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Original Article

Maintaining level of modifiable dementia risk scores is associated with better cognitive outcomes than increasing risk scores: A population-based prospective cohort study

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ABSTRACT

Background: A brain healthy lifestyle, consisting of good cardiometabolic health and being cognitively and socially active in midlife, is associated with a lower risk of cognitive decline years later. However, it is unclear whether lifestyle changes over time also affect the risk for mild cognitive impairment (MCI)/dementia, and rate of cognitive decline.

Objectives: To investigate if lifestyle changes over time are associated with incident MCI/dementia risk and rate of cognitive decline.

Design: Population-based prospective cohort study

Setting: Personality and Total Health (PATH) Through Life Study cohort (Australia).

Participants: 4,777 participants (50.4% women), recruited between 2000 and 2002, who were 40–44 and 60–64 years old at baseline, without a prevalent dementia diagnosis. Participants had to have cognitive outcome measures available after baseline.

Measurements: Various measurements (neurocognitive assessment, blood pressure) and survey responses (demographics, cognitive, social, and physical activity, smoking, alcohol consumption, body height and weight, depression, and previous diagnoses) were collected approximately every four years. A brain-healthy lifestyle was operationalized via two well-validated modifiable dementia risk scores, the LIfestyle for BRAin health (LIBRA) score and the modifiable part of the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI$_{mod}$). Their change over time was estimated using latent growth curve modelling, and their association with cognition and incidence of MCI/dementia was investigated using parallel process modelling and Cox regression analysis.

Results: Within those aged 60–64 years at baseline (n=2,409), 211 cases of incident MCI/dementia were recorded over a median follow-up time of 12.2 years. On average, individuals' LIBRA and ANU-ADRI$_{mod}$ increased (i.e., worsened) over time, but individuals whose scores increased one standard deviation (SD) less had a 19.0–24.6% lower risk for MCI/dementia (hazard ratio (95% confidence interval): LIBRA$_{change\ over\ time}$=0.754 (0.664–0.857), ANU-ADRI$_{mod,\ change\ over\ time}$=0.810 (0.71–0.915)), while controlling for the risk score at baseline and multiple potential confounders. Various associations between dementia risk score trajectories and cognitive performance trajectories were observed.

Conclusions: Efforts to maintain a brain healthy lifestyle could reduce the risk for MCI or dementia, and slow cognitive decline.

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1. Introduction

The identification of modifiable risk and protective factors for dementia has introduced the notion that dementia risk could be reduced by altering exposure to them [1]. Dementia risk scores which integrate several individual risk and protective factors have been developed and externally validated to predict cognitive decline, dementia incidence, and biomarkers of dementia-related brain pathology [2–7]. These risk scores combine several modifiable and/or non-modifiable risk factors into one numeric value. Therefore, they can be used to identify individuals at high risk and as a motivational tool to increase risk perception and guide risk modification [8]. Two well-validated risk scores that include multiple modifiable factors, are the LIfestyle for BRAin health (LIBRA) score and the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) [3,7,9]. LIBRA summarizes the presence of twelve modifiable risk and protective factors for cognitive decline and dementia, whereas ANU-ADRI combines 15 risk and protective factors, twelve modifiable and three non-modifiable [2,3,7,9].

While generally assumed, it has not been demonstrated that improvement of these risk scores over time is associated with a lower risk of cognitive impairment. Few studies have investigated trajectories of individual risk factors such as blood pressure [10], body mass index (BMI), glycemia, and blood lipid levels [10] in relation to dementia risk [11]. One previous study explored how change over time in the Cardiovascular Risk Factors, Ageing and Dementia (CAIDE) score related to change in neuro-imaging biomarkers in a subsample of participants of the 2-year Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). In this study, a reduction (i.e., improvement) in the CAIDE score over the study period was associated with less decline in hippocampal volume, specifically in the intervention group, but not the control group. No other neuroimaging markers were significantly associated with change in the CAIDE score [12]. Another study investigated how episodic memory and dementia incidence relate to cardiovascular risk factors over time, operationalized through trajectories of the Framingham Risk Score (FRS). A faster worsening of the FRS, as compared to a stable FRS, was associated with an increased risk of Alzheimer's disease, vascular dementia, and memory decline [13].

The current project aimed to assess whether changes over time in the LIBRA and ANU-ADRI scores are associated with cognitive decline, and incidence of mild cognitive impairment (MCI) or dementia in the Personality and Total Health (PATH) Through Life Study cohort. Additionally, we explored whether sociodemographic characteristics were predictive of these LIBRA and ANU-ADRI score trajectories. By understanding these patterns, it may become possible to target and tailor interventions to – not only those at the highest risk – but also those that are more (or less) likely to demonstrate change over time.

