Older adults (ages 66–89) had more risk factors than middle-aged (ages 45–65) and younger adults (ages 18–44). Polynomial regression revealed that each additional risk factor was associated with lower cognitive performance (equivalent to 3 years of aging), with a larger association as age increased. People with no risk factors in their forties to seventies showed similar cognitive performance to people 10 or 20 years younger with many risk factors.

**Interpretation:** Modifiable dementia risk factors amplify lifespan age differences in cognitive performance.

## KEYWORDS

aging, Cogniciti Brain Health Assessment, cognition, dementia, episodic memory, executive function, lifespan, modifiable risk factors, online studies

## 1 | INTRODUCTION

Dementia is considered the biggest global challenge for health care in the 21st century.<sup>1</sup> The lack of disease-modifying treatments for dementia, along with knowledge that neuropathology develops decades before disease onset,<sup>2</sup> has led to a growing interest in primary prevention approaches. The latest Lancet Commissions on dementia prevention, intervention, and care synthesized the available evidence to propose a novel life-course model of dementia risk, which proposes

that reversible lifestyle behaviors from different phases of the lifespan collectively account for 40% of dementias worldwide.<sup>1,3</sup> Thus 40% of dementias worldwide could be prevented or delayed if these risk factors were addressed.

The effects of individual modifiable risk factors on accelerated cognitive decline and dementia have been established.<sup>4–11</sup> Recent research has moved from a focus on individual risk factors toward a broader consideration of the cumulative impact of multiple factors.<sup>12</sup> Risk factors studied in combination indicate a dose-response gradient,

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whereby an increase in risk factors is correlated with greater cognitive decline and incident dementia, regardless of the type of risk factor.<sup>13–16</sup>

The model developed by the Lancet Commissions<sup>1,3</sup> takes a life-course perspective, which considers dementia as a product of the accumulation of risk factors over life (see<sup>17</sup> for details on a life-course perspective). Nevertheless, reviews on modifiable risk factor studies show that prevalence and dose-response data are minimal to non-existent in young and middle-aged adults.<sup>12,15,18</sup> Previous work has offered promising insights on risk factor prevalence and dose-response effects among older adults,<sup>1,15,18</sup> providing an opportunity to study whether this extends to young and middle-aged adults. Studying the period of early adulthood is important so that risk factors can be addressed as early as possible. Growing evidence suggests that aging-related cognitive decline begins in younger adulthood,<sup>19,20</sup> which extends the critical period for targeting risk factors from older adulthood to early adulthood.<sup>21</sup> In the current study, we build on past work, using a web-based assessment<sup>22</sup> to test whether the prevalence of modifiable risk factors for dementia and their dose-response relationship with cognition is moderated by age.

## 2 | METHODS

### 2.1 | Participants

Participants were recruited via in-person brain health workshops, advertisements, media outlets, and word of mouth. Participants were selected from those completing an online questionnaire and cognitive assessment, for which data collection began in 2014. We used data from 2016 to 2019, by which time eight dementia risk factors were queried. There were 93,363 test attempts from these 4 years. Attempts were excluded with technical errors or demographic inconsistencies (repetitions by the same person, technical issues with data recording, participants who appeared to report inaccurate demographic information, had missing demographic information, or reported health conditions known to significantly affect cognition, e.g., stroke, cancer,  $n = 55,544$  removed). Iterative trimming of cognitive data was done between subjects per age and per cognitive task to remove outliers ( $n = 15,702$  removed), using a recursive moving criterion for the standard deviation based on the sample size.<sup>23,24</sup> Data were removed for technical issues (incomplete or multiple recordings; 60%), for missing demographic information (20%), and for cognitive data cleaning (20%). Extensive data cleaning is typical in online research and is recommended to account for low quality or inaccurate recordings in online data.<sup>25</sup> The final sample was  $N = 22,117$  (age range = 18–89, mean = 64 years, SD = 12; 69% female).

