Can active life mitigate the impact of diabetes on dementia and brain aging?

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Introduction: We investigated whether lifelong exposure to stimulating activities (active life, AL) mitigates diabetes-associated dementia risk and brain aging.

Methods: In the Swedish National Study on Aging and Care-Kungsholmen, 2286 dementia-free older adults (407 with MRI volumetric measures) were followed over 12 years to detect incident dementia. AL index (low, moderate, high) combined education, work complexity, leisure activities, and social network.

Results: Participants with diabetes and low AL had higher dementia risk (hazard ratio [HR] = 2.36, 95% confidence interval [CI] 1.45–3.87) than patients who were diabetes-free with moderate-to-high AL (reference). Dementia risk in participants with diabetes and moderate-to-high AL did not differ from the reference. People with diabetes and low AL had the smallest brain volume, but those with diabetes and moderate-to-high AL exhibited total brain and gray-matter volumes that were similar to those of diabetes-free participants. AL did not modify the diabetes microvascular lesions association.

Discussion: AL could mitigate the deleterious impact of diabetes on dementia, potentially by limiting the loss of brain tissue volume.

Keywords: active life, brain volume, dementia, magnetic resonance imaging, resilience, type 2 diabetes, vascular brain lesions
represent the key to delaying the onset or slowing the progression of dementia symptoms.\textsuperscript{5–8} Recently, it has emerged that high late-life levels of engagement in mentally, socially, and physically stimulating activities as well as a rich social network mitigate the risk of dementia, even in people at high risk of dementia, such as those with pre-existing metabolic disorders (ie, diabetes).\textsuperscript{9} However, it is well-recognized that dementia develops from the synergistic interactions between environmental, genetic, cardio-metabolic, and psychosocial factors, not only in late-life, but throughout the entire life course.\textsuperscript{10} Therefore, it remains unclear whether an active life (hereafter, AL) characterized by lifelong exposure to cognitively, physically, and socially stimulating activities could buffer the risk of dementia associated with diabetes.

Neuroimaging studies show that diabetes contributes to brain alterations before the clinical onset of cognitive impairment and dementia.\textsuperscript{11} Diabetes has been associated with brain atrophy and accumulating vascular brain damages.\textsuperscript{11,12} However, whether AL can protect against diabetes-associated brain alterations is unknown. To further understand the possible protective effects of AL on diabetes-associated dementia, it is important to examine the interplay between AL and vascular brain damage as well as non-vascular brain damage.

In this study, we aimed to verify the hypothesis that exposure to cognitively, physically, and socially stimulating activities at different life stages can mitigate the risk of dementia and brain alterations associated with diabetes.

2 METHODS

2.1 Study design and participants

The participants were derived from the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), an ongoing longitudinal population-based study.\textsuperscript{13} At baseline (March 2001–June 2004), SNAC-K included 3363 people, aged ≥60 years, living at home or in institutions in Kungsholmen (central Stockholm, Sweden). The sample was stratified into 11 age-cohorts. The younger age-cohorts (60, 66, and 72) were followed-up every sixth year and the older age-cohorts (≥78 years) every third year, because of the more rapid changes in health and higher attrition in older age groups. Follow-up data were available until June 2016 for the current study. We excluded people with dementia (n = 310), schizophrenia or developmental disorders (n = 16), and type 1 diabetes (n = 8) at baseline. We further excluded 675 individuals who declined to participate in any follow-up and 68 with missing information on glycated hemoglobin (HbA1c). Thus, 2286 participants were included in the current study (Figure 1). During the 12-year follow-up, 673 people (29.4%) died and 349 (15.3%) were lost to follow-up (participation rate = 84.7%).

During baseline, a subsample of 555 non-institutionalized participants free of disability and dementia underwent structural brain magnetic resonance imaging (MRI) examination. Of these, 148 with neurological/neuropsychiatric conditions or sub-optimal MRI quality data were excluded, leaving 407 retained in the MRI analyses.