2. Methods

2.1. Population

The PATH cohort is a longitudinal, population-based study following over 7500 individuals from three birth cohorts (birth years: 1937–1941, 1956–1960 and 1975–1979). Participants were randomly recruited via electoral rolls from the Canberra and Queanbeyan regions in Australia. The cohort has been described elsewhere [14,15]. Here, we used data of two birth cohorts: individuals who were 40 to 44 (40+ cohort) and 60 to 64 (60+ cohort) years old at baseline. Participants were re-assessed approximately every 4 years for up to 12 years. Individuals were excluded if they had no cognitive outcome data after baseline, or if they had MCI/dementia at baseline (Fig. 1). All participants provided written informed consent. PATH was approved by the Australian National University Human Research Ethics Committee and conducted in compliance with the Declaration of Helsinki.

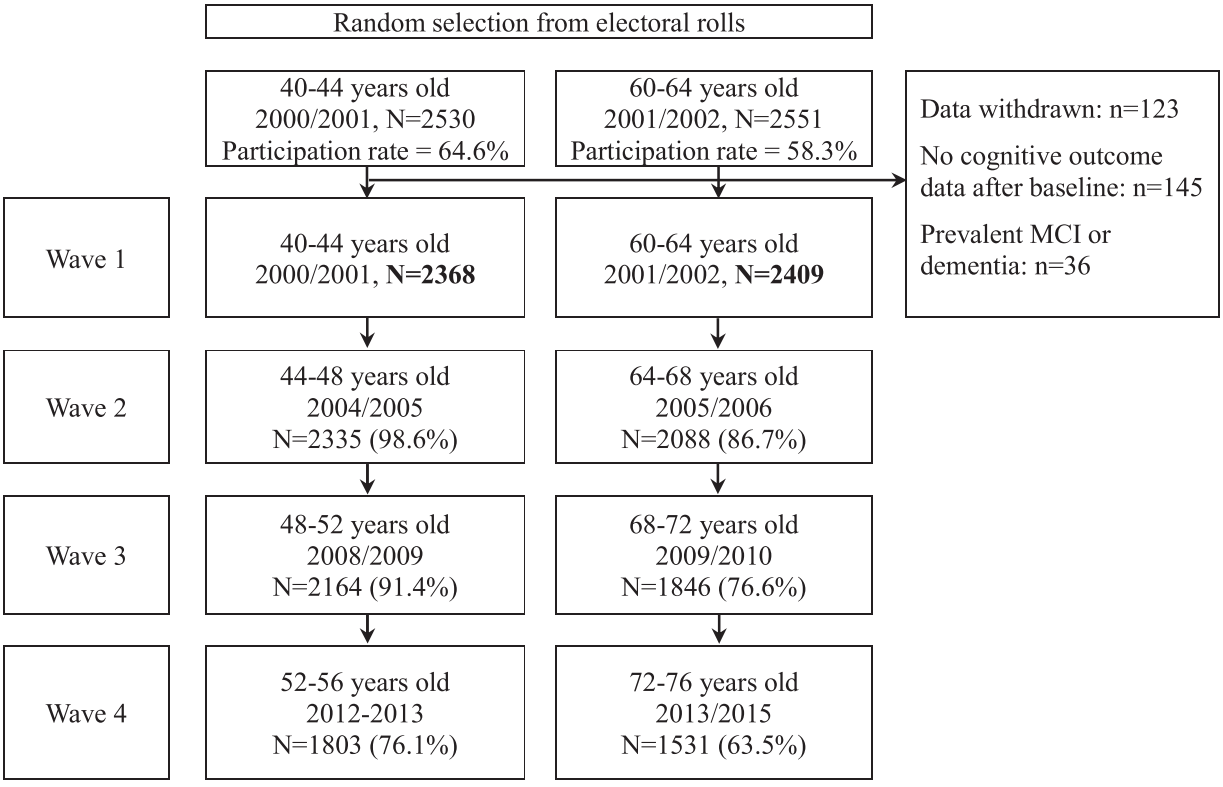

Fig. 1. The analytical sample of participants in the 40+ and 60+ age group of the Personality and Total Health (PATH) Through Life Study cohort [15]. Abbreviations: mild cognitive impairment (MCI).

2.2. Dementia risk scores

ANU-ADRI and LIBRA were calculated at each study wave, by adding or subtracting a predefined value based on the presence or level of each risk and protective factor [3]. For ANU-ADRI, two scores were calculated: one including all factors [2] and a second one excluding the non-modifiable factors age, gender, and years of formal education. This second score will be referred to as 'modifiable ANU-ADRI' ($ANU\text{-}ADRI_{mod}$) and was calculated to examine the evolution in the score due to changes in modifiable risk and protective factors, ultimately aiming to facilitate the interpretation of the results, and allowing for a direct comparison with LIBRA. The complete operationalization of both scores is shown in Table 1. The operationalization of social engagement deserves some additional explanation. Participants were assigned one point if (1) they

Table 1
Dementia risk score operationalization.

