Association Between the AHA Life's Essential 8 Score and Incident All-Cause Dementia: A Prospective Cohort Study from UK Biobank

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Abstract: This study aimed to investigate the association between the Life's Essential 8 (LE8) score and incident all-cause dementia (including Alzheimer's disease [AD] and vascular dementia) in UK Biobank. A total of 259,718 participants were included in this prospective study. Smoking, non-HDL cholesterol, blood pressure, body mass index, HbA1c, physical activity, diet, and sleep were used to create the Life's Essential 8 (LE8) score. Associations between the score (both continuous and as quartiles) and outcomes were investigated using adjusted Cox proportional hazard models. The potential impact fractions of 2 scenarios and the rate advancement periods were also calculated.

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Curr Probl Cardiol 2023;48:101934
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2023.101934

Over a median follow-up of 10.6 years, 4958 participants were diagnosed with any dementia. Higher LE8 scores were associated with lower risk of all-cause and vascular dementia in an exponential decay pattern. Compared with individuals in the healthiest quartile, those in the least healthy quartile had a higher risk of all-cause dementia (HR: 1.50 [95% CI: 1.37-1.65] and vascular dementia (HR: 1.86 [1.44-2.42]). A targeted intervention that increased the score by 10-points among individuals in the lowest quartile could have prevented 6.8% of all-cause dementia cases. Individuals in the least healthy LE8 quartile might develop all-cause dementia 2.45 years earlier than their counterparts. In conclusion, individuals with higher LE8 scores had lower risk of all-cause and vascular dementia. Because of nonlinear associations, interventions targeted at the least healthy individuals might produce greater population-level benefits. (Curr Probl Cardiol 2023;48:101934.)

Introduction

Dementia—a progressive deterioration in cognitive function—is the seventh leading cause of death and one of the major causes of disability and dependency.[1] Around 55 million people were living with dementia in 2020, and it is estimated to double every 20 years, reaching 139 million by 2050.[2] In the UK alone, more than 1 million people are expected to live with dementia by 2025.[3]

Ageing is one of the major risk factors for dementia, but several modifiable risk factors offer the potential to prevent or delay its onset. The Dementia Prevention, Intervention, and Care report from the Lancet Commission highlighted 12 modifiable risk factors,[1] including smoking, alcohol intake, physical inactivity and elevated body weight.[1] Most of these 12 factors were included in the Life Simple 7 (LS7) score; a lifestyle score proposed in 2010 by the American Heart Association (AHA) to encourage better cardiovascular health through 7 modifiable risk factors.[4] Studies have shown that adherence to the LS7 score was associated with lower dementia incidence,[5-7] concluding that a better score in the LS7 would substantially reduce the late-life dementia risk.[5-12]

In 2022, the AHA published an updated algorithm addressing the limitations of the LS7 score and incorporated sleep as an additional health

metric. The addition of sleep has been demonstrated to improve the performance of the score over the earlier LS7 score.[13] The new score was called "Life's Essential 8" (LE8).[14] Despite evidence of an association between the LS7 and dementia incidence in the US, investigation of the association between LE8 adherence and incident dementia is limited to one UK study in which dementia was included in a composite outcome—along with cardiovascular disease, diabetes and cancer—but not investigated in isolation.[15] In order to address this limitation, this study aimed to investigate the association between the LE8 score and incident all-cause dementia in the UK Biobank cohort.

Methods

UK Biobank recruited over 500,000 participants (5.5% response rate) from the general population between 2006 and 2010.[16] Participants (aged 37-73 years) attended one of the assessment centres across Scotland, England, and Wales,[17,18] where they completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere.[17,18] Outcomes were ascertained via record linkage to hospital admissions and death certificates.