### 2.2 | Online assessment

Participants completed a free, self-administered online assessment (the Cogniciti Brain Health Assessment, [www.cogniciti.com](http://www.cogniciti.com)) in their

#### RESEARCH IN CONTEXT

- 1. Systematic review:** Online databases were searched for papers on modifiable risk factors for dementia, cognitive performance/decline, prevalence, dose-response/cumulative effects, and lifespan/age-related effects. The dominant model suggests that risk factors accumulate over the lifespan, but empirical evidence is lacking in young and mid-adulthood.
- 2. Interpretation:** Risk factor prevalence, and a dose-response association with cognition, increased with age. Findings provide translatable implications, whereby each additional risk factor lowered cognitive performance by the equivalent of 3 years of aging. People with no risk factors in their forties to seventies perform as well on cognitive tasks as those with many risk factors who are 10 to 20 years younger.
- 3. Future directions:** Modifiable risk factor effects on cognition over the lifespan should be considered alongside age effects. Future work can examine the longitudinal effects of risk factors in a person over time to determine causality and the effects on dementia likelihood in addition to cognitive decline.

homes. The assessment has been psychometrically validated and demonstrated adequate internal consistency, test-retest reliability, alternate version reliability, and construct validity,<sup>22</sup> plus adequate convergent validity when compared to clinician-administered neuropsychological tests of the same constructs.<sup>26</sup> Moreover, the test was designed to be suitable for older adults,<sup>22</sup> and also provides greater sensitivity at the high end of function<sup>26</sup> than the Montreal Cognitive Assessment (MoCA),<sup>27</sup> offering the sensitivity to assess a relatively healthy sample.

The assessment consists of a background questionnaire (self-reported age, sex, level of education, and a history or current diagnosis of specific health conditions) and four cognitive tests with a representative measure per task administered in the following order: (1) a Spatial Working Memory task, measuring working memory as the number of clicks to recall locations of six shape pairs over two trials; (2) a Face-Name Association task, measuring associative memory as correctly recognized face and name pairs; (3) a number-word Stroop task, measuring processing speed and interference control as the response time when counting words for incongruent stimuli (e.g., “three three”); and (4) a Letter-Number Alternation task, an online version of the Trail Making Test Part B task, measuring set shifting as the total completion time for clicking alternating numbers and letters in ascending order (see<sup>22</sup> for further task and validation details). Scores per task were standardized to z-scores so that all tasks were in the same metric, and the direction was adjusted so that higher scores reflected better

performance on all tasks. The z-scores were averaged to calculate an overall cognitive score.

## 2.3 | Modifiable risk factors

Self-reported health conditions from the Cogniciti Brain Health Assessment questionnaire were used to assess eight modifiable risk factors. Risk factors were grouped by the life-course model according to the age periods in which they are shown to produce the highest risk for dementia: one early life factor (low education), four midlife factors (hearing loss, traumatic brain injury [TBI], alcohol or substance abuse, hypertension), and three late-life factors (smoking, diabetes, depression). Low education was defined as less than completion of high school, and smoking was defined as smoking currently or in the past 1 to 4 years, based on previous research.<sup>1,28</sup>

The median number of risk factors per participant was one (interquartile range [IQR] = 2). Composite risk scores were calculated per person for the total number of risk factors (range 0–8), and an adjusted risk amount (range 0–1) calculated by multiplying by the relative contribution of each factor (the weighted population attributable fraction [PAF] per factor from the life-course model<sup>1</sup>) and dividing by the total contribution (PAF). Weighted PAFs were used as they account for the contribution of each factor after adjusting for variance shared among factors (communality).

## 2.4 | Statistical analyses

Analyses were conducted with the R language and environment for statistical computing.<sup>29</sup> Statistical test results were interpreted alongside effect sizes, because large sample sizes can produce low *p*-values regardless of their theoretical or practical importance.

Prevalence was defined as the frequency (percentage) of risk factors per age period. For prevalence estimates, ages were grouped based on the life-course model according to the life periods in which they are shown to produce the highest risk for dementia.<sup>1</sup> Ages were thus

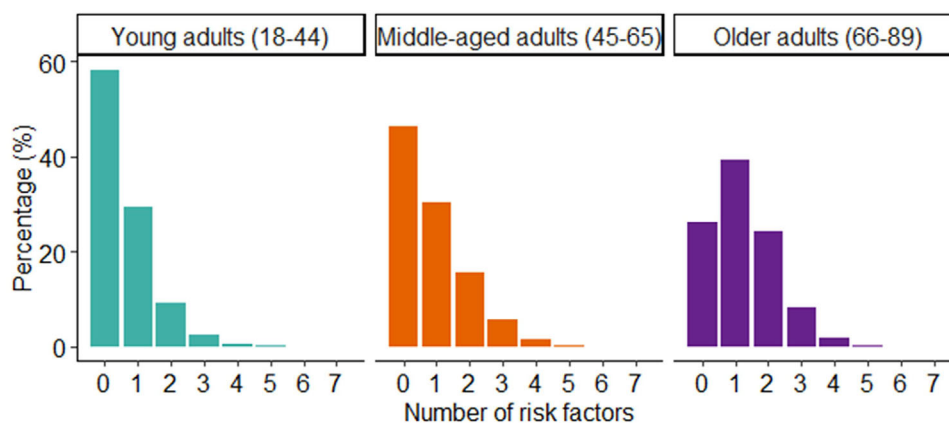
grouped into young adults (ages 18–44, *n* = 1686), middle-aged adults (ages 45–65, *n* = 8661), and older adults (ages 66–89, *n* = 11,770). Chi-square tests were used to test for differences in the frequency of each risk factor per age period, followed by post hoc analyses of Pearson residuals for each cell.