Risk and protective factors	LIBRA	ANU-ADRI
Age and gender	*Not included*	Self-reported, < 65 years = 0 (men and women) 65- 70 = +1 (men), +5 (women) 71–75 = +12 (men), +14 (women) 76–80 = +18 (men), +21 (women)
Total years of formal education	*Not included*	Self-reported, > 11 years = 0 8–11 years = +3 < 8 years = +6
Depression	Goldberg depression scale score > 4 defined as indicative for depression [38] = +2.1	Goldberg depression scale score > 4 defined as indicative for depression [38] = +2
Hypertension	Measured systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg, or antihypertensive medication use = +1.6	*Not included*
Diabetes	Self-reported diagnosis = +1.3	Self-reported diagnosis = +3
Smoking	Self-reported current smoker = +1.5	Self-reported never smoker: 0 past smoker: +1 current smoker: +4
Obesity	BMI ≥ 30 kg/m^2 = +1.6 Based on self-reported weight and height	25 kg/m^2 ≤ BMI < 30 kg/m^2 = +2 BMI ≥ 30 kg/m^2 = +5 Based on self-reported weight and height
Physical inactivity	Physically inactive: < 150 minutes moderate-intensity physical activity per week and < 75 minutes vigorous-intensity physical activity per week = +1.1 Based on self-reported time spent doing mild, moderate, and high-intensity physical activity	Low activity: <1.5h of moderate-intensity and <0.5h of vigorous-intensity physical activity/week) = 0 Medium activity: ≥1.5h of moderate-intensity physical activity or ≥0.5h (but <1.5h) of vigorous-intensity physical activity/week = −2 High activity: ≥1.5h of vigorous-intensity physical activity/week = −3 Based on self-reported time spent doing mild, moderate, and high-intensity physical activity
Low social engagement	*Not included*	Low engagement: 0–2 points = +6 Low-medium engagement: 3 points = +4 Medium-high engagement: 4 points = +1 High engagement: 5 points = 0 Based on five self-reported domains of social engagement (marital status, social network size, club membership, living arrangements, and satisfaction with relationships)
Coronary heart disease	Self-reported heart disease (proxy) = +1.0	*Not included*
Traumatic brain injury (TBI)	*Not included*	Self-reported history of TBI with loss of consciousness = +4
Chronic kidney disease	*Not available*	*Not included*
Dyslipidemia	*Not available*	*Not available*
Pesticide exposure	*Not included*	*Not available*
Low-to-moderate alcohol consumption	Self-reported units/week: Adherence to the current Australian guidelines of max. 10 units/week = −1.0	Self-reported units/week: 0.25–20.5 standard units/week (men) and 0.25–13.5 standard units/week (women) = −3
High cognitive activity	Included activities: reading about special subjects; going to recitals, concerts, or musicals; reading literature; reading scientific books or magazines; solving math's or chess puzzles (all surveyed). Engagement in ≥ 4 activities in the last 6 months = −3.2	Included activities: reading about special subjects; going to recitals, concerts, or musicals; reading literature; reading scientific books or magazines; solving math's or chess puzzles (all surveyed). Low activity: engagement in ≤ 1 activity in the last 6 months = 0 Medium activity: engagement in 2–3 activities in the last 6 months = −6 High activity: engagement in ≥ 4 activities in the last 6 months = −7
Healthy diet	Mediterranean diet adherence: *not available*	Fish consumption: *not available*
Theoretical total range	−4.2 to +10.2	Complete ANU-ADRI: −13.0 to +51.0 Modifiable ANU-ADRI ($ANU\text{-}ADRI_{mod}$): −13.0 to +24.0

Abbreviations: LIfestyle for BRAin health index (LIBRA), Australian National University Alzheimer's Disease Risk Index (ANU-ADRI), body mass index (BMI), traumatic brain injury (TBI).

were married, (2) they had at least five close friends (reported at wave 3), (3) they were member of any kind of club, (4) they received satisfactory social support from their friends, family, and partner (based on a six-item survey on social support). There was no information available on living arrangements so a point for this domain was assigned based on the other four domains pro rata [2].

2.3. Cognitive functioning

An extensive neurocognitive assessment was carried out at each study wave by trained interviewers. Short-term episodic memory was assessed with the immediate recall of the California Verbal Learning Test (CVLT), which asks participants to immediately recall a list of 16 nouns from the first trial (Trial A) of the CVLT that had been verbally presented to them [16]. The Symbol Digit Modalities Test (SDMT) was used to assess processing speed [17]. Herein, participants use a coded key to match symbols with digits. The task is scored by counting the correct number of written substitutions within 90 seconds. Both scores were standardized into z-scores using the sample mean and standard deviation (SD) at baseline.