Ethics Information

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382).[16] This work was conducted under the UK Biobank application number 7155. More information about the UK Biobank protocol can be found online (http://www.ukbiobank.ac.uk)

Life's Essential 8 Score

Following the AHA original score, we previously published a LE8 score that was also used for this study.[19] The score included the same elements (body mass index (BMI), self-reported physical activity, self-reported sleep, blood pressure, non-HDL cholesterol, Hb1Ac, smoking, and diet quality) and similar cut-off points as suggested by Lloyd-Jones et al.[20] More information about the score is available in Supplementary Table 1 and can be found elsewhere.[19]

Each of the 8 health metrics was scored from 0 to 100, with a lower score indicating the least healthy while a higher score indicated the healthiest, as suggested by Lloyd-Jones et al.[20] The mean LE8 score for each individual was derived by summing the 8 health metrics and

dividing them by 8. The score was treated as both a continuous variable and as quartiles (quarters) of distribution in the analyses.

Outcomes

All-cause incident dementia (including Alzheimer's disease [AD] and vascular dementia) was extracted from hospital episode records for incidence and death register for mortality. AD and vascular dementia were defined using the following International Classification of Diseases 10th revision (ICD-10),[21] codes: G30 (Alzheimer's disease) and F01 (vascular dementia). All-cause dementia (hereafter "dementia") was defined as F00 (dementia in Alzheimer's disease), F01, F02 (dementia in other diseases) or F03 (unspecified dementia) and G30.

The date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Dates and causes of hospital admissions were identified via record linkage to Health Episode Statistics (HES) (England and Wales) and the Scottish Morbidity Records (SMR01) (Scotland). Details of the linkage procedure can be found at http://content.digital.nhs.uk/services. Hospital admissions data were available until September 2021 in England, July 2021 in Scotland and February 2018 in Wales. Therefore, incident event models were censored on these dates or the date of death if this occurred earlier. Mortality data were available until the end of October 2021. Therefore, mortality follow-up was censored on this date. Only the first eligible event was used in all analyses.

Covariates

Age at baseline was derived from dates of birth and baseline assessment. Sex was self-reported. Deprivation (area-based socioeconomic status) was derived from the postcode of residence, using the Townsend index.[22] Ethnicity was self-reported and categorised into white, and non-White. Frequency of alcohol intake was self-reported at baseline and categorised as: daily/almost daily, 3-4 times a week, once/twice a week, 1-3 times a month, special occasions only, or never. The average time spent driving, using a computer, and watching television were summed to derive the total time spent on sedentary behaviors. Prevalent morbidity (excluding dementia and neurological conditions) was ascertained during a nurse-led interview at baseline. Participants were classified as having no prevalent morbidity or $\geq$1 prevalent morbidity based on 43 long-term

conditions selected initially for a large epidemiological study in Scotland and subsequently adapted for UK Biobank.[23,24] The reaction-time test (timed test of symbol matching) was completed through a touch-screen test in milliseconds across trials that contained matching pairs as a proxy for cognitive health at baseline,[25] given the strong inter-correlations between multiple cognitive abilities generally and in UK Biobank.[26] Due to the skewed distribution, this variable was transformed to a logarithm scale before it was included in the analyses.

Statistical Analyses

Descriptive baseline characteristics by quartiles of the LE8 score are presented as means with standard deviations (SD) for quantitative variables and as frequencies and percentages for categorical variables.

Nonlinear associations between the LE8 score and incident dementia (including AD and vascular dementia) were investigated using penalised cubic splines fitted in Cox proportional hazard models. From the fitted model, we obtained adjusted hazard ratios (HR) across the entire range of LE8 scores using the cohort median (72 points) as the reference (HR = 1.00). We also fitted LE8 scores as a categorical variable for interpretability, dividing the score into quartiles considering UK Biobank participants are healthier than the general population[27] and quartiles give an equal distribution. Associations between quartiles of the LE8 score and the outcomes were investigated using Cox-proportional hazard models, with the time of follow-up used as the timeline variable. Individuals in the highest quartile were used as the referent category. Results are reported as HR and their 95% confidence intervals (95% CI).