HIGHLIGHTS

\begin{itemize}
\item The role of active life (AL) in diabetes-related dementia and brain aging is unclear.
\item High AL decreases the diabetes-associated risk of dementia by 30%.
\item AL could preserve brain volume, thereby overriding diabetes-associated vascular brain damage.
\item AL may be a key dementia prevention strategy in high-risk people with diabetes.
\end{itemize}

The ethical committee at Karolinska Institutet and the regional ethical review board in Stockholm approved all parts of SNAC-K, including linkage with registries. All participants or their next-of-kin (in case of cognitively impaired participants) provided written informed consent.

2.2 Data collection

In SNAC-K, trained staff used standard protocols (available at http://www.snac.org) to collect the data.

Smoking (never vs. current/former) and alcohol consumption (no/occasional vs. light-to-heavy drinking) were dichotomized. Body mass index (BMI) was categorized into underweight (<20 kg/m\textsuperscript{2}), normal weight (<25 kg/m\textsuperscript{2}), overweight (>25–29.97 kg/m\textsuperscript{2}), or
obese (≥30 kg/m²). Global cognitive function was assessed with the Mini-Mental State Examination (MMSE). Blood pressure was measured twice at a 5-minute interval from the left arm with the participant in a sitting position, and a two-measurement average was used.

Diagnoses of medical conditions were identified according to the International Classification of Diseases, Tenth Revision (ICD-10) based on the physician’s examination, self-report, medication use, or information from the Swedish National Patient Register (NPR), which covers all inpatient and outpatient care in Sweden. Medical conditions included hypertension (blood pressure ≥140/90 mm Hg), heart disease (atrial fibrillation, ischemic heart disease, and heart failure), and cerebrovascular diseases (Appendix A). Depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Apolipoprotein E (APOE) allelic status was dichotomized into any ε4 carriers versus non-carriers. Finally, participants’ vital status was determined using death certificates from the Swedish Cause of Death Registry and medical records at hospital discharge.

**2.3 Diabetes status**

Diabetes and prediabetes, assessed at baseline, were ascertained using standard diagnostic criteria from the American Diabetes Association. Diabetes was identified based on self-reported medical history, glucose-lowering medication use, medical records from the NPR (ICD-10 code E11). In prediabetes, the HbA1c ranged between 5.7 and 6.4%, whereas in diabetes, the HbA1c was 6.5% or above.

**2.4 Active life (AL) indicator**

AL includes four stimulating experiences, at different life stages, that were derived from the following questions at baseline:

1. Years of formal education (early life).
2. Five longest-held occupations ranked according to substantive work complexity, which refers to how much cognitive engagement is needed to perform job tasks (adulthood). The substantive work complexity rating has been described in detail in a previous report. Briefly, the US Dictionary of Occupational Titles was used to derive the ratings, and afterwards matched with analogous Swedish occupations by two independent raters.
3. Late-life engagement in 26 activities categorized into mental, social, and physical activities. A leisure activity index was created by summing the scores for the three types of activities (range 0–6). For a detailed description see Appendix B.
4. Late-life social network, encompassing the size of the network and the extent of received social support. Briefly, two separate indices were created for network size (marital status, living arrangements,
number of children, and frequency of contacts) and social support (satisfaction with contacts, perceived support, and sense of affinity and belonging to various groups). These two standardized indices were averaged to generate an overall social network index.

Using structural equation modeling, a continuous latent indicator of AL was generated from the abovementioned measures of lifelong cognitively, physically, and socially stimulating activities. This indicator was divided into tertiles, designating low, moderate, and high AL. For a detailed description of the operationalization of AL in SNAC-K, see Dekhtyar et al.18

2.5 | Dementia

Dementia was diagnosed according to the DSM-IV-TR criteria, using a validated three-step procedure. Two independent physicians made preliminary clinical diagnoses by reviewing the participant’s neurological, cognitive, and physical status. In case of disagreement an external neurologist made the final diagnosis.9 Physicians also identified dementia cases among deceased participants by consulting death certificates and medical records, when available.

