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

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Declarations of interest: none

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Abstract

Background: Modifiable lifestyle behaviours can reduce dementia risk by 40%, but their prevalence and association with cognition throughout the adult lifespan is less well understood.

Methods: Associations between eight 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 ($N = 22,117$, aged 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 each additional risk factor was associated with a drop in cognitive performance (equivalent to three 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 ten or twenty years younger with many risk factors.

Interpretation: Modifiable dementia risk factors may be more important than age in predicting cognitive performance.

Funding: This work was supported by a research grant from the Natural Sciences and Engineering Council (NSERC) of Canada (RGPIN-2017-06057) to NA; and an Alzheimer Society of Canada PDF (20-16) to AL.

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

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 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 three 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 ten to twenty years younger.
3. Future directions: Modifiable risk factor effects on cognition over the lifespan should be considered alongside age effects. Future work can examine longitudinal effects of risk factors in a person over time to determine causality, and effects on dementia likelihood in addition to cognitive decline.

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Dementia is considered the biggest global challenge for healthcare in the 21st century [1]. The lack of disease-modifying treatments for dementia, along with knowledge that neuropathology develops decades before disease onset [2], 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 [1, 3] in which they state that reversible lifestyle behaviours from different phases of the lifespan collectively account for 40% of dementias worldwide [1].

The effects of individual modifiable risk factors on accelerated cognitive decline and dementia have been established [4-11]. Recent research has moved from a focus on individual risk factors towards a broader consideration of the cumulative impact of multiple factors [12]. Risk factors studied in combination indicate a dose-response gradient, whereby an increase in risk factors is correlated with greater cognitive decline and incident dementia, regardless of the type of risk factor [13-16].

The model developed by the Commissions [1, 3] takes a life-course perspective, which considers dementia as a product of the accumulation of risk factors over life (See [17] 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 [12, 15, 18]. Previous work has offered promising insights on risk factor prevalence and dose-response effects among older adults [1, 15, 18], offering 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 [19, 20], which extends the critical period for targeting risk factors from older adulthood to early adulthood [21]. In the current study, we

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build on past work to test whether prevalence of modifiable risk factors for dementia and their dose-response relationship with cognition is moderated by age.

We used a web-based dataset. Online testing allows collection of a large sample of individuals from different ages, to gain insights on how risk factor effects vary by age. The online assessment we used has been psychometrically validated, and demonstrated adequate internal consistency, test-retest reliability, alternate version reliability, and construct validity [22], plus adequate convergent validity when compared to clinician-administered neuropsychological tests of the same constructs [23]. Moreover, the test was designed to be suitable for older adults [22], and also provides greater sensitivity at the high end of function [23] than the Montreal Cognitive Assessment [24], offering sensitivity to assess a relatively healthy sample. The use of measures ostensibly sensitive to 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 [25]).

Methods

Participants

Participants were selected from those completing an online questionnaire and cognitive assessment, for which data collection began in 2014. We used data from 2016-2019, by which time eight dementia risk factors were queried. There were 93,363 test attempts from these four 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

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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 [26, 27]. Removed data was due to technical issues (incomplete or multiple recordings; 60%), for missing demographic information (20%), and for cognitive data cleaning (20%). Extensive data cleaning is recommended to account for low quality or inaccurate recordings in online data [28].

The final sample was $N = 22,117$ (age range = 18–89, $M = 64$ years, $SD = 12$; 69% females). Ages were grouped based on the life-course model [1] into young adults (ages 18–44, $n = 1,686$), middle-aged adults (ages 45–65, $n = 8,661$), and older adults (ages 66–89, $n = 11,770$).

Online Assessment

Participants completed a free, self-administered online assessment (the Cogniciti Brain Health Assessment, www.cogniciti.com) in their homes. It consists of a background questionnaire (self-reported age, sex, level of education, and specific health conditions) and four cognitive tests with a representative measure per task administered in the following order: (a) a Spatial Working Memory task, measuring working memory as the number of clicks to recall locations of six shape pairs over two trials; (b) a Face-Name Association task, measuring associative memory as correctly recognized face and name pairs; (c) 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 (d) a Letter-Number Alternation task, an online version of the Trails B task, measuring set shifting as the total completion time for clicking

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alternating numbers and letters in ascending order (see [22] 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.

