Participating in Mental, Social, and Physical Leisure Activities and Having a Rich Social Network Reduce the Incidence of Diabetes-Related Dementia in a Cohort of Swedish Older Adults

Anna Marseglia,[1] Hui-Xin Wang,[1,2] Debora Rizzuto,[1] Laura Fratiglioni,[1,3] and Weili Xu[1,4]

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OBJECTIVE

The effect of a healthy lifestyle on diabetes-related dementia remains unknown. We examined whether an active lifestyle and rich social network may counteract the increased risk of dementia in people with diabetes.

RESEARCH DESIGN AND METHODS

Dementia-free older adults from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) (*n* = 2,650) were followed up for 10 years. Diabetes was ascertained on the basis of medical history, medication use, medical records, or glycated hemoglobin (HbA_{1c}) ≥6.5% and prediabetes as HbA_{1c} between 5.7 and 6.5%. Dementia was diagnosed by specialists following standard criteria. An active lifestyle was defined as a moderate to high (vs. low) level of engagement in leisure activities or a rich social network (having moderate to rich [vs. poor] social connections and support). Hazard ratios (HRs) of dementia risk were derived from Cox regression models.

RESULTS

There were 246 incident dementia cases during follow-up. Those with diabetes (*n* = 243), but not those with prediabetes (*n* = 921), had greater risk of dementia (adjusted HR 2.0 [95% CI 1.4–2.9]) than diabetes-free participants. Participants with diabetes but low level of engagement in leisure activities (HR 4.2 [95% CI 2.2–8.2]) or a poor social network (HR 3.4 [95% CI 1.9–6.1]) had greater dementia risk than diabetes-free participants with moderate to high levels of leisure activity engagement or a moderate to rich social network. In participants with diabetes, an active lifestyle (high level of engagement in leisure activities or a rich social network) was associated with less of a raised risk (HR 1.9 [95% CI 1.1–3.4]).

CONCLUSIONS

An active and socially integrated lifestyle may significantly counteract the detrimental effect of diabetes on dementia risk.

[1]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden

[2]Stress Research Institute, Stockholm University, Stockholm, Sweden

[3]Stockholm Gerontology Research Center, Stockholm, Sweden

[4]Department of Epidemiology and Biostatistics, School of Public Health, Tianjin Medical University, Tianjin, China

Corresponding author: Anna Marseglia, anna.marseglia@ki.se, or Weili Xu, xuweili@tmu.edu.cn and weili.xu@ki.se

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Both type 2 diabetes (hereafter referred to as diabetes) and dementia are among the top health burdens worldwide. Currently, 425 million adults live with diabetes, whereas 352 million have prediabetes worldwide, and these numbers are expected to rise in the coming three decades (1). Among people aged ≥60 years, 5–7% have dementia (2). Diabetes is an established risk factor for dementia; it confers an almost twofold greater risk and accounts for ∼3% of all dementia cases (3).

Thus far, antidementia drugs have shown limited efficacy in treating dementia. Therefore, recent research has focused on identifying modifiable lifestyle behaviors that could help prevent or delay dementia onset. Of the lifestyle behaviors, leisure activities and social network have received the most attention lately, as they are major lifestyle components and can have a substantial impact over the life span. In older adults, participating in leisure activities has been associated with beneficial effects on various health conditions, such as cardiometabolic outcomes (4). In the past decade, prospective studies have shown that engagement in mentally, physically, or socially stimulating leisure activities is related to a decreased dementia risk in older adults (2,5). Similarly, several indicators of a rich social network (e.g., social connections or social support) have also been related to a decreased dementia risk, independently and in combination with higher level of engagement in leisure activities (6–8).

Diabetes and dementia share common lifestyle risk factors (e.g., physical inactivity, sedentary lifestyle) (9,10). Therefore, it is reasonable to hypothesize that some lifestyle behaviors such as engagement in leisure activities and having a rich social network could protect people with diabetes from dementia. In the current study, we aimed to assess whether greater engagement in leisure activities and a richer social network may compensate for the increased risk of dementia in people with diabetes, using 10-year longitudinal data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K).