2.6 | Brain MRI volumetric measures

The baseline MRI protocol and details of imaging processing are described in Appendix C. In brief, T1-weighted images were segmented into gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid volume (CSFV) using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) in Matlab 10.12 Total brain tissue volume (TBV) was calculated by adding GMV and WMV. Total intracranial volume (TIV) was obtained by summing GMV, WMV, and CSFV. FreeSurfer automated segmentation was used to extract hippocampal volume (HV).20 A neuroimaging expert (G.K.) visually inspected all the segmentations and manually drew white-matter hyperintensity volumes (WMHVs) on fluid-attenuated inversion recovery (FLAIR) images.21 In data analyses, we used MRI measures adjusted by TIV.12,22

2.7 | Statistical analysis

Incidence rates (IRs) of dementia per 1000 person-years and 95% confidence intervals (CIs) were estimated across diabetes status (diabetes, prediabetes, and diabetes-free) and AL status (low, moderate, and high). To assess the associations of diabetes status and the AL indicator with dementia, we used separate Cox proportional hazards models, estimating hazard ratios (HRs) and 95% CIs of dementia. No violation of the proportional hazard assumption was observed using the Schoenfeld residuals test. Follow-up time was estimated as the time from study entry until dementia, death, or the last examination.

We investigated whether AL mitigated the diabetes-associated dementia risk. First, multiplicative and additive interactions between diabetes and AL in predicting dementia risk were tested, by estimating the relative excess risk due to interaction (RERI, additive) and incorporating the cross-product between diabetes and AL (multiplicative) in Cox regression models.23 Second, we created a categorical variable by combining diabetes (no vs. yes) with AL (low vs. moderate-to-high) to test for effect modification.23 We obtained four groups: (1) diabetes-free with moderate-to-high AL, (2) diabetes-free with low AL, (3) diabetes with moderate-to-high AL, and (4) diabetes with low AL. To assess a possible effect modification of AL on diabetes-associated dementia risk, the categorical variable designating the combinations of diabetes and AL was entered as the exposure in the models. The reference group in all analyses was “diabetes-free with moderate-to-high AL.”

In the MRI subsample, we explored the baseline associations between AL and brain volumetric measures. Linear regressions were used to estimate the mean differences ($\beta$ coefficients) and 95% CIs in brain volumes for each group of the categorical variable relative to “diabetes-free with moderate-to-high AL.”

Age, sex, smoking, BMI, hypertension, heart diseases, and cerebrovascular diseases (CVDs), depression, and APOE ε4 status were considered as potential confounders and adjusted for in the analyses.

Supplementary analyses included sensitivity analysis to address possible reverse causation related to prodromal dementia, multiple imputations for missing values on the covariates, and further adjustment for possible confounders (Appendix D). All analyses were performed using Stata SE, version 16.0 (StataCorp LP., College Station, Texas, USA).

3 | RESULTS

3.1 | Characteristics of study participants

Table 1 lists the characteristics of the study population according to diabetes status. At baseline, there were 781 individuals (34.2%) with prediabetes and 189 (8.3%) with diabetes. Participants with diabetes were older, more likely to be male, had lower education, and were less engaged in leisure activities than diabetes-free participants. They also had more vascular risk factors (VRFs) and CVDs (Supplementary Table 1).

In the MRI subsample, 123 (30.2%) had prediabetes and 28 (6.9%) had diabetes. Participants with diabetes were older and more likely to have CVDs. No differences were observed across diabetes status in relation to AL, VRFs, depression, or APOE ε4.

3.2 | AL and diabetes-associated dementia risk

During follow-up (median = 11.3 [interquartile range, 5.9–11.7] years), 361 people (15.8%) developed dementia (IR = 16.3 cases per 1000 person-years; 95% CI 14.7–18.1). The IRs of dementia by diabetes status and AL per 1000 person-years during 12-years follow-up in the SNAC-K dementia-free cohort are displayed in Table 2.
TABLE 1  Baseline characteristics of the study population by diabetes status (n = 2286)