The dose-response relationship between number of risk factors and cognition with age was measured with quadratic regression models that regressed cognitive performance for each task on age (linear and polynomial terms), and composite risk score (either number of risk factors or weighted PAF). Age was modeled as a continuous variable using linear and polynomial terms based on past evidence from lifespan cognition studies,<sup>30–32</sup> including on the current data set.<sup>20</sup> Polynomial terms were examined for total risk factors, but they did not improve model fit,  $\Delta R^2 < 0.01$ . Continuous predictors (age and number of risk factors) were mean-centered so that coefficient estimates could be meaningfully interpreted.<sup>33,34</sup> Regression analyses were weighted by the sample size per risk amount (either number of risk factors or weighted PAF) per age, because although the sample size was large, there was an uneven distribution of sample size and risk factors by age (Figure 1; Table S1). Risk amounts were excluded from regression analyses if there were fewer than 15 people for that amount in each age period (three or more risk factors for young adults, *n* = 9; six or more risk factors for middle-aged adults and older adults, *n* = 4 and *n* = 9, respectively), as visual examination of the data showed that these appeared to be unreliable data with outliers.

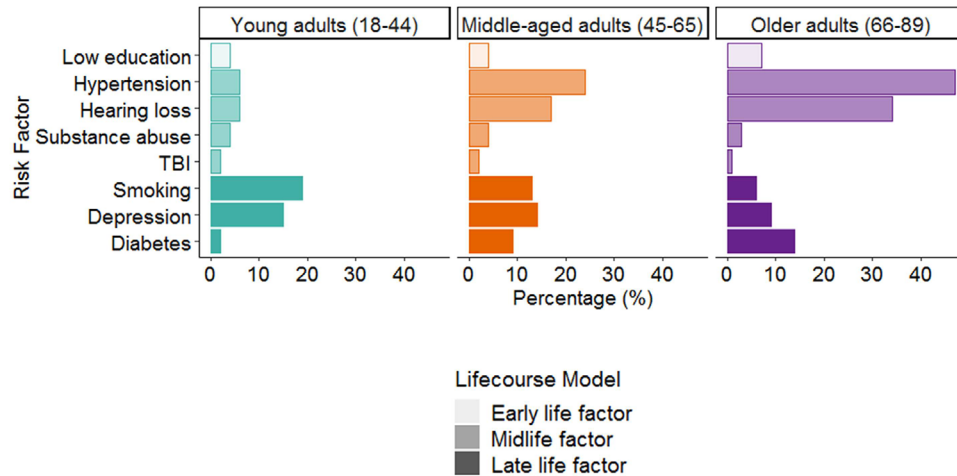
## 3 | RESULTS

### 3.1 | Prevalence of risk factors by age period

Most young and middle-aged adults had no risk factors (58% and 46%, respectively), whereas most older adults had one risk factor (39%, Figure 1). The most common factors in young adults were smoking (19%) and depression (15%), and the least common were diabetes (2%) and TBI (2%; Figure 2). The most common factors in middle-aged adults were hypertension (24%), hearing loss (17%), smoking (13%),



**FIGURE 1** Prevalence (% frequency) of number of risk factors per age period



**FIGURE 2** Prevalence (% frequency) of individual risk factors per age period

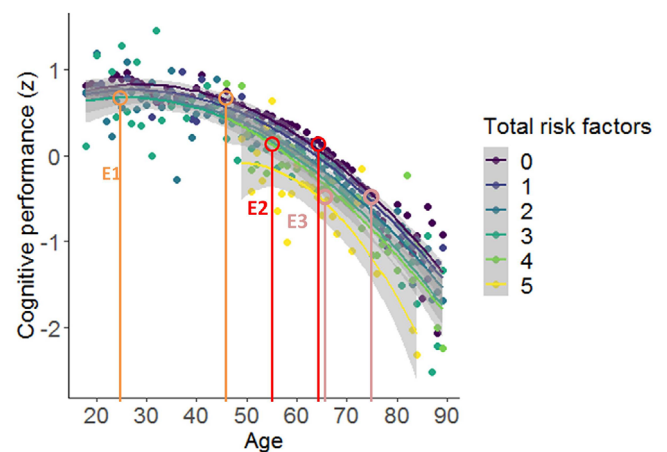
and depression (14%); the least common were low education (4%) and TBI (2%). The most common factors in older adults were hypertension (47%) and hearing loss (34%), and the least common were substance abuse (3%) and TBI (1%).