RESEARCH DESIGN AND METHODS

Study Population

SNAC-K is an ongoing population-based longitudinal study of the older population in central Stockholm; data collection has previously been described in detail (11). Briefly, from March 2001 through June 2004, 3,363 participants aged ≥60 years living at home or in institutions in Kungsholmen (urban area in central Stockholm, Sweden) were recruited to participate in the baseline assessment. The younger age cohorts (60, 66, and 72 years old) were followed every 6 years (2007–2010 [the 72-years-old age cohort was further assessed in 2010–2013]) and the older age cohorts (≥78 years old) every 3 years (2004–2007, 2007–2010, and 2010–2013) because of more rapid changes in health and a higher attrition rate in older age-groups. For the current study, follow-up data were available until 2013. At baseline, 322 participants with prevalent dementia were excluded, 273 declined to participate in follow-up examinations, 90 were missing data on glycated hemoglobin (HbA_{1c}), 16 had schizophrenia or developmental disorders, and 14 had type 1 diabetes. Thus, 2,648 dementia-free participants remained for the current study (Supplementary Fig. 1).

SNAC-K was approved by the Karolinska Institutet ethics committee and the regional ethics review board in Stockholm, Sweden. Written informed consent was collected from all participants or a proxy (a close family member or guardian).

Data Collection

Information on sociodemographic factors (age, sex, and education), vascular risk factors (smoking and alcohol consumption), anthropometrics (body weight and height), medical conditions, current medication use, lifestyle (leisure activities and social network), and cognitive function was collected through structured interviews and clinical examinations by trained staff (protocol available at www.snac.org).

Highest level of formal education attained was recorded as elementary, professional schools, high school, or university. Smoking status was dichotomized as never versus former/current. Alcohol consumption was categorized into no/occasional versus drinking (including light to heavy drinking). Weight and height were measured without shoes and heavy clothes. BMI was calculated as weight in kilograms divided by the square of height in meters and categorized into underweight (<20 kg/m^2), normal weight (≥20–25 kg/m^2), overweight (≥25–30 kg/m^2), or obese (≥30 kg/m^2). During the physician examination, arterial blood pressure was measured twice at a 5-min interval on the left arm in a sitting position. Peripheral blood samples were collected for laboratory tests. HbA_{1c} was measured, and the *APOE* gene was genotyped (carriers of any ε4 allele vs. noncarriers).

Data on medical conditions were also available from the Swedish National Patient Registry (NPR), which covers inpatient care from 1987 and outpatient care since 2001. Medical conditions, including hypertension, as well as heart diseases and cerebrovascular diseases (CVDs), were ascertained based on the physician examination, self-report, medication use, or NPR data (12). Depression (no vs. yes) was diagnosed according to DSM-IV revised criteria (13). Medical records at hospital discharge during the study period and death certificates from the Swedish Cause of Death Registry were used to assess participants' vital status.

Lifestyle

Modifiable lifestyle behaviors included two variables: leisure activities and social network.

Leisure Activities

During the baseline nurse interview, participants were asked which of a list of 26 predefined activities they engaged in and how often they had engaged in them over the past 12 months (Supplementary Appendix A). Response alternatives for physical activities included daily, weekly, monthly, less frequently, or never. As in a previous study (5), activities were categorized as mental, social, or physical. Mental activities included those that were predominantly cognitive and required little to no social engagement (reading books, playing chess/cards, playing a musical instrument, listening to music, using the Internet or playing computer games, and painting/drawing/working with clay). Level of engagement in mental activity was coded as low (one or more activities), moderate (two to three activities), or high (four or more activities). Social activities included those involving social interactions (sports events, cinema/theater/concerts, museums/art exhibitions, restaurants/bar/cafés, bingo, dancing, church service, traveling,

volunteering, study circles/courses, and other social meetings). Level of engagement in social activity was coded as low (no activities), moderate (one activity), or high (two or more activities). Physical activities included those for which the predominant component was light to vigorous physical exercise (walking, jogging, bicycling, gym/golf/other sports, gardening, strolling through the woods and countryside, picking mushrooms/berries, going hunting/fishing, and home repair or car/other mechanical repair). Level of engagement in physical activity was coded as low (performed less than one time/week), moderate (performed at least one time/week), or high (performed more than one time/week). A "leisure activity index" was created by summing the three types of activities (range 0–6), and level of engagement was coded as low (score 0–1), moderate (score 2–3), or high (score 4–6).