2.4. MCI and dementia incidence (only in 60+ cohort)

MCI and dementia were diagnosed using a two-step process described in detail elsewhere [18,19]. First, participants were screened for potential cognitive decline based on their performance on several cognitive tests. Participants who screened positive, were further clinically assessed and a consensus diagnosis was reached. At wave 4, the procedure for screening and clinical diagnosis was modified, and is described in detail elsewhere [20]. At wave 1–2, MCI was clinically diagnosed based on Petersen criteria [21]. At wave 3–4, this was done using Winblad criteria [22]. Dementia was diagnosed based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [23]. Due to a limited number of incident dementia cases, MCI and dementia were combined as outcome.

2.5. Covariates

Participants were surveyed about their gender, marital state, employment status, 1st language, and whether they had children. Socioeconomic position (SEP) was operationalized as the response (yes/no) to a survey item on whether they had to go without their basic needs being met due to financial hardship in the past year. APOE ε4 carriership was determined from DNA extracted from buccal swabs as previously described [24].

2.6. Statistical analysis

Sample characteristics are described using counts and percentages, means and SD, or medians and interquartile ranges. Analyses were carried out between March 2023 and April 2024. All analyses were done two-sided with an alpha level of 0.05 in R. Used packages are listed in Appendix p 8.

2.6.1. LIBRA and ANU-ADRI$_{mod}$ trajectories over time

Trajectories of the two dementia risk scores were modelled using latent growth curves (e.g., for ANU-ADRI$_{mod}$ see Appendix Fig. 1 on p 5). All models were fit using full information maximum likelihood (FIML) estimation on the 40+ and 60+ cohorts separately. To identify the best-fitting trajectory shape, linear and curvilinear unconditional models were compared against each other using Bayesian information criterion (BIC, smaller BIC values are better and a value that is $\geq$ 10 smaller suggests an improved model). Additionally, root mean square error of approximation, Comparative Fit Index, Tucker-Lewis Index, and Standardized Root Mean Square Residual were used to confirm good model fit [25]. Sociodemographic predictors of the dementia risk score trajectories were explored by adding these to the latent growth curve model. This was first done univariably, and then multivariably by backward selection.

2.6.2. Dementia risk score trajectories over time, and the risk for incident MCI/dementia

The association between dementia risk score trajectories and MCI/dementia incidence was investigated in the 60+ cohort by using the individual intercepts (estimated baseline score) and slopes (estimated linear change over time)) as predictors in Cox proportional hazard regression analysis, with MCI/dementia as outcome. Survival time was calculated as the time between the first assessment date at wave 1, and the date of the last assessment in case of no MCI/dementia diagnosis. In case of incident MCI/dementia, the date of diagnosis was calculated as the midpoint between the wave when the diagnosis was made and the previous wave. The proportional hazard assumption was examined by testing Schoenfeld residuals. Three models were run (model 1: crude; model 2: model 1 + baseline age, gender, and years of formal education; model 3 (main model): model 2 + SEP, APOE ε4 carriership, and speaking English as 1st language).

2.6.3. Dementia risk score trajectories, and cognitive performance over time

The association between dementia risk score trajectory and cognitive performance over time was examined using parallel process models. Herein, both the dementia risk score trajectory, the cognitive performance trajectory, and the covariance between these two, were modelled (e.g., for processing speed in Appendix Fig. 2 on p 5). The most appropriate shape for the processing speed and episodic memory trajectories was first determined by inspection of the different model fit criteria outlined above. Three models were run (model 1: crude; model 2: model 1 + baseline age, gender, and years of formal education; model 3 (main model): model 2 + SEP, APOE ε4 carriership, and speaking English as 1st language).

2.6.4. Multiple imputation of dementia risk scores

Multiple imputation was used to deal with missing values in any of the risk and protective factors included in LIBRA or ANU-ADRI. When participants were not assessed at a certain wave (none of the factors available), these were not imputed. Imputation was done by multivariate imputation by chained equations, using all non-missing risk and protective factors, age, gender, and total years of formal education, and outcome measures (i.e., standardized scores for immediate recall of the CVLT and the SDMT, and MCI/dementia diagnoses (in the 60+ cohort only)). Imputation was done for the 40+ and 60+ cohorts separately. Ten imputed datasets were created, and the results of all individual analyses were combined using Rubin's rules [26,27].

3. Results

In total, 4777 participants (50.4% women) were included. Detailed sample characteristics are listed in Table 2. All analyses were done on complete cases and on multiple imputed datasets. Details on missing data can be consulted in Appendix Table 1. Results obtained on complete cases can be found in Appendix Tables 2-8.