Risk factors were not equally distributed across age periods,  $\chi^2(14, N = 22,729) = 2442, p < .0001$ , with a large effect size, Cramer's  $V(\phi_c) = 1.2$ .<sup>35</sup> The largest differences in the distribution of risk factors by age periods were for depression and smoking in young and middle-aged adults, substance abuse in middle-aged adults, and hypertension and hearing loss in older adults, all  $p$ 's  $< .0001$ .

### 3.2 | Dose-response relationship of number of risk factors and age on cognitive performance

Preliminary analyses showed a significant effect of number of risk factors on cognitive performance, indicating a dose-response association whereby each additional factor was linked to poorer cognitive performance. Stepwise hierarchical regression revealed that adding linear and polynomial age terms resulted in models with a significantly better fit than a model with number of risk factors only ( $\Delta\chi^2$  test,  $p$ 's  $< .0001$ ), explained more variance ( $\Delta R^2 = 0.44$  and  $\Delta R^2 = 0.06$ ), and maintained model parsimony ( $\Delta BIC = -1410$  and  $\Delta BIC = -2758$ ;  $> -2$  is ideal).

Quadratic regression revealed that age, number of risk factors, and their interaction explained 58% of the variance in cognitive performance:  $F(4, 22090) = 7471, p < .0001$ . Cognitive performance decreased significantly as age increased (linear age term:  $\beta = -0.04, p < .0001$ , with a small effect size,  $f^2 = 0.04$ <sup>35</sup>; polynomial age term:  $\beta = -.0006, p < .0001$ , with a small effect size,  $f^2 = 0.13$ ), as the number of risk factors increased ( $\beta = -.11, p < .0001$ , with a minimal effect size,  $f^2 = 0.0001$ ), and as age and the number of risk factors increased together ( $\beta = -.001, p < .0001$ , with a minimal effect size,  $f^2 = 0.004$ ). The interaction between age and number of risk factors indicates that the dose-response association was moderated by age (Figure 3). A comparison of regression coefficients provided translatable applications, revealing that each additional risk factor was associated with a lower-



Interpretation Examples:

E1: Ages 40-50 with no risk factors ( $M=0.7, SE=0.01$ ) have the same cognitive performance as Ages 20-30 with 3 risk factors ( $M=0.7, SE=0.02$ )

E2: Ages 60-70 with no risk factors ( $M=0.2, SE=0.01$ ) have the same cognitive performance as Ages 50-60 with 4 risk factors ( $M=0.3, SE=0.02$ )

E3: Ages 70-80 with no risk factors ( $M=-0.2, SE=0.01$ ) have the same cognitive performance as Ages 60-70 with 5 risk factors ( $M=-0.4, SE=0.02$ )

Note. The design of interpretation examples is inspired by Habes et al. [36]

**FIGURE 3** Dose-response effect of number of risk factors on cognitive performance per age. Note. Each dot shows the mean performance per number of risk factors. The lines show fitted polynomial curves. The gray shading around the curves indicates a 95% confidence interval envelope.

ing in cognitive performance nearly equal to 3 years of aging (the main effect of number of risk factors,  $\beta = -0.11$ , is nearly three times larger than the main effect of age,  $\beta = -0.04$ ).

A similar dose-response association was found for the weighted PAF across ages, indicating that the association persists after controlling for shared variance among risk factors (see Supplemental material). Targeted post hoc  $t$ -tests revealed similarities in mean cognitive performance of people with the lowest number of risk factors for one age decade and the highest risk number of risk factors for people one or two decades younger. As depicted in Figure 3 (inspired by Habes et al.<sup>36</sup>). Specifically, there were no significant differences between cognitive performance for people with no risk factors in their forties

compared to people with three risk factors two decades younger, or between people with no risk factors in their fifties, sixties, and seventies compared to people with four or five risk factors one decade younger ( $p$ 's > .05).