Social Network

At baseline, data on social network were collected in the nurse interview (Supplementary Appendix B), which explored two components of social network: social connection (marital status, cohabitation status, parenthood, friendships, and social network size and frequency of direct or remote contacts with parents, children, relatives, neighbors, and friends) and social support (reported satisfaction with aforementioned contacts; perceived material and psychological support; sense of affinity with association members, relatives, and residence area; and being part of a group of friends) (14,15). Raw scores on the five items on social connection and the five items on social support were standardized into *z* scores and averaged to create a social connection index and a social support index. Each index was divided into tertiles on the basis of the scores' distributions: T1 (poor social network [−0.27 or lower] or support [−0.10 or lower]), T2 (moderate social network [−0.26 to 0.39] or support [−0.09 to 0.33]), and T3 (rich social network [>0.39] or support [>0.33]). Finally, an overall social network index was generated by averaging the social connection and social support indices. It was then divided by distribution into tertiles: low (−0.14 or lower), moderate (−0.13 to 0.30), or rich (>0.30).

Prediabetes and Diabetes

HbA_{1c} (%) level was measured with Swedish Mono S filament high-performance liquid chromatography, and 1.1% was added to equate the measured HbA_{1c} values with international values (16). Diabetes was ascertained on the basis of self-reported medical history, hypoglycemic drug use, diagnosis in the NPR (ICD-10 code E11), or HbA_{1c} ≥6.5% (48 mmol/mol) (16). Those who did not have diabetes but had HbA_{1c} of ≥5.7–6.5% (39–48 mmol/mol) were categorized as having prediabetes (17).

Dementia

At each wave, the clock-drawing test, Digit Span test forward and backward, and tasks of orientation, calculations, and judgment were administered by a trained psychologist (18). Global cognitive function was measured with the Mini-Mental State Examination (MMSE). All-cause dementia (referred to hereafter as dementia unless the type is specified) was diagnosed in accordance with the DSM-IV criteria, using a validated three-step procedure (19). Two examining physicians independently made preliminary diagnoses of dementia based on the participant's physical, neurological, and cognitive status. In case of disagreement, a third senior neurologist was consulted to reach concordant diagnoses. Standard criteria (20,21) were used to diagnose Alzheimer disease (AD) and vascular dementia (VaD). Participants with features of both AD and VaD were classified as having mixed-type dementia. For participants who died during the follow-up, one physician made the diagnosis of dementia and its subtypes by consulting death certificates and, when available, medical records at hospital discharge.

Statistical Analysis

χ^2 tests or one-way ANOVA, followed by pairwise mean comparisons with Bonferroni correction, was used to describe the baseline characteristics of the study participants by diabetes status.

Incidence rates (IRs) and 95% CIs of dementia per 1,000 person-years in people with diabetes, with prediabetes, and who were diabetes-free were calculated as the number of events during the follow-up period divided by person-years of follow-up. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% CIs of dementia or dementia subtypes associated with baseline diabetes, prediabetes, leisure activities, and social network. Follow-up time was calculated as the time from study entry until dementia diagnosis, death, or last examination. The proportional hazard assumption was tested for all predictors and covariates in a multivariate model, using the Schoenfeld residuals regressed against follow-up time; no violation of proportionality was observed.

Statistical interactions between diabetes and each lifestyle and social network indicator in predicting dementia were examined in separate Cox regression models. First, we assessed whether leisure activities or social network (separately) modulated the association between diabetes and dementia risk. Second, we combined leisure activities and social network into the lifestyle variable and examined whether this combined variable modulated the association between diabetes and dementia risk.

To assess the possibility that an active lifestyle would counteract diabetes-related dementia risk, we created an indicator variable. The variable combined diabetes status (no vs. yes) with level of leisure activities (low vs. moderate to high) and social network (poor vs. moderate to rich). This dummy variable divided the participants in four groups: *1*) those who were diabetes-free and had a low level of leisure activities and a poor social network ("diabetes-free inactive"); *2*) those who were diabetes-free but had at least one active leisure activity or a rich social network ("diabetes-free active"); *3*) those with diabetes, a low level of leisure activities, and a poor social network ("diabetes inactive"); and *4*) those with diabetes, at least one active leisure activity, or a rich social network ("diabetes active").