Participants with missing data for any of the metrics included in the LE8 score (n = 227,792), dementia or neurological conditions at baseline (n = 11,534) or missing data for one or more covariates (n = 3253), were excluded from all analyses. In addition, analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n = 115) (Supplementary Fig 1). All analyses were adjusted sequentially using the following models: model 0 was unadjusted; model 1, was adjusted for age, sex, deprivation, and ethnicity; and model 2, as per model 1 but additionally included morbidity count, log reaction time and lifestyle factors (alcohol intake and total sedentary time).

In sensitivity analyses, we investigated whether the associations between LE8 score quartiles and outcomes differed by population groups. For these analyses, we stratified by age ($<$ and $\geq$60 years), sex (men and

women), deprivation (Townsend index ≤ and >the median), and ethnicity (white and non-White). An interaction term between the subgroups, the quartiles of the LE8 score, and the outcomes was fitted into the model to test for interaction.

The population attributable fraction (PAF) was estimated to calculate the proportion of incident dementia cases attributable to nonfollowing the recommendations of the LE8 score, assuming causality.[28] PAFs were estimated based on the adjusted HR derived from the nonlinear associations. The potential impact fractions (PIF) of 2 scenarios were also calculated to evaluate which counterfactual scenarios may have a more substantial public health impact, under the assumption that the effect of the intervention on the LE8 score was constant across the range of LE8 values.[29] The first scenario represented a general intervention approach which would increase the score across the whole population by 2.5 points. The second scenario represented a targeted intervention which would reduce the number of people with low LE8 scores, by increasing by 10-points the scores of those individuals in the lowest quartile (score <66.25). The 2 scenarios correspond to the same population level improvement in LE8 score (2.5-points improvement in the whole population vs 10-points in one-quarter of the population). Moreover, the rate advancement periods (RAPs) − that is, the number of additional chronologic years that would be required to yield the equivalent risk rate for dementia incidence among the quartiles − was also estimated as described previously.[30] To calculate RAPs, we divided the logarithm coefficient (HR) for the incidence for the quartiles referent to people in the highest quartile for the incidence associated with each yearly increase in age, eg, $\frac{\log(HR_{quartiles})}{\log(HR_{Age})}$. These analyses were run for all the outcomes that were significantly associated with the LE8 in the Cox proportional models.

Finally, to contrast the associations of the LE8 and LS7 scores with the outcomes of interest, the scores were standardised to z-scores (per 1-SD increase). Additionally, to compare the predictive ability of the LE8 score vs the previous LS7 score, a Harrell's C-index—which estimates the probability of concordance between observed and predicted responses—was calculated using model 2.[31]

Stata 17 statistical software (StataCorp LP) and R 4.0.5 were used to perform all analyses. A *P*-value ≤0.05 was considered statistically significant. This study follows the STROBE reporting guidelines for cohort studies.[32]

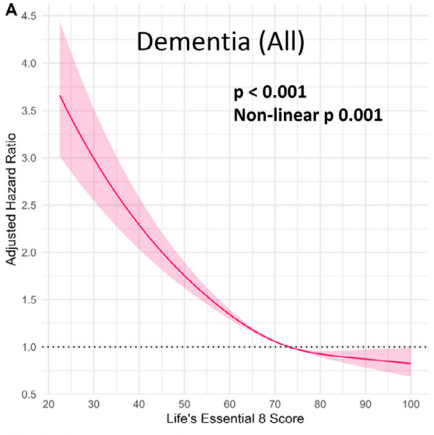
TABLE 1. General cohort characteristics at baseline of participants included by quartiles of the LE8 score