## 4 | DISCUSSION

We used a web-based data set to enable a large-scale investigation of the number of modifiable risk factors and cognitive performance over the adult lifespan. We extend past demonstrations of risk factor prevalence and a dose-response association in older adults,<sup>12,15</sup> to show that these findings vary over the adult lifespan. We found that risk factors are more prevalent as age increases, and also show a larger dose-response association with cognition as age increases. These results offer the encouraging finding that age differences on cognition are not fixed across people, but rather are influenced by the number of modifiable risk factors.

This study represents the largest attempt to examine risk factors and age over the adult lifespan. By comparison, the largest lab studies have been under 10,000 people, with similar geographic and demographic backgrounds.<sup>37</sup> We used cross-sectional data, which offers correlational associations between risk factors and cognitive outcomes. Although observational effects are not always replicated in experimental studies,<sup>12,38</sup> a meta-analysis confirmed a consistent causal effect of risk factors on longitudinal cognitive decline ( $n > 40,000$ <sup>15</sup>).

Online data collection enabled a collection of individuals from different ages and countries. However, most participants were from North America; hence results may not generalize outside of this continent. Although online assessment makes testing more accessible to individuals who are too busy or not capable of attending in-person testing, the sample reflects individuals who had web literacy, access to a computer and Internet connection, and were self-motivated to take the online test. Sex differences are expected to influence the current findings and are explored in a separate paper.<sup>39</sup> The use of measures ostensibly sensitive to the downstream effects of dementia risk factors was achieved by the combination of online testing (to obtain large sample sizes) and a sensitive assessment suited to detect changes in people with risk factors (e.g., distributed damage due to subtle vascular brain changes, white matter changes, and reduced reserve capacity, leading to earlier onset of clinically-evident neurodegeneration<sup>40</sup>).

### 4.1 | The dose-response association of risk factors and cognition differs with age

We demonstrate, for the first time, that the dose-response association, in which each additional risk factor was associated with lower cognitive performance, varied with age. Examining the unstandardized regression estimates (as was done in<sup>33</sup>) provided translatable and applicable real-world implications. Across participants, each additional risk factor was associated with an equivalent drop in cognitive performance as

3 years of aging. Moreover, people with fewer modifiable risk factors showed better cognitive performance than people at their age with many risk factors, and strikingly, people with no risk factors had cognitive performance similar to that of people who were 10 or 20 years younger.

Our findings indicate that age differences in cognitive performance over the lifespan are moderated by the number of risk factors. The effects of risk factors and age on cognition have been studied widely in isolation, but we observed a clear combination of these effects. This interaction bolsters past calls to go beyond considering age as a covariate in risk factor studies, and similarly, to consider dementia risk factors in aging studies.<sup>15,16</sup> Cognitive aging findings indicate an increase in differences among people on cognition (inter-individual variability) over the adult lifespan,<sup>20,41</sup> which could be explained by a rise in individual differences in risk factors, for example, modifiable risk factors effectively predict individual longitudinal cognitive trajectories in older adults.<sup>42</sup>

Young adults had a smaller dose-response association than middle-aged and older adults, which highlights the usefulness of including this age period rather than extrapolating from past studies of only middle-aged and older adults. We speculate that young adults may be slightly buffered against the negative effects of risk factors, based on the existing evidence on cognitive reserve.<sup>43</sup> However, longitudinal evidence suggests that they are vulnerable to the long-term effects of these risk factors later in life,<sup>15</sup> and that a depletion of cognitive reserve over time is linked to faster cognitive aging and a higher risk of dementia.<sup>43,44</sup>

The impact of each additional risk factor on cognition highlights the value of existing recommendations for individuals to reduce as many risk factors as possible, and to prevent further accumulation when risk factors are present. Similarly, ideal interventions would lower many risk factors concurrently, which aligns with evidence that interventions that address multiple risk factors simultaneously have been the most successful in preventing dementia.<sup>37,45</sup> People with many risk factors could also be advised to build cognitive reserve via protective factors (e.g., exercise, cognitively stimulating activities) to mitigate the effects of modifiable risk factors.<sup>43</sup>

We measured overall cognitive performance, as our past work has shown age-related decline on the cognitive tasks measured in the current sample, and that a general factor of variance shared across tasks underlies performance on individual tasks.<sup>20</sup> Furthermore, past studies consistently show similar effects of risk factors on various cognitive tasks, including tasks measuring the constructs in the current study.<sup>15</sup> Past work shows that the observed dose-response trend on cognitive decline also applies to the likelihood of dementia.<sup>15</sup>