Finally, we calculated the population-attributable fraction of the association between dementia and an active lifestyle in participants with diabetes. Baseline age, education, smoking, BMI, hypertension, CVDs, depression, and *APOE* ε4 were considered as potential confounders in multivariate analyses.

In sensitivity analyses, multiple imputation by chained equations was performed for missing values to obtain five data sets, which were pooled together using Rubin's rule to obtain valid

statistical inferences. Cox regression models were repeated by excluding the incident dementia cases during the first 3 years of follow-up to address potential reverse causality or by excluding participants with baseline MMSE ≤27 (Supplementary Appendix C).

All reported *P* values were two sided, and *P* values <0.05 were considered statistically significant. Data were analyzed using Stata SE, version 14.0 (StataCorp, College Station, TX).

RESULTS

Characteristics of Study Population

Of the 2,648 participants (mean ± SD age 73.6 ± 10.5 years [range 60–102]) at baseline, 920 (34.7%) had prediabetes and 243 (9.2%) had diabetes. Table 1 shows participants' baseline characteristics. Participants with prediabetes or diabetes were more likely than those who were diabetes-free to be older; male; consume less alcohol; have a lower level of education, higher BMI, hypertension, and CVDs; and be less engaged in leisure activities (mental, social, or physical) or have a poorer social network. There were no significant differences among the groups in smoking, depression, or *APOE* status.

During the 10-year follow-up, only 233 people declined to participate in the follow-up examinations (participation rate 91.2%). During the study period, 725 people (27.4%) died who had been dementia free at their last SNAC-K assessment. Their dementia status was derived from death certificates or medical records at hospital discharge as described in RESEARCH DESIGN AND METHODS.

Prediabetes, Diabetes, and Dementia

During the follow-up (mean ± SD 6.4 ± 1.8 years [range 2.1–10.3], accounting for 15,924 person-years), 246 participants (9.3%) were diagnosed with dementia (15.4 cases per 1,000 person-years): 128 (58.9%) with AD, 25 (10.2%) with VaD, and 33 (13.4%) with mixed dementia. In the multiadjusted (by baseline age, sex, education, smoking, BMI, hypertension, CVDs, and *APOE* ε4) Cox regression models, participants with diabetes had twice the risk of dementia (Table 2). Greater risk was detected for VaD (HR 7.1 [95% CI 2.2–22.9]) and mixed dementia (HR 2.6 [95% CI 0.9–7.2]; *P* = 0.078) but not AD (HR 1.3 [95% CI 0.7–2.6]) in those with diabetes than in those who were diabetes-free. Prediabetes was not significantly associated with dementia risk.

In the multiadjusted Cox regression analyses, moderate or high level of engagement in leisure activities and a moderate or rich social network were associated with a decreased risk of dementia (Table 2). We therefore merged them into single categories: "moderate to high" for leisure activities and "moderate to rich" for social network.

Modulating Effect of Leisure Activities or Social Network on Diabetes-Related Dementia Risk

Table 3 shows the effects of diabetes (no vs. yes) plus leisure activities and of diabetes plus social network (poor vs. moderate to rich) on dementia risk. Participants with diabetes and moderate to high level of engagement in leisure activities, as well as those with diabetes and a moderate to rich social network, had a dementia risk similar to that of participants without diabetes but with low level of engagement or a poor social network. Among participants with diabetes, moderate to high level of engagement in leisure activities was associated with a smaller risk of dementia than that for low level of engagement; however, the difference was not statistically significant (*P* = 0.263). Those with diabetes and a richer social network had a significantly smaller dementia risk than those with diabetes and a poor social network (risk difference 0.75 [95% CI 0.004–1.49]). Thus, a rich social network reduced dementia risk in people with diabetes by >70%. There was no indication of a multiplicative interaction between diabetes status and the leisure activity index (*P* = 0.633) or social network index (*P* = 0.288).