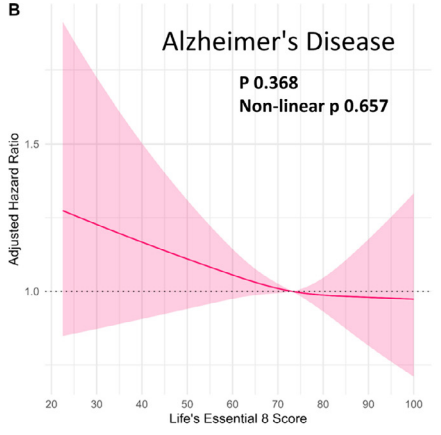
	Total	First quartile (Least healthy)	Second quartile	Third quartile	Fourth quartile (Healthiest)
n, (%)	259,718 (100)	68,411 (26.3)	63,878 (24.6)	64,029 (24.7)	63,40 (24.4)
Baseline age (years), mean (SD)	56.3 (8.1)	58.0 (7.7)	57.3 (8.0)	56.1 (8.2)	53.9 (8.2)
Sex, n (%)					
Women	135,081 (52.0)	25,878 (37.8)	30,126 (47.2)	35,329 (55.2)	43,748 (69.0)
Men	124,637 (48.0)	42,533 (62.2)	33,752 (52.8)	28,700 (44.8)	19,652 (31.0)
Deprivation index, mean (SD)	−1.44 (2.99)	−0.88 (3.23)	−1.48 (2.96)	−1.69 (2.85)	−1.77 (2.79)
Ethnicity, n (%)					
White	247,349 (95.2)	64,703 (94.6)	60,791 (95.2)	61,095 (95.4)	60,760 (96.8)
Asians	5571 (2.2)	1418 (2.0)	1382 (2.1)	1387 (2.2)	1384 (2.2)
Others	6789 (2.6)	2290 (3.4)	1705 (2.7)	1547 (2.4)	1256 (2.0)
Morbidity count, n (%)					
0	95,127 (36.6)	15,225 (22.3)	21,177 (33.2)	26,417 (41.3)	32,308 (51.0)
≥1	164,591 (63.4)	53,186 (77.7)	42,701 (66.8)	37,612 (58.7)	31,092 (49.0)
Alcohol frequency intake, n (%)					
Daily or almost daily	55,427 (21.3)	16,953 (24.8)	14,790 (23.2)	13,227 (20.7)	10,457 (16.5)
3-4 times a week	63,236 (24.4)	14,550 (21.3)	15,872 (24.8)	16,415 (25.6)	16,399 (25.9)
Once or twice a week	67,605 (26.0)	16,278 (23.8)	16,046 (25.1)	17,073 (26.7)	18,208 (28.7)
1-3 times a month	28,034 (10.8)	7124 (10.4)	6518 (10.2)	6930 (10.8)	7462 (11.8)
Special occasions only	26,970 (10.4)	8025 (11.7)	6322 (9.9)	6129 (9.6)	6494 (10.2)
Never	18,446 (7.1)	5481 (8.0)	4330 (6.8)	4255 (6.6)	4380 (6.9)
Sedentary time (h/day), mean (SD)	5.0 (2.2)	5.7 (2.5)	5.2 (2.2)	4.8 (2.1)	4.4 (1.9)
Reaction time (seconds), (log scale)	6.6 (0.3)	5.7 (2.5)	6.6 (0.3)	6.6 (0.2)	6.5 (0.2)

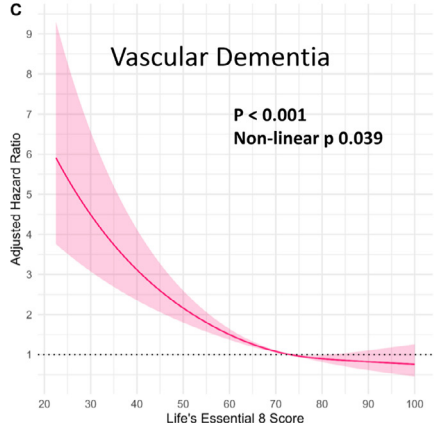
n, number; SD, standard deviation; h/d, hours per day.