| Characteristics          | Diabetes-free n = 1316 | Prediabetes n = 781 | Diabetes n = 189 | P  |
|--------------------------|------------------------|---------------------|------------------|----|
| Age cohorts, years       | 71.1 ± 9.77            | 77.5 ± 10.2         | 74.2 ± 9.6       | <.001 |
| 60 and 66                | 674 (51.2)             | 283 (36.2)          | 68 (33.9)        | <.001 |
| 72 and 78                | 373 (28.3)             | 251 (32.1)          | 68 (36.0)        |       |
| 81, 84, and 87           | 197 (15.0)             | 175 (22.4)          | 41 (21.7)        |       |
| 90+                      | 72 (5.5)               | 72 (9.2)            | 16 (8.5)         |       |
| Female                   | 838 (63.7)             | 528 (67.6)          | 97 (51.3)        | <.001 |
| Any APOE ɛ4              | 383 (29.9)             | 224 (29.4)          | 40 (22.2)        | .103  |
| MMSE score               | 29.0 ± 1.3             | 28.8 ± 1.4          | 28.6 ± 1.5       | <.001 |
| Early life               |                        |                     |                  |      |
| Education, years         | 12.9 ± 5.0             | 11.7 ± 3.8          | 11.5 ± 4.0       | <.001 |
| Elementary               | 150 (11.4)             | 125 (16.0)          | 35 (18.5)        | <.001 |
| Professional schools     | 531 (40.4)             | 353 (45.2)          | 85 (45.0)        |       |
| High school              | 141 (10.7)             | 77 (9.9)            | 24 (12.7)        |       |
| University               | 492 (37.4)             | 226 (28.9)          | 45 (23.8)        |       |
| Adulthood                |                        |                     |                  |      |
| Work complexity          | 5.2 ± 1.8              | 4.7 ± 1.8           | 4.9 ± 1.9        | <.001 |
| Late-life                |                        |                     |                  |      |
| Leisure activities index | 2.6 ± 1.5              | 2.4 ± 1.5           | 2.3 ± 1.5        | <.001 |
| Social network index     | 0.11 ± 0.5             | 0.06 ± 0.5          | 0.04 ± 0.6       | .020  |
| Active life              |                        |                     |                  |      |
| Low                      | 342 (26.1)             | 260 (33.6)          | 66 (35.5)        | <.001 |
| Moderate                 | 429 (32.8)             | 263 (34.0)          | 70 (37.6)        |       |
| High                     | 539 (41.2)             | 251 (32.4)          | 50 (26.9)        |       |

Data are presented as means ± standard deviations or number (proportion %). Proportions were compared with χ² test and means with one-way ANOVA. Abbreviations: APOE ɛ4, apolipoprotein ɛ4 allele; MMSE, mini-mental state exam.

Missing data: APOE ɛ4 = 63, MMSE = 99, Education = 2, Work complexity = 18, Leisure activities index = 266, Social network index = 111, Active life = 16. Diabetes was identified for participants with medical history/records of diabetes, glucose-lowering medication use, or HbA1c ≥ 6.5%. Prediabetes was defined as HbA1c of ≥ 5.7–6.4% in participants without diabetes. The diabetes-free group included participants without diabetes and HbA1c of < 5.7% indicating normoglycemia.

Pairwise means comparison using the Bonferroni correction: P < .05 (reference group = baseline participants who were diabetes-free).

Multi-adjusted Cox regression models showed that people with diabetes had a 44% higher dementia risk than diabetes-free participants. Conversely, moderate and high AL (middle and top tertiles) were associated with a decreased dementia risk. The trend was statistically significant (P < .001), suggesting that the higher the AL score the lower the dementia risk. In subsequent analyses, we merged the high and middle tertiles of AL into a single category of “moderate-to-high.”

3.3  The joint exposure to diabetes and AL in relation to dementia

We assessed whether AL mitigated diabetes-associated dementia risk. We found no statistically significant multiplicative (HR for cross-product = 1.05 [95% CI 0.52–2.14]) or additive (RERI = 0.11, P = .770) interactions between diabetes and AL in relation to dementia. Next, we examined whether AL modified the effect of diabetes on dementia by incorporating the categorical variable combining diabetes and AL into multi-adjusted Cox regression models (Table 3).

People with diabetes and low AL had a 2.4-fold higher risk of dementia than diabetes-free with moderate-to-high AL (95% CI 1.45–3.87). However, dementia risk did not differ between those with diabetes but moderate-to-high AL and the reference group (diabetes-free with moderate-to-high AL). Within people with diabetes, moderate-to-high AL was associated with a 28% reduced risk of dementia (risk difference in comparison to low AL = 0.72 [95% CI 0.11–1.33]).