Modulating Effect of an Active Lifestyle on Diabetes-Related Dementia Risk

Figure 1 shows the effect of diabetes and lifestyle (in which leisure activities and social network were combined) on the risk of dementia. Those in the diabetes inactive group had a nearly sixfold greater risk of dementia than those in the diabetes-free active group. The adjusted HR of dementia in participants with diabetes and an active lifestyle was higher than in the diabetes-free active group but lower than in the diabetes inactive group (HR 1.93 [95% CI 1.08–3.46]). Indeed, the diabetes active group's risk was similar to that of diabetes-free older adults with an inactive lifestyle (HR 1.63 [95% CI 0.94–2.84]; *P* = 0.083) (Supplementary Table 1). Supplementary Fig. 2 shows the Kaplan-Meier survival curves for the four different groups.

No multiplicative interaction between diabetes and active lifestyle was detected (*P* = 0.267). In participants with diabetes, the proportion of cases of diabetes attributable to an active lifestyle was 0.48 (95% CI 0.01–0.97). Thus, if all older adults with diabetes had an active lifestyle, ~48% of diabetes-related dementia cases could be prevented. In Cox regression models stratified by sex, the effect of diabetes on dementia risk was modulated in both active females and males (Supplementary Table 2).

CONCLUSIONS

In this large-scale, population-based longitudinal study of dementia-free older adults followed for up to 10 years, we found that *1*) diabetes was associated with a twofold greater risk of dementia, especially of vascular origin, but the relationship between prediabetes and dementia risk was not evident, and *2*) the increased risk for dementia in people with diabetes can be counteracted by active engagement in leisure activities or a rich social network.

A large body of evidence has shown a 1.5- to 2.5-fold greater risk of dementia in older adults with diabetes than in those without (22). In support of previous findings, our results show that diabetes, especially of vascular origin, plays a role in the etiology of dementia. Furthermore, it has been suggested that diabetes-related neurocognitive deterioration could start in the prediabetes stage (23,24). Prediabetes was associated with worse memory function in a cohort of cognitively healthy Swedish older adults (23). Furthermore, impaired glucose metabolism, which characterizes prediabetes, has been related to smaller brain volumes, suggesting that cerebral changes may already occur in people with prediabetes (24). On the other hand, studies on the link between prediabetes and dementia are relatively sparse and results are inconsistent. In the Kungsholmen project, prediabetes (identified using random plasma glucose) was associated with a 70% increased

Table 1—Baseline characteristics of the study population by diabetes status (n = 2,648)

	Diabetes-free	Prediabetes	Diabetes	*P*
n	1,485	920	243	
Age cohorts, years	72.1 ± 10.2	75.6 ± 10.6*	75.5 ± 9.8*	<0.001
60 and 66	708 (47.6)	305 (33.2)	70 (28.8)	<0.001
72 and 78	429 (28.9)	291 (31.6)	93 (38.3)	
81, 84, and 87	232 (15.7)	205 (22.3)	51 (21.0)	
≥90	116 (7.8)	119 (12.9)	29 (11.9)	
Female sex	946 (63.7)	601 (65.3)	120 (49.4)	<0.001
Education				
Elementary	192 (12.9)	155 (16.9)	55 (22.6)	<0.001
Professional schools	606 (40.9)	421 (45.8)	107 (44.0)	
High school	155 (10.4)	83 (9.0)	27 (11.1)	
University	530 (35.7)	260 (28.3)	54 (22.2)	
Current smoker	760 (51.4)	505 (55.2)	136 (56.7)	0.102
Alcohol consumption	1,076 (72.7)	567 (61.9)	125 (51.9)	<0.001
BMI, kg/m^2	25.1 ± 3.7	25.7 ± 4.1*	27.0 ± 4.5*	<0.001
Underweight (<20)	92 (6.2)	54 (5.9)	10 (4.1)	<0.001
Normal (≥20–25)	698 (47.0)	379 (41.2)	75 (30.9)	
Overweight (≥25–30)	563 (37.9)	361 (39.2)	95 (39.1)	
Obese (≥30)	132 (8.9)	126 (13.7)	63 (25.9)	
Hypertension	1,012 (68.2)	651 (70.8)	193 (79.4)	0.002
Heart diseases	274 (18.4)	253 (27.5)	115 (47.3)	<0.001
Cerebrovascular diseases	79 (5.3)	67 (7.3)	27 (11.1)	0.002
Depression	72 (4.9)	49 (5.4)	12 (5.0)	0.872
HbA_{1c}, %	5.3 ± 0.2	5.9 ± 0.2*	7.1 ± 1.3*	<0.001
Any *APOE* ε4	419 (29.6)	251 (28.9)	54 (23.8)	0.203
MMSE score	28.9 ± 1.4	28.7 ± 1.5*	28.5 ± 1.5*	<0.001
Leisure activity index				
Low	348 (26.6)	271 (34.7)	70 (35.5)	<0.001
Moderate	609 (46.5)	339 (43.4)	88 (44.7)	
High	352 (26.9)	170 (21.8)	39 (19.8)	
Social network index				
Poor	409 (28.8)	268 (31.1)	88 (39.3)	0.005
Moderate	482 (33.9)	314 (36.5)	64 (28.6)	
Rich	530 (37.3)	279 (32.4)	72 (32.1)	