Results

After removing participants with missing data or without data available for the LE8 score, 259,718 participants were included in the analyses (Supplementary Fig 1). The participant characteristics by LE8 quartiles are shown in Table 1. In summary, participants with a healthier score were younger, more likely to be women, less deprived and spent fewer hours in sedentary activities. In contrast, those in the least healthy category had a higher prevalence of multimorbidity (77.7%) and drank more alcohol (Table 1).







Endpoint	LE8 Score	Adjusted Hazard Ratio (95% CI)
Dementia (All)	40	2.29 (2.02, 2.58)
	60	1.31 (1.27, 1.36)
	80	0.92 (0.89, 0.95)
Alzheimer's Disease	40	1.16 (0.90, 1.50)
	60	1.05 (0.97, 1.13)
	80	0.98 (0.93, 1.04)
Vascular Dementia	40	3.11 (2.35, 4.11)
	60	1.48 (1.36, 1.62)
	80	0.89 (0.79, 0.99)

FIG. Nonlinear association between the continuous Life's Essential 8 score and dementia incidence. (A) represents all-cause dementia, (B). Alzheimer's disease, and (C). Vascular dementia. All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up. Analyses were adjusted by age, sex, deprivation, ethnicity, morbidity count, alcohol intake, log reaction time and total sedentary time.

Over a median follow-up of 10.6 (interquartile range: 9.8-11.2) years, 4958 (1.9%) participants were diagnosed with any dementia. Of these diagnoses, 1476 (29.8%) were AD and 764 (15.4%) were vascular dementia. Figure shows the nonlinear associations between the LE8 score and dementia outcomes. Higher LE8 scores were associated with lower risk of all-cause and vascular dementia in an exponential decay pattern, highlighting that better LE8 scores were associated with a lower risk of dementia. Greater risk reductions were evident in the lowest LE8 region. The lowest risk was observed in individuals with a score of 80 or higher, those who had 0.89 (0.79; 0.99) and 0.92 (0.89-0.95) lower risk of vascular and all-cause dementia, respectively. These 2 outcomes also had nonlinear associations (*P* nonlinear: <0.001 and 0.039 for all-cause and vascular dementia, respectively). There was no evidence that LE8 score was associated with AD (Fig).

Associations between LE8 quartiles and the outcomes of interest are shown in Table 2. In the unadjusted model (model 0), compared with individuals in the healthiest quartile, those who were in quartile 2 or in the least healthy (quartile 1) had a higher risk of all-cause dementia (HR $_{\text{quartile 2}}$: 2.11 [1.92-2.31]; HR $_{\text{least healthy quartile}}$: 3.09 [2.83-3.34]), AD (HR $_{\text{quartile 2}}$: 1.80 [1.54-2.10]; HR $_{\text{least healthy quartile}}$: 1.88 [1.61-2.19]) and vascular dementia (HR $_{\text{quartile 2}}$: 2.77 [2.13-3.61]; HR $_{\text{least healthy quartile}}$: 4.40 [3.43-5.64]). In the other 2 models, there was a dose-response relationship for all outcomes except AD. For instance, in the minimally adjusted model (model 1), and compared to those in the healthiest quartile (quartile 4), those in the least healthy had 1.68-times (1.54-1.84) higher risk of all-cause dementia. When the analysis was further adjusted for lifestyle factors (model 2), associations were attenuated but remained (HR $_{\text{quartile 2}}$: 1.23 [1.12-1.35]; HR $_{\text{least healthy quartile}}$: 1.50 [1.37-1.65]). The strongest association was observed for the risk of vascular dementia among individuals in the lowest LE8 quartile who had 1.86-times (1.44-2.42) higher risk than people in the highest quartile (model 2, Table 2). Similar associations were identified in the subgroup analyses stratified by sociodemographic status, where the magnitude of the association was stronger in people younger than 60 years, men, and more deprived participants. Detailed results can be found in Supplementary Tables 2-4.