Modifiable Risk Factors

Eight modifiable risk factors were assessed, 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 one to four years, based on previous research [1, 29].

Participants reported a total of 22,729 risk factors. 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). The adjusted risk amount was calculated by multiplying by the relative contribution of each factor (measured as the population attributable fraction per factor, PAF, from the life-course model [1]) and dividing by the total PAF, in order to account for variance shared among factors (communality).

Statistical Analyses

Analyses were conducted with the R language and environment for statistical computing [30]. Prevalence was defined as the percentage of risk factors per age period. A dose-response

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relationship was defined by the association (i.e., the slope, β) between risk factors and cognitive performance. Age was modelled with linear and polynomial terms, as quadratic models account for effects of age on cognition better than linear models in lifespan studies of the measured constructs [31-33], and on the current dataset [20]. Polynomial terms were also examined for total risk factors, but they did not improve model fit, $\Delta R^2 < 0.01$. Continuous predictors (age and total risk) were mean-centered so that coefficient estimates could be meaningfully interpreted [34, 35]. Regression analyses were weighted by the sample size per risk amount (either total number of risk factors or adjusted risk amount) per age, because although the sample size was large, there was an uneven distribution of sample size and risk factors by age (Figure 1; Supplemental Table 1). 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).

Results

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%), and depression (14%); the least common were low education (4%) and TBI (2%). The most common factors in older adults were

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hypertension (47%) and hearing loss (34%), and the least common were substance abuse (3%) and TBI (1%).

A chi-square test revealed that risk factors were not equally distributed across age periods, $\chi^2(14, N = 22,729) = 2442, p < .0001$, with a large effect size, $\phi_c = 1.2$ [36]. Post-hoc analyses of Pearson residuals for each cell indicated that 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 $< .0001$.

Dose Response Relationship of Total Risk Factors and Age on Cognitive Performance

Preliminary analyses showed a significant effect of total 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 total 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 (with linear and polynomial terms), total risk factors, and their interaction, explained a significant amount of the variance in cognitive performance, $F(4, 22090) = 7471, p < .0001$, with a large effect size, $R^2 = .58$ [37]. Cognitive performance significantly decreased as age increased (linear age term, $\beta = -0.04, p < .0001$; polynomial age term, $\beta = -.0006, p < .0001$), as the number of risk factors increased ($\beta = -.11, p < .0001$), and as age and the number of risk factors increased together ($\beta = -.001, p < .0001$). The interaction between age and total risk factors indicates that the dose response association was moderated by age (Figure

3). Comparison of regression coefficients provided translatable applications, revealing that each additional risk factor was associated with a lowering in cognitive performance nearly equal to three years of aging (the main effect of total 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 adjusted risk amount 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 (Table 1). 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.

Discussion

We used a web-based dataset to enable a large-scale investigation of eight modifiable risk factors and cognitive performance over the adult lifespan. Past studies have been instrumental in demonstrating the prevalence and dose-response association of risk factors in older adults [12, 15], which we build on to show that risk factor prevalence and the dose-response association varies over the adult lifespan. Our results extend previous findings to show that risk factors are more prevalent as age increases, and also show a larger dose-response association with cognition as age increases.

The Dose-Response Association of Risk Factors and Cognition Differs with Age

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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 previously done in [34]), provided translatable and applicable real-world implications. Across participants, the strength of the effect for total risk factors is about three times larger than that for age, indicating that each additional risk factor is associated with the equivalent drop in cognitive performance as three 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 similar cognitive performance to people who were ten or twenty years younger.

Our findings indicate that risk factors may be more important than age in predicting cognitive performance, at least in a relatively healthy sample. Results offer the encouraging finding that age differences on cognition are not fixed across people, but rather are influenced by the presence of modifiable lifestyle behaviours. Effects of risk factors and age on cognition have been widely studied in isolation, but we observed a clear interaction 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 [15, 16]. Accounting for risk factors may solve a piece of the puzzle for cognitive aging research. Studies have shown that there is a rise in differences among people on cognition (inter-individual variability) over the adult lifespan [20, 38], which could be explained by a rise in individual differences in risk factors, e.g., modifiable risk factors effectively discriminate between people with stable versus declining longitudinal cognitive trajectories [39].