Data are means ± SD or *n* (%) unless otherwise indicated. Missing data: education = 3, smoking = 14, alcohol consumption = 12, *APOE* ε4 = 134, MMSE = 129, leisure activity index = 362, social network index = 142. *APOE* ε4, apolipoprotein E4 allele. *Pairwise means comparison using the Bonferroni correction: $P < 0.05$ (reference group = baseline participants who were diabetes-free).

risk of dementia among participants aged ≥75 years (25). Afterward, other cohort studies examined the relationship between other markers of prediabetes (e.g., impaired glucose tolerance and fasting plasma glucose) and dementia. In the population-based Uppsala Longitudinal Study of Adult Men (ULSAM), researchers found associations between low early insulin response or insulin sensitivity and an increased risk of dementia in older men without diabetes; however, they found no associations between fasting blood glucose or impaired glucose tolerance and increased dementia risk (26). In the current study, we found no significant association between prediabetes and dementia among older adults. We believe that methodological differences in the assessment of prediabetes (e.g., using HbA_{1c}, fasting/random plasma glucose, oral glucose tolerance test [OGTT]), the number of measurements, and differences in age of the study populations might explain the discrepancies in these findings.

Although existing research has focused on understanding the risk factors for diabetes-related dementia, little has been done to understand which modifiable lifestyle behaviors can help older adults with diabetes delay the onset of dementia. Many studies have addressed the associations either between lifestyle behaviors and dementia in people without diabetes (2) or between lifestyle behaviors and the risk of diabetes (27,28), but thus far, the joint effect of lifestyle behaviors and diabetes on dementia has not been addressed. Data from epidemiological studies seem to support the notion that engagement in mental, physical, or social leisure activities may protect older adults from dementia (29,30). Prospective studies have also reported that active participation in various leisure activities has protective effects (2,31) or that components of social networks (i.e., marital status, network size/nature, and satisfaction with interactions) do (7,8). These studies, however, did not take into account participants' metabolic conditions, which greatly influence cognitive progression in healthy aging. On the other hand, findings from two major diabetes prevention trials—the Diabetes Prevention Program (DPP) (32) and the Finnish Diabetes Prevention study (33)—have shown that modifying leisure physical activity can substantially reduce the risk of future diabetes in at-risk adults, even more than pharmacotherapy. Nevertheless, these studies have exclusively focused on the physical component of leisure activities, disregarding their social and mental components. A number of studies have shown that a rich social network and a high level of social support are associated with better glucose regulation in people without diabetes (34) and with better diabetes self-management (35).

To the best of our knowledge, no epidemiological study has investigated whether a more comprehensive active lifestyle that is physically, cognitively, and socially stimulating can counteract the harmful effects of diabetes on the brain and, thus, on cognitive deterioration. We found that moderate to high levels of engagement in leisure activities and a moderate to rich social network were associated with a dramatically decreased risk of dementia in people with diabetes. Our results highlight the need for future behavioral interventions that integrate mental, social, and physical aspects of lifestyle to investigate how and to what extent dementia can be prevented in people with diabetes. Recently, the first promising findings from a multidomain randomized controlled trial suggested that healthy dietary changes, physical exercise, cognitive training, and effective management of vascular risk factors may enhance cognitive functioning in older people at risk for dementia

Table 2—IR per 1,000 person-years and HR with 95% CIs of all-cause dementia over 10-year follow-up from three separate Cox regression models for diabetes status, leisure activities, or social network