Assuming causality, 22.8% and 28.7% of all-cause and vascular dementia incidence may be attributable to the lifestyle and health factors measured by the LE8 score, respectively (Table 3). Our scenario analysis showed that both a general and a targeted intervention would greatly impact vascular dementia (followed by all-cause dementia). A general intervention that increased the score by 2.5 points across the whole

TABLE 2. Associations between the life's essential 8 score and dementia incidence

	Total n	Events	Quartile 4 (healthiest)	Quartile 3		Quartile 2		Quartile 1 (least healthy)		Trend	
			HR (95% CI)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause dementia											
Model 0	259,718	4958	1.00 (Ref.)	1.37 (1.24; 1.52)	<0.001	2.11 (1.92; 2.31)	<0.001	3.09 (2.83, 3.34)	<0.001	1.47 (1.43; 1.51)	<0.001
Model 1	259,718	4958	1.00 (Ref.)	1.00 (0.90; 1.11)	0.971	1.31 (1.19; 1.44)	<0.001	1.68 (1.54; 1.84)	<0.001	1.22 (1.19; 1.26)	<0.001
Model 2	259,718	4958	1.00 (Ref.)	0.97 (0.87; 1.07)	0.514	1.23 (1.12; 1.35)	<0.001	1.50 (1.37; 1.65)	<0.001	1.18 (1.14; 2.32)	<0.001
Alzheimer's disease incidence											
Model 0	259,718	1476	1.00 (Ref.)	1.16 (0.97; 1.37)	0.096	1.80 (1.54; 2.10)	<0.001	1.88 (1.61; 2.19)	<0.001	1.25 (1.20; 1.31)	<0.001
Model 1	259,718	1476	1.00 (Ref.)	0.84 (0.70; 0.99)	0.039	1.11 (0.95; 1.30)	0.196	1.04 (0.89; 1.21)	0.645	1.04 (0.99; 1.10)	0.076
Model 2	259,718	1476	1.00 (Ref.)	0.82 (0.69; 0.98)	0.028	1.08 (0.92; 1.27)	0.332	0.98 (0.84; 1.16)	0.834	1.03 (0.98; 1.08)	0.304
Vascular dementia incidence											
Model 0	259,718	764	1.00 (Ref.)	1.68 (1.26; 2.24)	<0.001	2.77 (2.13; 3.61)	<0.001	4.40 (3.43; 5.64)	<0.001	1.63 (1.52; 1.75)	<0.001
Model 1	259,718	764	1.00 (Ref.)	1.18 (0.88; 1.57)	0.266	1.60 (1.23; 2.09)	0.001	2.18 (1.69; 2.81)	<0.001	1.32 (1.23; 1.42)	<0.001
Model 2	259,718	764	1.00 (Ref.)	1.12 (0.84; 1.49)	0.450	1.47 (1.12; 1.92)	0.005	1.86 (1.44; 2.42)	<0.001	1.25 (1.16; 1.35)	<0.001

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by the LE8 quartiles. Participants in the highest quartile were used as the reference group. All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up. Model 0, was unadjusted; model 1 was adjusted by age, sex, deprivation and ethnicity; model 2 as per model 1 but additionally by morbidity count, alcohol intake, log reaction time and total sedentary time.

TABLE 3. Population attributable fraction and potential impact fraction of the LE8

	Population attributable fraction % (95% CI)	Scenarios General intervention (increasing by 2.5 points the score in the whole population)	Targeted intervention (increasing by 10 points the score in individuals in the lowest quartile of the score)
All-cause dementia incidence	22.8 (22.4; 23.2)	4.01 (3.61; 4.41)	6.82 (6.62; 7.01)
Vascular dementia incidence	28.7 (27.9; 29.6)	5.52 (4.52; 6.50)	9.38 (8.87; 9.87)

Data were estimated using the analyses of Figure and Supplementary Figure 2.

population would have prevented 5.5% (4.52%-6.50%) of incident vascular dementia cases. In contrast, a targeted intervention that increased, by 10 points, the score among individuals in the lowest quartile (score ≤66.25 points) would have potentially prevented 9.38% (8.87%-9.87%) of cases (Table 3 and Supplementary Fig 2). This is due to the nonlinear relationship whereby the greatest risk reduction could be achieved among the least healthy.