3.1. LIBRA and ANU-ADRI$_{mod}$ trajectories

Fig. 2 shows the principle of estimating a linear trajectory (i.e., an intercept and slope) for two random participants based on their measurements.

Model fit measures for both risk score trajectories can be consulted in Appendix Table 9. In the 40+ cohort, LIBRA at baseline (i.e, intercept) was estimated at –0.02 (SD=2.38, p=0.700). LIBRA increased on average with 0.10 points (SD=0.92, p<0.001) every four years, suggesting modifiable risk scores worsen over time. Intercept-slope covariance was non-significant (covariance = –0.11, SD=3.11, p=0.080). In

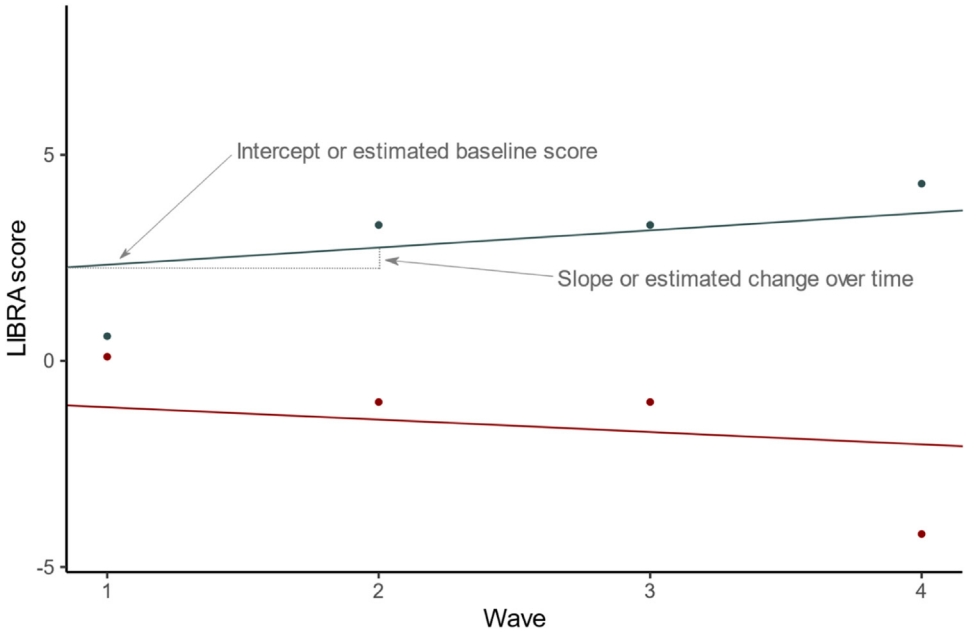

Fig. 2. Estimation of dementia risk score trajectories using latent growth curve modelling based on repeated measurements. Examples of estimated LIfestyle for BRAin health (LIBRA) trajectories and the individual measurements on which they are based of two different participants are shown. The estimated trajectory can be described by its intercept, or the estimated baseline score, and its slope, or the estimated linear change over time.

the 60+ cohort, LIBRA at baseline was estimated at 0.78 (SD=2.36, p<0.001) and increased with 0.13 points (SD=0.88, p<0.001) every four years. Intercept and slope covaried significantly (–0.23, SD=2.80, p<0.001), suggesting that higher baseline LIBRA scores are associated with less increase over time. As for ANU-ADRI$_{mod}$, the estimated intercept was –2.92 (SD=5.21, p<0.001) and ANU-ADRI$_{mod}$ increased with 0.47 (SD=1.70, p<0.001) every four years in the 40+ cohort. Intercept and slope covaried significantly (-0.86, SD=10.9, p<0.001). In the 60+ cohort, a trajectory intercept of –3.22 (SD=5.15, p<0.001) and slope of 0.38 (SD=1.77, p<0.001) were estimated. They did not covary (p=0.937). Full unconditional model estimates are included in Appendix Table 10.

3.2. Modifiable dementia risk score trajectories and risk for incident MCI/dementia

When considering incident MCI/dementia in the 60+ cohort, both a higher risk score intercept and larger slope were independently and consistently associated with an increased risk for MCI/dementia. Detailed results are shown in Table 3. Every SD increase in risk score slope was associated with a 23.4–32.6% higher risk for MCI/dementia in the fully controlled model. In other words, every SD decrease in risk score slope was associated with a 19.0–24.6% lower risk for MCI/dementia.