### 4.2 | Risk factor prevalence differs with age

Most middle-aged and older adults (over 70%) reported no to one risk factor, and very few had more than six risk factors (less than 1%). Risk factors were self-reported, but our findings align with other online

research.<sup>46</sup> Our prevalence estimates indicate a relatively healthy sample, and concur with past work that over 70% of middle-aged and older adults report no to one risk factor and that less than 1% have more than six risk factors.<sup>13</sup> Similarly, our results coincide with the findings that nearly 80% of young adults have no to one risk factor and less than 1% have more than three risk factors.<sup>13</sup>

Our findings on prevalence show, as expected, that risk factors are more common in older adults. However, we also show that different risk factors are prevalent in young adults compared to older adults. Smoking and depression were prevalent in young and middle-aged adults, substance abuse in middle-aged adults, and hypertension and hearing loss in older adults. Our prevalence findings suggest that prevention messages could be tailored by age period to increase specificity and effectiveness, but further epidemiological work using representative populations is needed to confirm prevalence estimates.

### 4.3 | Connection to the life-course model of Livingston et al. (2020)

The life-course model<sup>1</sup> was employed to classify risk factors in the current study because it offers an evidence-based a priori framework of dementia risk factors. A limitation is the risk factor of “moderate alcohol consumption” from the model was measured as “alcohol or substance abuse,” which is not the same. Other risk factors have been linked to dementia risk, such as cognitive engagement and sleep disturbances,<sup>37</sup> but were not included in the life-course model because they lacked strong or consistent evidence,<sup>1</sup> and were not measured in the current study. Likewise, the life-course model includes factors such as social isolation and physical activity; however, data on these factors were not acquired in the present study.

The findings provide empirical evidence for the central theoretical claims of the life-course model: the detrimental cumulative impact of risk factors and that this detrimental impact varies with age. Nevertheless, our findings on risk factor prevalence by age period do not fully align with the hypothetical age periods allocated to risk factors in the life-course model. Smoking and depression are considered late-life factors in the life-course model, but were more common in young and middle-aged adults than in older adults. Hypertension is considered a midlife factor but was most common in older adults. The model developers based their classification on when the factors typically occur (e.g., low education in early life), or when they are shown to contribute to dementia risk (e.g., depression in later life), but they also claim that risk factors are relevant at all ages.<sup>13</sup> It is possible that the prevalent factors we observed have more detrimental effects in later life, or that the effects from earlier life are reversible if not continued into later life (e.g., quitting smoking reverses the risk of developing dementia<sup>28</sup>). However, these risk factors have also been understudied in early adulthood, and this lack of evidence may miss risk-factor effects. For example, hypertension is considered a midlife factor, but hypertension in young adulthood impacts cognition in midlife.<sup>47,48</sup>

We found similar results for composite indices for number of risk factors and an adjusted risk amount (weighted by PAF values from

the life-course model, comparable to past studies). This agrees with a review suggesting that different risk indices have similar predictive power.<sup>16</sup> Although it could be argued that combining risk factors loses information about individual factors, longstanding work suggests that risk factors in aggregate may be strongly associated with dementia even when independent factors do not have significant effects on cognitive decline.<sup>15,16</sup> Examining cumulative risk is also needed to control for the shared variance among risk factors.<sup>1,3</sup>

## 5 | CONCLUSIONS

Dementia has a long preclinical period,<sup>2</sup> which highlights a need to study risk factors and cognitive impacts long before a clinical diagnosis of dementia. The life-course model offers encouraging evidence that a large percentage of dementia risk is modifiable. Our findings align with current recommendations that targeting dementia prevention over the lifespan offers large potential benefits for individuals and society at large.<sup>1,3</sup>

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### CONFLICT OF INTEREST

None.

### AUTHOR CONTRIBUTIONS

Annalise A. LaPlume developed the study concept and design, under the supervision of Nicole D. Anderson, Angela K. Troyer, and Brian Levine. Test development, validation, and data collection were conducted by Angela K. Troyer and Brian Levine, along with a team of researchers (Troyer et al., 2014<sup>22</sup>). Database access was coordinated by Larissa McKetton. Annalise A. LaPlume performed the data cleaning and pre-processing, analysis, and interpretation, under the supervision of Nicole D. Anderson, Angela K. Troyer, and Brian Levine. Annalise A. LaPlume drafted the manuscript. Nicole D. Anderson, Angela K. Troyer, Brian Levine, and Larissa McKetton provided revisions.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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