Based on RAPs analyses, individuals in the least healthy LE8 quartile might develop all-cause dementia, on average, 2.45 years earlier than individuals in the healthiest quartile. Similar trends were observed for vascular dementia (3.00 years earlier) (Table 4).

Lastly, Supplementary Table 5 shows the associations and predictions risk between the standardised LE8 and LS7 scores. Overall, there was a lower risk of all-cause and vascular dementia per 1-unit increment in the standardised LE8 and LS7 scores. However, the decreased risk was greater using the LE8 score (HR $_{\text{all-cause dementia}}$: 0.80 [0.78-0.82] and HR $_{\text{vascular dementia}}$: 0.73 [0.67-0.78]). Interestingly, while both LE7 and LE8 had very strong discriminatory performance, particularly for vascular

TABLE 4. Rate advancement periods analyses

	Quartile 4 (healthiest)	Quartile 3	Quartile 2	Quartile 1 (least healthy)
All-cause dementia incidence	0 (Ref.)	-0.18 (−0.84; 0.39)	1.25 (0.68; 1.72)	2.45 (1.90; 2.88)
Vascular dementia incidence	0 (Ref.)	0.55 (−0.91; 1.79)	1.86 (0.59; 2.92)	3.00 (1.91; 3.96)

All analyses were performed excluding participants with all-cause dementia and neurological disorders at baseline. Analyses were adjusted by age, sex, deprivation, ethnicity, morbidity count, alcohol intake, log reaction time, and total sedentary time.

dementia (C-index = 0.84), no evidence that LE8 was better than LE7 was found.

Discussion

Using the LE8 score, we identified that individuals with higher AHA LE8 scores had a lower incident dementia risk, especially vascular dementia. Although the LE8 score was initially created to assess and promote better cardiovascular health, the score is a simple tool that can be implemented to determine overall individual health beyond predicting CVD risk, as noted in our study. Our findings suggested that an overall healthy lifestyle was not associated with AD risk, which could indicate the differential aetiology between AD[33] and the other dementia types.

Our modelled scenarios showed that targeted interventions for those with the least healthy lifestyle could have a more significant impact than mass interventions at the population level. For instance, the PIF analyses highlighted that almost one-tenth of the cases of vascular dementia could be prevented by the least healthy individuals improving their LE8 score by just 10 points; for example, by increasing either their sleep duration in 1 hour per day or their physical activity performed during the week.[34]

Our RAPs analyses highlighted that following healthier lifestyle patterns could delay the effect of ageing on cognitive decline. For instance, the healthiest individuals had the same risk of vascular and all-cause dementia as unhealthy individuals who were 2.4-3.0 years younger. Our subgroup analyses also found that associations were stronger in people younger than 60. The latter highlights the importance of early prevention and suggests that the onset of subclinical dementia could start earlier in life. Therefore, preventing or delaying the onset of dementia could significantly reduce the economic burden, which was estimated to be £25 billion per year in the UK in 2021 and is projected to rise to £47 billion by 2050.[35]

Our results are not the first to show the potential of a healthy lifestyle in dementia prevention. Previous studies identified that higher adherence to the former AHA guidelines, based on the LS7 score, was associated with lower dementia risk.[5-12] In particular, a recent systematic review and dose-response meta-analysis—that included 311,654 participants from 14 longitudinal studies—highlighted that maintaining optimal cardiovascular health would reduce the late-life dementia risk but not the global cognitive decline rate.[7] One study previously investigated the association between the LE8 score and dementia.[15] Including 135,199 UK Biobank participants, Wang et al.[15] investigated the association of