3.3. Modifiable dementia risk score trajectories and cognitive performance

Next, the relationship between risk score trajectories and cognitive performance trajectories was investigated. A linear model fitted best for episodic memory trajectories and trajectories of processing speed in the 40+ cohort. Processing speed trajectories in the 60+ cohort demonstrated a better fit in a curvilinear model. Lower risk scores at baseline were consistently associated with a better episodic memory and faster processing speed at baseline in both age groups (all p<0.050). Additionally, a lower ANU-ADRI$_{mod}$ intercept was associated with less decline in processing speed over time, specifically in the 40+ cohort (covariance=-0.06, p=0.024, fully controlled model 3). A lower LIBRA intercept was also associated with less decline in processing speed, although exclusively in the 60+ cohort and only significantly in model 2 (covariance$_{linear\ slope}$=-0.07, p-value=0.028; p-value≈0.06 in the crude and fully controlled model). Less worsening in LIBRA over time was predictive for less decline in episodic memory in the 60+ cohort (covariance=-0.02, p=0.005, model 3). Less worsening in both LIBRA and ANU-ADRI$_{mod}$ over time was also associated with a faster processing speed at baseline in the 60+ cohort (LIBRA covariance=-0.04, p-value=0.022; ANU-ADRI$_{mod}$ covariance=-0.08, p=0.009; model 3). In the 40+ cohort, however, less worsening of ANU-ADRI$_{mod}$ over time was associated with a slower processing speed at baseline (covariance=0.07, p=0.025, model 3). See Appendix Tables 13–14 for full parallel process model estimates.

3.4. Sociodemographic predictors of LIBRA and ANU-ADRI$_{mod}$ trajectories

Lastly, predictors of the risk score trajectories were explored. Detailed results are included in Appendix Tables 11–12. In multivariable models of the risk score trajectories, lower or better baseline LIBRA and ANU-ADRI$_{mod}$ scores were consistently associated with female gender (only in 60+ for ANU-ADRI$_{mod}$), more years of formal education, and a higher SEP in both age groups (all p<0.050). A lower baseline risk score was also consistently associated with having children in the 40+ cohort and speaking English as 1st language in the 60+ cohort (all p<0.050). Additionally, being married was associated with better baseline ANU-ADRI$_{mod}$ scores in both age groups (all p ≤0.001). Being married was also associated with better baseline LIBRA scores, specifically compared to separated (p=0.001) or divorced (p=0.031) individuals in the 40+ cohort and compared to widowed individuals in the 60+ cohort (p=0.015).

Faster worsening of both LIBRA and ANU-ADRI$_{mod}$ over time was consistently associated with having children in the 40+ cohort, and unemployment in the 60+ cohort (all p<0.050). Specifically for LIBRA, faster worsening of the score over time was associated with a higher SEP in the 40+ cohort (p=0.029), and female gender in the 60+ cohort (p=0.030). Specifically for ANU-ADRI$_{mod}$, being divorced was associated with less worsening of the score over time compared to being married in both age groups (all p<0.050). Living together was also associated with less worsening of ANU-ADRI$_{mod}$ over time compared to being married, but exclusively in the 40+ cohort (p<0.001).

4. Discussion

This prospective cohort study demonstrated that more stable modifiable dementia risk scores (LIBRA and ANU-ADRI$_{mod}$) over time were associated with a lower risk of incident MCI/dementia, compared to

Table 2
Study population characteristics.

	40+ cohort	60+ cohort
Sample, n	2368	2409
Age, mean (SD)	42.6 (1.5)	62.5 (1.5)
Women, n (%)	1250 (52.8)	1157 (48.0)
Years of formal education, median (IQR)	15 (13–16)	14 (12–16)
Marital state, n (%)		
Married	1695 (71.6)	1803 (74.9)
Living together (de facto)	189 (8.0)	75 (3.1)
Separated	111 (4.7)	63 (2.6)
Divorced	166 (7.0)	231 (9.6)
Widowed	16 (0.7)	172 (7.2)
Single	190 (8.0)	62 (2.6)
1st language English, n (%)	2168 (91.6)	2112 (87.8)
APOE ε4 carriership, n (%)		
ε4−/ε4−	1561 (72.1)	1645 (73.2)
ε4−/ε4+	560 (25.9)	555 (24.7)
ε4+/ε4+	43 (2.0)	48 (2.1)
ANU-ADRI, mean (SD)	-2.7 (5.5)	-2.1 (5.9)
Modifiable ANU-ADRI, mean (SD)	-3.1 (5.2)	-3.2 (5.2)
LIBRA, mean (SD)	0.0 (2.4)	0.8 (2.4)
Cognitive performance at baseline, mean (SD)		
Immediate recall	7.9 (2.2)	7.2 (2.3)
Symbol digit modalities test	60.3 (9.2)	49.8 (9.7)
Incident MCI or dementia, n (%)	NA	211 (8.8)
Conditions at baseline, n (%)		
Coronary heart disease	65 (2.8)	361 (15.0)
Hypertension	585 (24.7)	1517 (63.1)
Diabetes	43 (1.8)	176 (7.3)
Traumatic brain injury	126 (5.3)	135 (5.6)
Body mass index classification		
Healthy weight	1076 (45.5)	951(39.5)
Overweight	829 (35.0)	986 (40.0)
Obese	462 (19.5)	469(19.5)
Depression	495 (20.9)	230 (9.6)
Lifestyle factors at baseline		
Physically inactive, n (%)	1215 (51.3)	1579 (65.6)
Smoking status, n (%)		
Never	1217 (51.4)	1236 (51.4)
Former	717 (30.3)	904 (37.6)
Current	434 (18.3)	267 (11.1)
Alcohol consumption (standard units/week), median (IQR)	4 (0.9 – 9.0)	4 (0.4 – 9.0)
Social activity level, n (%)		
Low	449 (18.9)	220 (9.2)
Low-medium	876 (37.0)	722 (30.0)
Medium-high	900 (38.0)	1151 (47.8)
High	143 (6.0)	313 (13.0)
Cognitive activity, n (%)		
Low	362 (15.3)	410 (17.1)
Intermediate	1145 (48.4)	1246 (51.8)
High	861 (36.3)	750 (31.2)