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

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studies that included only middle-aged and older adults. We speculate that young adults may be slightly buffered against negative effects of risk factors, based on existing evidence on cognitive reserve [40]. However, longitudinal evidence suggests they may be vulnerable to long-term effects of these risk factors later in life [15], and that a depletion of cognitive reserve over time is linked to faster cognitive aging and a higher risk of dementia [40, 41].

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 [42, 43]. People with many risk factors could also be advised to build cognitive reserve to mitigate effects of modifiable risk factors, such as through exercise or cognitively stimulating activities [40].

We used cross-sectional data, which offers correlational associations between risk factors and cognitive outcomes. Past work has indicated that observational effects are not always replicated in experimental studies [12, 42]. However, a meta-analysis confirmed a consistent causal effect of risk factors on longitudinal cognitive decline and incident dementia in people with no cognitive decline at baseline ($n > 40,000$ [15]).

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 [20]. Further, past studies consistently show similar effects of risk factors on various cognitive tasks, including tasks

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measuring the constructs of episodic memory and executive function measured in the current study [15]. Although we did not study dementia incidence, past work shows the observed dose-response trend applies to likelihood of dementia as well as cognitive decline [15].

Risk Factor Prevalence Differs with Age

Most middle aged and older adults (over 70%) reported no to one risk factor, and very few had over six risk factors (less than 1%). Risk factors were self-reported, but our findings align with another online study [46]. 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 over six risk factors [13]. Similarly, our results coincide with findings that nearly 80% of young adults have no to one risk factor, and less than 1% have over three risk factors [13].

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, 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.

Connection to Livingston et al.'s (2020) Life-course Model

The life-course model [1] was employed to classify risk factors in the current study as 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

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abuse', which is not the same. Several other risk factors have been linked to dementia risk, such as cognitive engagement and sleep disturbances, but were not included in the life-course model for lacking strong or consistent evidence [1], and were not measured in the current study.

Likewise, the life-course model includes factors such as social isolation and physical activity, but data on these factors was not acquired in the present study.

The finding that a dose-response relationship of risk factors on cognition is moderated by age provides empirical evidence for the life-course model theoretical claim that cognitive decline results from the accumulation of risk factors over life. Our results support two key claims of the model: the role of age, and the cumulative impact of risk factors 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 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 have been shown to contribute to risk of dementia (e.g., depression and hearing loss in later life), but the developers also expect risk factors to be relevant at other age periods [1, 3]. It is possible that the prevalent factors we observed have more detrimental effects in later life, or that effects from earlier life are reversible if not continued into later life (e.g., quitting smoking reverses the risk of developing dementia [28]). However, it is also possible that these risk factors have been understudied in early adulthood, and the lack of evidence on early life may miss effects of risk factors. For example, hypertension is considered a midlife factor, but hypertension in young adulthood impacts cognition in midlife [44, 45].

We found similar results for composite indices for total risk factors and an adjusted total risk amount (using 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 [16]. While it could be argued that combining risk factors loses information about individual factors, longstanding work suggests that risk factors in an aggregate may be strongly associated with dementia even when independent factors do not have significant effects on cognitive decline [15, 16]. Examining cumulative risk is also needed to control for the shared variance among risk factors [1, 3].

Sex differences are expected to influence the current findings on risk factor prevalence and cognitive impacts. Exploring the effects of modifiable risk factor separately for men and women is important as women are at higher risk of dementia than men [47]. Examining sex differences in cumulative risk factor effects is out of scope for this study, but is explored in a separate paper [48].

Conclusions

Dementia has a long preclinical period [2], which highlights a need to study risk factors and cognitive impacts long before a clinical diagnosis of dementia. The life-course model that emerged from the Lancet Commissions on dementia offers encouraging evidence that that a large percentage of the risk for cognitive decline and dementia is modifiable. We echo the Lancet Commission's recommendation that an "ambitious" approach towards prevention offers large potential benefits for both individuals and society at large [1, 3].