3.4  The joint exposure to diabetes and AL in relation to brain volumes

Finally, we tested whether AL modified the association between diabetes status and brain abnormalities using separate age- and
TABLE 2  Incidence rates (IR) per 1000 person-years and hazard ratios (HRs) of dementia over 12-year follow-up from two separate Cox regression models for diabetes status or active life (SNAC-K dementia-free cohort)

| Diabetes status | No. events/ person-year | IR (95% CI) | Cox regression models |
|-----------------|--------------------------|-------------|-----------------------|
|                 |                          |             | HR (95% CI)           | HR (95% CI)          |
| Diabetes-free   | 180/13,060               | 13.8 (11.9–16.0) | Reference             | Reference            |
| Prediabetes     | 137/7389                 | 18.5 (15.7–21.9) | 0.98 (0.78–1.23)      | 0.95 (0.75–1.21)     |
| Diabetes        | 44/1689                  | 26.0 (19.4–35.0) | 1.40 (1.00–1.94)      | 1.44 (1.00–2.05)     |

Active life

|                | No. events/ person-year | IR (95% CI) | Cox regression models |
|----------------|--------------------------|-------------|-----------------------|
|                |                          |             | HR (95% CI)           | HR (95% CI)          |
| Low            | 183/5619                 | 32.6 (28.2–37.6) | Reference             | Reference            |
| Moderate       | 113/7407                 | 12.7 (12.7–18.3) | 0.70 (0.55–0.89)      | 0.70 (0.54–0.91)     |
| High           | 55/9009                  | 6.11 (4.69–7.95) | 0.40 (0.29–0.54)      | 0.46 (0.33–0.64)     |

P-value for trend 0.64 (0.56–0.75) 0.69 (0.59–0.80)

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

a Basic-adjusted Cox regression for baseline age, sex, and education (when diabetes was the exposure).

b Multi-adjusted Cox regression for baseline age, sex, education (only when diabetes was the exposure), smoking, BMI, hypertension, heart diseases, cerebrovascular diseases, depression, and APOE ε4.

c Diabetes was identified for participants with medical history/records of diabetes, glucose-lowering medication use, or HbA1c ≥6.5%. Prediabetes was defined as HbA1c of ≥5.7–6.5% in participants without diabetes. The diabetes-free group included participants without diabetes and HbA1c >5.7% indicating normoglycemia.

TABLE 3  Hazard ratios (HRs) and 95% CIs of the effect of diabetes plus active life on dementia (SNAC-K dementia-free cohort)

| Joint effect | n   | Basic-adjusteda HR (95% CI) | Multi-adjustedb HR (95% CI) |
|--------------|-----|-----------------------------|------------------------------|
| Active life  | Diabetes |                           |                              |
| Moderate-to-high | No   | 976 | Reference | Reference |
| Low          | No   | 394 | 1.63 (1.20–2.22) | 1.73 (1.24–2.40) |
| Moderate-to-high | Yes | 128 | 1.28 (0.78–2.09) | 1.44 (0.85–2.44) |
| Low          | Yes  | 100 | 2.62 (1.66–4.15) | 2.36 (1.45–3.87) |

Abbreviations: CI, confidence interval; HR, hazard ratio.
a Cox regression model for baseline age and sex.
b Cox regression models for baseline age, sex, smoking, body mass index, hypertension, heart diseases, cerebrovascular diseases, depression, and APOE ε4.

sex-adjusted linear regression models (Figure 2). Participants with diabetes and low AL had the smallest TBV ($β = -47.1$ [95% CI $-89.7$ to $-4.51$], $P = .030$), particularly in the GMV. TBV and GMV in participants with diabetes and moderate-to-high AL did not significantly deviate from the mean volumes of the diabetes-free with moderate-to-high AL group. Similar trends were observed for HV (although not statistically significant), but not for WMV and WMHV (Figure 2 and Supplementary Table 2).

Results from supplementary analyses are reported in Appendix D.