Numbers are rounded as they can vary between imputed datasets. Physical inactivity as defined within LIBRA. Abbreviations: mild cognitive impairment (MCI), LIfestyle for BRAin health (LIBRA), Australian National University Alzheimer's Disease Risk Index (ANU-ADRI), standard deviation (SD), interquartile range (IQR), not applicable (NA). Missing: marital state (n=4), 1st language English (n=4), APOE ε4 carriership (n=365), immediate recall (n=8), symbol digit modalities test (n=31).

Table 3
Hazard ratio (95%CI) for incident MCI/dementia as predicted by dementia risk score trajectories, per standard deviation increase in intercept or slope.

	Model 1	Model 2	Model 3
LIBRA intercept	1.405 (1.224 – 1.614)	1.287 (1.109 – 1.493)	1.272 (1.090 – 1.484)
LIBRA slope	1.314 (1.162 – 1.485)	1.307 (1.154 – 1.480)	1.326 (1.167 – 1.507)
ANU-ADRI$_{mod}$ intercept	1.384 (1.211 – 1.581)	1.304 (1.133 – 1.500)	1.269 (1.095 – 1.472)
ANU-ADRI$_{mod}$ slope	1.249 (1.110 – 1.404)	1.237 (1.099 – 1.392)	1.234 (1.093 – 1.393)

Model 1: crude (with both the intercept and slope included in the model); Model 2: model 1 + baseline age, gender, years of formal education; Model 3: model 2 + APOE ε4 carriership, socioeconomic position, and speaking English as 1st language. Abbreviations: LIfestyle for BRAin health (LIBRA), modifiable part of the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI$_{mod}$), confidence interval (CI).

worsening scores, over 12 years follow-up. Moreover, more stable LIBRA scores over time were associated with slower memory decline, in those who were 60–64 years old at baseline. Sociodemographic characteristics predictive of the investigated LIBRA and ANU-ADRI$_{mod}$ trajectories were identified.

Both modifiable risk scores, on average, worsened with aging. Importantly, individuals whose modifiable risk scores worsened less had a significantly lower risk of an MCI/dementia diagnosis over 12 years, after controlling for multiple confounders. Moreover, this is the risk in addition to the one conferred by the risk score at baseline. Furthermore, less worsening or improvements in LIBRA over time were associated with slower memory decline, specifically in the 60+ cohort. No similar association was observed for change in ANU-ADRI$_{mod}$, in neither age group. The reason for this is unclear but may be related to differences in included factors in the risk scores. Both score trajectories behaved somewhat differently and demonstrated different associations with sociodemographic variables. Evidence potentially indicative of 'reverse causation' with regards to processing speed was also observed in the 60+ cohort, where a slower processing speed at baseline was associated with more worsening in both risk scores over time. Surprisingly, in the 40+ cohort, a slower processing speed at baseline was associated with less worsening of ANU-ADRI$_{mod}$ over time. This may be related to the negative covariance between baseline ANU-ADRI$_{mod}$ scores and ANU-ADRI$_{mod}$ change over time, specifically present in the 40+ cohort. In this age group, individuals with worse ANU-ADRI$_{mod}$ scores at baseline, on average, demonstrated less worsening of the score over time. Simultaneously, a worse baseline score was associated with a slower processing speed at baseline. Almost no other studies have explored the relationship between trajectories of modifiable dementia risk factors, and rate of change in cognitive performance. One study looked at FRS trajectories of individuals with a wide range of ages at baseline (35–85 years). They also observed that a faster worsening FRS was associated with a higher risk for episodic memory decline. Processing speed was not investigated [13]. More research on the relationship between lifestyle factors, their change over time, and cognitive trajectories is needed to disentangle their complex interplay.