			HR (95% CI)	
	No. events/person-years	IR (95% CI)	Basic adjustment*	Multiadjusted†
Diabetes status				
Diabetes-free	121/9,068	13.3 (11.2–15.9)	Reference	Reference
Prediabetes	88/5,517	16.0 (12.9–19.7)	0.97 (0.73–1.27)	0.93 (0.69–1.25)
Diabetes	37/1,339	27.6 (20.0–38.1)	2.00 (1.38–2.91)	2.24 (1.50–3.34)
Leisure activity index				
Low	91/4,028	22.6 (18.4–27.7)	Reference	Reference
Moderate	61/6,512	9.4 (7.3–12.0)	0.56 (0.40–0.78)	0.61 (0.43–0.86)
High	18/3,597	5.0 (3.2–7.9)	0.38 (0.23–0.64)	0.42 (0.24–0.72)
Social network index				
Poor	106/4,203	25.2 (20.8–30.5)	Reference	Reference
Moderate	70/5,372	13.0 (10.3–16.5)	0.61 (0.45–0.83)	0.72 (0.52–1.00)
Rich	42/5,617	7.5 (5.5–10.1)	0.44 (0.30–0.64)	0.55 (0.37–0.82)

*Adjusted for baseline age, sex, and education. †Adjusted for baseline age, sex, education, smoking, BMI, hypertension, CVDs, depression, and *APOE* ε4.

(36). However, this intervention did not include direct leisure activities/social network components. Future behavioral interventions should be designed to help us understand the extent to which an overall active lifestyle could counteract dementia risk in older adults with diabetes.

The interplay between several biological and psychosocial mechanisms may explain the potential compensatory effects of an active lifestyle in older adults with diabetes. At the biological level, an active lifestyle may help enhance cardiovascular health and reduce the risk of atherosclerosis and future vascular dementia. Furthermore, an active lifestyle can increase brain/cognitive reserve, helping preserve or improve neuronal activity and networks or providing new compensatory networks that can be used during brain changes due to underlying neurovascular pathology, thus slowing cognitive decline (37). Finally, at the psychosocial level, a rich social network can help older adults with diabetes cope better with their health and make better use of health resources so that they can maintain a healthy lifestyle. This can lead to improved adherence to diabetes treatments and, therefore, better glycemic control (35), exposing the older person less to hyperglycemia, which likely may be a major etiological mechanisms underlying dementia in people with diabetes (38).

Strengths of this study include the longitudinal design with a long follow-up and very high participation rate, relatively large sample size, integration of clinical diagnoses from the examining physicians and data from national registries, and dementia status derived from death certificates or medical records at hospital discharge in participants who died during follow-up. Also, thanks to the in-depth interviews with the respondents, we had the possibility to assess the joint effect of leisure activities and social network (an active lifestyle) on diabetes-related dementia. Additionally, to address potential reverse causation, in a sensitivity analysis, we included dementia-free participants at baseline and excluded participants with dementia during 3 years of follow up, and the findings were similar. However, some limitations need to be acknowledged. First, measurement errors might have occurred because of the use of self-reported questionnaires on leisure activities and social network. Indeed, participants with poor cognitive function might report inaccurate information, which could lead to differential misclassification. We therefore repeated all analyses excluding participants with potential global cognitive dysfunction; results remained similar. Second, selection bias might have occurred as a consequence of nonresponse over the follow-up. However, the proportion of people who declined to participate in the follow-up assessments was very small (8.6%), and sensitivity analyses using multiple imputation produced estimates similar to results of the complete case analyses. Hence, we might have underestimated the true

Table 3—HRs and 95% CIs of the effect of leisure activities plus diabetes on dementia and of social network plus diabetes on dementia

Joint effect	*n*	HR (95% CI)*	*P*
Leisure activity index			
Diabetes-free			
Moderate to high	961	Reference	
Low	348	2.17 (1.36–3.48)	0.001
Diabetes			
Moderate to high	127	2.63 (1.31–5.25)	0.006
Low	70	4.16 (2.14–8.01)	0.000
Social network index			
Diabetes-free			
Moderate to rich	1,012	Reference	
Poor	409	1.23 (0.80–1.86)	0.346
Diabetes			
Moderate to rich	136	1.60 (0.87–2.99)	0.143
Poor	88	3.38 (1.87–6.11)	0.000

*Models adjusted for baseline age, sex, education, smoking, BMI, hypertension, CVDs, depression, and *APOE* ε4.