Acknowledgements

We thank individuals who contributed to test creation or database management (Dr. Lynn Hasher, Dr. Gillian Rowe, Dr. Malcolm Binns, Dr. Kelly Murphy, Dr. Larry Leach, Michael Meagher, and Caitlin Johnston). Aggregate data, analytical code, and study materials will be made available upon request (this is what we are legally able to share as per the ethics agreement with participants). The study was approved by the Baycrest Research Ethics Board (REB# 15-05). The research aims and analysis plan were pre-registered prior to statistical analyses (but after data were collected) at

https://osf.io/um57g/?view_only=537f2f49c39b41b2be068b36e7cee2df.

Author Contributions

AL developed the study concept and design, under the supervision of NA, AT, and BL. Test development, validation, and data collection were conducted by AT and BL, along with a team of researchers (Troyer et al., 2014). Database access was co-ordinated by LM. AL performed the data cleaning and preprocessing, analysis, and interpretation, under the supervision of NA, AT, and BL. AL drafted the manuscript. NA, AT, BL, and LM provided revisions.

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LIFESPAN COGNITIVE EFFECTS OF DEMENTIA RISK FACTORS

Figure 1

Prevalence (% frequency) of Total Risk Factors per Age Period

LIFESPAN COGNITIVE EFFECTS OF DEMENTIA RISK FACTORS

Figure 2

Prevalence (% frequency) of Individual Risk Factors per Age Period.

Figure 3

Dose-Response Effect of Total 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 grey shading around the curves indicates a 95% confidence interval envelope.

LIFESPAN COGNITIVE EFFECTS OF DEMENTIA RISK FACTORS

Table 1

Age decades and Total risk factor levels with no significant differences in cognitive performance

Ages 40-50, 0 risk factors	=	Ages 20-30, 3 risk factors
Ages 50-60, 0 risk factors	=	Ages 40-50, 3 risk factors
Ages 60-70, 0 risk factors	=	Ages 50-60, 4 risk factors
Ages 70-80, 0 risk factors	=	Ages 60-70, 5 risk factors

Supplemental Material

Dose Response Relationship for Adjusted Risk Amount Factors By Age Period

Preliminary analyses showed a significant effect of adjusted risk amount on cognitive performance, indicating a dose-response association whereby each additional factor lead to a drop in cognitive performance. Stepwise hierarchical regression revealed that adding linear and polynomial age terms resulted in models with a significantly better fit ($\Delta\chi^2$ test, $p < .0001$), that explained more variance ($\Delta R^2=0.45$ and $\Delta R^2=0.05$) and remained parsimonious ($\Delta BIC=-1531$ and $\Delta BIC=-2540$). Next, quadratic regression was used to examine the association between total risk factors and age (with linear and polynomial terms) on cognitive performance. The results of the regression revealed that age, adjusted risk amount, and their interaction explained a significant amount of the variance in cognitive performance, $F(4, 22090) = 7423$, $p < .0001$, $R^2 = .57$. Cognitive performance was significantly predicted by a linear age term ($\beta = .003$, $p < .0001$), a polynomial age term ($\beta = -.0006$, $p < .001$), adjusted risk amount ($\beta = -.3$, $p = .13$), and an age by adjusted risk amount interaction ($\beta = -.007$, $p < .0001$). Therefore, cognitive performance decreased as age increased, as risk amount increased, and as both age and risk amount increased, indicating that the dose response association was moderated by age (Supplemental Figure 1).

Supplemental Figure 1

Dose-Response Relationship of Adjusted Risk Amount on Cognitive Performance Across Age.

Note. Each dot shows the mean performance per risk amount. The line shows the fitted polynomial curve.

LIFESPAN COGNITIVE EFFECTS OF DEMENTIA RISK FACTORS

Supplemental Table 1

Frequency Distribution of Total Risk Factors by Age Period.

	0	1	2	3	4	5	6	7
Young adults (18-44)	890	447	141	38	7	2	0	0
Middle-aged adults (45-65)	4092	2693	1372	493	132	36	3	1
Older adults (64-89)	3103	4616	2846	963	217	16	9	0