LE8 score with life expectancy free of a composite outcome of 4 major noncommunicable diseases (CVD, diabetes, cancer and dementia) by sex. Their study found that a higher LE8 score (≥80 points) was significantly associated with longer life expectancy free of major chronic disease in both sexes. For instance, men and women with higher scores lived 6.9 (6.1-7.7) and 9.4 (8.5-10.2) years longer without any of the 4 diseases compared with their counterparts with lower scores. Since they only investigated dementia as a part of a composite outcome, it was not possible to determine if the improved outcomes were explained entirely by other conditions, such as the known association with cardiovascular disease. Also, their study did not include landmark analysis, nonlinear associations or PAF/PIF analyses as were performed in this study. Our study, therefore, meaningfully extends the evidence that the population burden of vascular and all-cause dementia may be reduced by following the LE8 recommendations and that intervention targeted at the least healthy individuals could produce the greatest benefits.

Strengths and Limitations

Using UK Biobank, we assessed our research question using a large, prospective, and well-characterised general population cohort of middle-aged and older adults with data available on a wide range of potential confounders. We were also able to test if the associations were linear or not and whether they were consistent across subgroups. Moreover, we identified how many years earlier individuals in the least healthy LE8 category would develop the outcomes investigated. Unfortunately, this study is not exempt from limitations. Firstly, UK Biobank is not representative of the UK population in terms of lifestyle and prevalent diseases. Therefore, whilst risk estimates can be generalised,[36] summary statistics such as prevalence and incidence cannot be generalised to the UK population.[27] Secondly, despite a comprehensive list of confounding factors in the analyses, this study cannot rule out unmeasured or residual confounding as with other observational studies. Thirdly, diet and alcohol intake were self-reported at baseline. Consequently, recall and misclassification bias is possible, and the consumption might have changed over follow-up. We tried to limit potential reverse causation by using a 2-year landmark analysis. Fourthly, we used a modified diet measurement, different from the original AHA LE8 score, since not all the diet information was available in the UK Biobank study. However, we used a similar or proxy variable to mitigate these differences. Fifthly, our primary analyses used data from hospital admission and death records. Thus, milder cases of

dementia not requiring hospitalisation and undiagnosed cases will not have been included; leading to incomplete ascertainment. Sixthly, PAF and PIF calculations assume causality, which the findings of this study cannot confirm. Also, they cannot be directly extrapolated to the general population, where the prevalence of risk factors may differ. An intervention study including both clinical- and cost-effectiveness analysis is needed to compare the different approaches to intervention suggested in this study. Finally, the mean LE8 score assumes equal weighting for each health metric which is counter-intuitive given that different risk factors have differential weightings for different outcomes.

In conclusion, individuals with higher LE8 scores had lower risk of all-cause and vascular dementia. This was especially true in people younger than 60 years. Because of the nonlinear associations, interventions targeted at the least healthy individuals might produce greater population-level benefit, with meaningful impact achievable from relatively small increases, such as increasing sleep duration or physical activity.

Author Contributions

F.P-R, S.D and F.K.H contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. F.P-R performed the literature search. F.P-R performed the analyses with support from S.D and F.K.H. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission. F.P.R and S.D contributed equally to this work and are joint first authors. F.K.H is the guarantor.

Data Statement

All UK Biobank information is available online on the webpage www.ukbiobank. Data access are available through applications. This research was conducted using the application number 7155.

Declaration of Competing Interest

N.S declares consulting fees and/or speaker honoraria from Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi; and grant support paid to his university from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics. None of these disclosures are directly related to the study,

nor its conception, analyses or interpretation. The other authors declare none conflict of interest.

Acknowledgments

The authors are grateful to UK Biobank participants. This research has been conducted using the UK Biobank resource under application number 7155.

Funding

UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government and the British Heart Foundation. All authors had final responsibility for submission for publication.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2023.101934.

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