4 | DISCUSSION

In this large-scale population-based cohort study with long-term follow-up, moderate-to-high AL appeared to attenuate diabetes-associated dementia risk by nearly 30%. Furthermore, people with diabetes and low AL had the smallest brain volumes, but those with diabetes and moderate-to-high AL exhibited volumes similar to those of diabetes-free individuals with moderate-to-high AL. We found no interaction or effect modification between AL and diabetes in relation to WMHV, a marker of vascular brain damage.24 Altogether, these results suggest that AL mitigates the detrimental effect of diabetes on dementia, potentially by limiting the loss of brain tissue volume.

Consistent with the literature, we found that diabetes was associated with near doubling of dementia risk.25 In a recent study, we reported that having a socially integrated and active lifestyle in late-life mitigated dementia risk in older adults with diabetes.9 In this study, we took a further step, showing that high AL, achieved through engagement in cognitively, physically, and socially stimulating experiences, from early to late life, was linked with reduced diabetes-associated risk of dementia. This finding suggests that compensatory mechanisms that enable cognitive preservation, are present and are effective not only...
FIGURE 2  Joint exposure to diabetes plus active life in relation to brain volumes
Abbreviations: AL, active life; WMHs, white-matter hyperintensities.
The figure shows the mean differences (β-coefficients) and 95% confidence intervals in the volumes (mL) of total brain (A), gray matter (B), white matter (C), and WMHs (D) across four groups were generated by combining diabetes (no, yes) and AL (low, moderate-to-high). Diabetes was identified for participants with medical history/records of diabetes, glucose-lowering medication use, or HbA1c ≥ 6.5%. Prediabetes was defined as HbA1c of ≥ 5.7–6.5% in participants without diabetes. The diabetes-free group included participants without diabetes and HbA1c of < 5.7% indicating normoglycemia. All brain volumes were adjusted for total intracranial volume. Linear regression models were adjusted for age and sex.

*P ≤ .05

in healthy older adults,26,27 but also in those with diabetes, a major metabolic risk factor for dementia.

Furthermore, our study showed that among people with diabetes, moderate-to-high AL was associated with larger brain volume than low AL. This suggests that higher AL may mitigate the deleterious effect of diabetes on the brain, thereby preserving brain volume. Such a compensatory mechanism was not found in relation to vascular markers of pathology (WMHs). Regardless of the level of AL, people with diabetes had greater WMHV, likely reflecting more brain vascular damage. Diabetes affects the vascular system and accelerates atherosclerosis, leading to vascular brain abnormalities and neuroapoptosis.28,29 Previous studies have consistently shown associations between diabetes and brain atrophy.11,30 Although less consistently, studies have also shown associations between diabetes and a higher burden of small vessel disease (eg, WMHs),11,30–32 a major contributor to vascular cognitive impairment in aging.33

The mechanisms underlying the influences of AL on dementia are not fully understood. It has been hypothesized that lifelong engagement in cognitively, physically, and socially stimulating activities may provide resilience against dementia through neuroprotective (ie, restricting the development of primary neurodegenerative pathologies, such as amyloidoses, tauopathies, TDP-43 proteinopathies) and compensatory (ie, promoting preservation of cognitive function in the face of brain damage) mechanisms.27,34,35 This would enable the brain to either avoid the damage altogether, or to better cope with emerging neuropathology, preserving cognitive function and delaying dementia onset.34,36 On one hand, our finding of greater, thus preserved, gray matter volume in participants with moderate-to-high AL, tentatively supports the neuroprotective influence of AL. On the other hand, compensatory influences cannot be excluded, because greater availability of more intact gray matter in people with moderate-to-high AL may underpin the recruitment of alternative brain structures mobilized to restrict the spread of brain pathological damage (eg, from the accumulation of microvascular lesions).12,37,38

Based on our findings, it is plausible to hypothesize that neuroprotective and compensatory mechanisms are not separate entities, but rather they co-exist. Particularly, exposure to cognitively, physically, and socially stimulating activities may enhance brain plasticity, thus supplying greater brain reserve and preserving brain function (neuroprotection). Greater availability of brain reserve could, later in life,
overide the vascular brain damage associated with diabetes (compensation), preserving cognitive function. Future longitudinal clinical-pathological studies are needed to test this hypothesis, advancing our understanding of the mechanisms underlying the mitigating effects of AL in the diabetes-dementia association. In addition, it is important to understand whether there is a threshold level of pathological burden beyond which AL ceases to restrain neuropathological damage, and how this would affect cognitive progression.