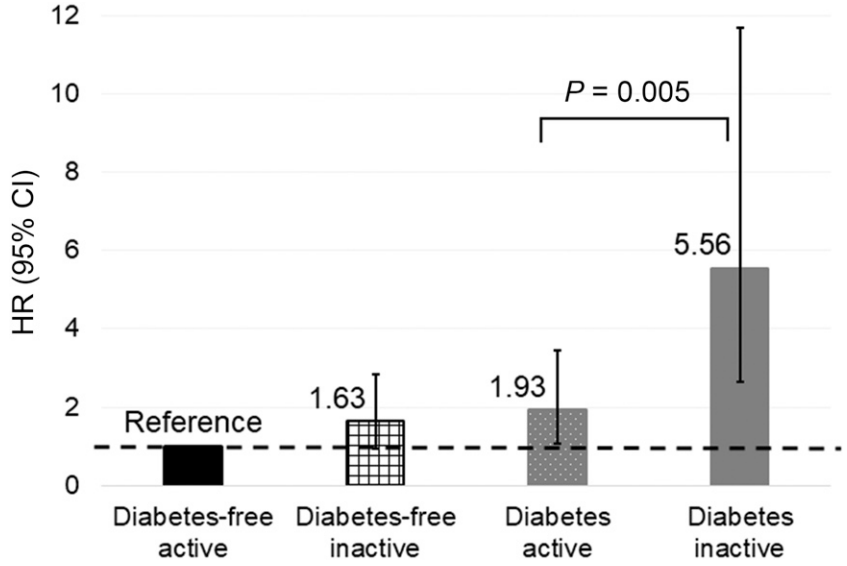

Figure 1—Joint effect of diabetes and lifestyle (combining leisure activities and social network) on dementia. HRs (95% CIs) of dementia from Cox regression models adjusted for baseline age, sex, education, smoking, BMI, hypertension, cardiovascular disease and CVDs, depression, and *APOE* ε4. "Inactive" refers to a low level of leisure activities and poor social network (leisure activity index and social network index = 0). "Active" refers to having at least one moderate to high leisure activity index or moderate to rich social network index. $P = 0.005$ refers to the difference in risk for dementia in the "diabetes inactive" and "diabetes active" groups.

associations among diabetes, an active lifestyle, and dementia. Finally, prediabetes and diabetes were identified on the basis of a one-time measurement of HbA_{1c}, which measures an average proportion of hemoglobin proteins bound by glucose over the past 3 months (39). As such, HbA_{1c} captures only chronic hyperglycemia (not acute or fluctuating glycemic levels), and its sensitivity in diagnosing prediabetes and diabetes is inferior to oral glucose tolerance tests (40). Thus, a proportion of cases might have not been detected. On the other hand, these people would have been misclassified as diabetes-free, leading to a dilution and thus underestimation of the investigated associations. Finally, potential residual confounding because of unmeasured factors (e.g., environmental or geographical) cannot be completely ruled out. In light of these limitations, the magnitude of our findings can be generalized only to populations with characteristics similar to those of the SNAC-K participants.

In summary, our study provides the first evidence that an active lifestyle—characterized by a high level of engagement in leisure activities and a rich social network—could significantly counteract the detrimental effects of diabetes on dementia. Intervention studies are needed in older adults to establish whether and to what extent late-life active lifestyle behaviors buffer the risk of diabetes-related cognitive impairment and how long the potential neuroprotective benefits last. These studies should also explore the underlying interplay between biological and psychosocial mechanisms in the relationships among lifestyle behaviors, diabetes, and cognitive impairment.

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Author Contributions. A.M. conducted the literature search, analyzed data, interpreted the findings, and wrote, reviewed, and edited the manuscript. A.M. and W.X. conceptualized and designed the study. L.F. designed, initiated, and directed SNAC-K. A.M., H.-X.W., D.R., L.F., and W.X. contributed to the data interpretation and revision of the manuscript and approved the final draft. A.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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