Multiple sociodemographic characteristics were associated with LIBRA and ANU-ADRI$_{mod}$ trajectories. As expected, more education, high SEP, and current employment were associated with better estimated baseline scores. Employment was also consistently predictive of less worsening of both risk scores over time in the 60+ age group. Education is linked to cognitive reserve, better health literacy, and better access to (preventative) health services, while employment tends to offer a steady level of cognitive and social activity [28,29]. For ANU-ADRI$_{mod}$, being married was associated with a better baseline score compared to all other marital states, which is likely partially explained by ANU-ADRI's social engagement scoring which includes marital state. Being married was also predictive for a better baseline LIBRA score, specifically compared to being separated or divorced in the 40+ cohort and being widowed in the 60+ cohort. Marriage appears to offer social engagement and is commonly associated with better lifestyle behaviors [30,31]. A vast amount of research has demonstrated that marriage is also associated with a lower risk for dementia, lower mortality, and better health outcomes, especially for men [30,31]. A few unexpected associations were also observed: female gender, high SEP, having children and being married (compared to being divorced or living together) were associated with more worsening of risk scores in one or both age groups. These observations may be related to these groups tending to have better baseline scores, and thus "more to lose". Indeed, the negative covariance between individual intercepts and slopes for the risk indices suggest that those with worse scores at baseline showed less worsening over time, probably due to ceiling effects. Additionally, people in midlife with children might have less time to engage in healthy lifestyles.

These findings highlight the value of modifiable dementia risk scores. Both LIBRA and ANU-ADRI have been developed to allow for an easy calculation using commonly available information from health records, and can still be calculated when some factors are missing [3,7,9]. They can be used to identify individuals at high risk and aid in improving risk perception [8]. Tools have already been developed that allow individuals to get insight into their own risk and potential room for improvement [32–34]. This could be further extended into primary care (e.g., routine health checks) where tools based on these risk scores could be used to facilitate risk communication and guide risk modification via provision of lifestyle advice and management of health conditions, in order to prevent worsening of the risk score over time [8,34].

This study focused on modifiable risk scores at baseline and their change over time as two separate predictors of cognitive decline. Future work could consider how these two characteristics combine into potentially common trajectories (e.g. stable-low risk, low-to-high risk, etc.). Strengths of the current study include the large representative sample consisting of individuals in middle- and older-age; and the availability of extensive health, lifestyle, and cognitive data. Additionally, the used methodological approach made it possible to investigate overall evolution in LIBRA and ANU-ADRI$_{mod}$ scores for each individual. The use of modifiable dementia risk scores further provided a comprehensive image of the participants' lifestyle and health conditions, considering that an individual may improve on one risk factor and worsen on another simultaneously. These findings show how modifiable risk fluctuates with sociodemographic circumstances over the adult life course.

This study also had certain limitations. First, due to its observational nature reverse causation could have played a role in these results. It is possible that individuals who receive an MCI or dementia diagnosis show a worsening in their risk profile in the 12 years before diagnosis because of the condition's preclinical stage. Certain modifiable risk factors have indeed been shown to be associated with preclinical dementia (e.g., depression, low social activity) but the opposite is seen for blood pressure and BMI [11,35–37]. Future work could aim for longer follow-up times and may exclude the last five to ten years before dementia diagnosis, when modelling modifiable risk factor trajectories, to prevent the possibility of modelling changes in risk factors that happen during the preclinical stage [11]. Second, ANU-ADRI and LIBRA were developed based on estimates with risk factor exposure later in life. Therefore, the used weights may not be optimal for middle-aged participants. Furthermore, not all risk and protective factors included in LIBRA or ANU-ADRI were available in this cohort. As such, dietary pattern, dyslipidemia, chronic kidney disease, and pesticide exposure, were not considered in the investigated trajectories. Third, social engagement in the 60+ cohort at baseline had a relatively high amount of missing data points (24.7%). However, considering that social engagement is only one of the nine modifiable risk and protective factors included in ANU-ADRI$_{mod}$ here, and the highly similar results obtained in a sensitivity analysis on complete cases, the risk for bias was considered low. Fourth, cognitive performance z-scores were based on the sample mean and SD at baseline, and not on external population data. Fifth, findings on sociodemographic predictors of the modifiable risk score trajectories were exploratory and need replication in other cohorts.

This study demonstrated that both baseline values of – and change in – modifiable dementia risk scores over time are associated with incident MCI/dementia and trajectories of cognitive performance. Although results are observational, they support the potential for dementia risk reduction by altering exposure to risk and protective factors. More fine-grained information is needed to study the time-lagged associations between lifestyle trajectories and cognition in depth.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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Supplementary materials

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