Altogether, our results highlight that promoting cognitively, physically, and socially stimulating experiences over the entire lifespan could represent a novel non-pharmacological approach to prevent dementia. This is in line with emerging evidence showing that late-life multi-domain lifestyle interventions, simultaneously targeting various cognitive and lifestyle factors (eg, cognitive training, exercise, diet), can improve cognitive function in older individuals with elevated dementia risk.39 Furthermore, our results highlight the importance of interventions not only in late-life but also earlier, helping to achieve the largest dementia risk reduction.

Alongside resilience-related mechanisms of neuroprotection and compensation, AL may relate to diabetes-associated dementia through socioeconomic characteristics.35,40,41 For example, higher socioeconomic status could lead to more material resources (eg, better education and/or work characteristics), health behaviors (eg, adhering to treatment regimens, regular blood glucose monitoring, satisfactory foot care, screening for complications) in people with diabetes,42,43 or psychosocial factors. This may further help preserve brain integrity even in the face of diabetes, thereby reducing the dementia risk.

4.1 | Strengths and limitations

Strengths of this study include the longitudinal design, long follow-up time, and integration of structural neuroimaging and clinical data from different sources. Moreover, SNAC-K has reliable clinical dementia diagnoses that combine the validated three-step procedure with death certificates and medical records at hospital discharge for participants who died during follow-up. This allowed for identifying the cases of dementia among the deceased, thereby minimizing the influence of death on dementia incidence. By restricting the study sample to cognitively intact participants (sensitivity analysis), we also addressed possible reverse causation, in which people in the prodromal dementia phase could have disengaged from healthy lifestyles and socially stimulating environments; all findings remained similar.

Some limitations need to be pointed out. First, information about the four AL contributors (education, occupation, leisure activities, and social network) was self-reported. This could have led to misclassification of the exposure in people with cognitive impairment, underestimating the strength of the observed associations. To assess the extent of this, in sensitivity analyses, we restricted the sample to cognitively intact participants and the results remained similar. Moreover, the use of structural equation modeling allowed for the correction of unreliability in observed factors by attenuating measurement error.18 Second, diabetes status was determined using HbA1c, which reflects chronic hyperglycemia, but does not capture acute/fluuctuating glycemic levels.44 Therefore, a proportion of (pre)diabetes cases might have not been detected, leading to an underestimation of the observed associations. Moreover, we were unable to explore the role of insulin in the diabetes-AL-brain aging association, due to the lack of insulin data in SNAC-K. Considering the growing evidence on the role of insulin (eg, hyperinsulinemia and insulin-resistance) in the etiology of dementia and primary neuropathology,45 future studies including different markers of insulin homeostasis alongside glycemia are needed to explore the biological pathways underlying the diabetes-dementia association. Third, non-response during follow-up might have introduced selection bias. However, sensitivity analyses using multiple imputations yielded similar results. Fourth, participants taking anti-diabetic treatment may adjust their lifestyle as consequence of the therapeutic indications for diabetes. Therefore, the reduced dementia risk attributable to AL could be, in fact, driven by the effective treatment of diabetes—that is, normal glucose or normoglycemia (HbA1c <5.7%). However, about 80% of the diabetes cases in SNAC-K had elevated glycemic levels despite anti-diabetic medication use. We further found no differences in AL between participants on versus off anti-diabetic treatment (Supplementary Table 5).

4.2 | Conclusions

Our study provides the first evidence that cognitively, physically, and socially stimulating experiences throughout life can mitigate the deleterious effects of diabetes on dementia and the brain. Hence, despite the presence of a major risk factor for dementia (diabetes), having an active life could provide resilience (by enabling neuroprotection and compensation), likely buffering the cerebrovascular damage. These results suggest that high lifelong stimulation may represent an appropriate and effective means to prevent and delay dementia, especially in people with diabetes. Future interventions to reduce diabetes-associated dementia and brain damage need to incorporate aspects of AL. Finally, the extent of vascular and non-vascular neuropathology that an AL can mitigate requires further investigation.

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SUPPORTING INFORMATION

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