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Featured Article

Leisure activity and social integration mitigate the risk of dementia related to cardiometabolic diseases: A population-based longitudinal study

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Abstract

Introduction: The effect of comorbid cardiometabolic diseases (CMDs), including diabetes, heart diseases, and stroke, on dementia remains unclear.
Methods: A cohort of 2648 dementia-free adults aged ≥60 years was followed up for 12 years. An active lifestyle was defined in accordance with the engagement in leisure activities and/or a social network. Cox models were used in data analysis.
Results: The multiadjusted hazard ratio (HR, 95% confidence interval) of dementia was 1.41 (1.07–1.86) for one, 2.38 (1.58–3.59) for two, and 4.76 (2.04–11.13) for three CMDs. In joint exposure analysis, the HR of dementia was 3.36 (2.14–5.30) for participants with CMDs plus an inactive lifestyle and 1.32 (0.95–1.84) for those with CMDs plus an active lifestyle (reference: no CMDs plus active lifestyle). An active lifestyle delayed dementia onset by 3.50 years in people with CMDs.
Discussion: CMDs, especially when comorbid, are associated with increased dementia risk; however, leisure activities and social integration mitigate this risk.
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Keywords: Cardiometabolic diseases; Dementia; Leisure activities; Social network; Population-based cohort study

1. Introduction

It was estimated that 46.8 million people were living with dementia worldwide in 2015, and this number will almost double every 20 years, reaching 74.7 million in 2030 [1]. The global economic burden of dementia is estimated to be one trillion US dollars [2]. Currently, there is no cure for dementia; thus, it is particularly important to identify modifiable factors, such as lifestyle behaviors, that can compensate for the increased risk of dementia that results from other medical conditions.

Because of population aging, the co-occurrence of chronic diseases is becoming more common among older adults. Type 2 diabetes, heart diseases (i.e., coronary heart diseases and heart failure), and stroke have been defined as cardiometabolic diseases (CMDs) [3,4]. The prevalence of any CMDs is about 20% in adults aged ≥60 years [3]. Individual CMDs have been associated with the risk for dementia. Diabetes nearly doubles dementia risk [5], whereas coronary heart disease and heart failure are related to a 27% to 60% increased risk [6], and stroke confers a 1.59-fold

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increased risk [7]. However, evidence about the magnitude of dementia risk in older adults who have more than one CMD remains unclear.

Both leisure activities and social network have been associated with a decreased dementia risk [8,9]. Moreover, active participation in leisure and/or social activities can prevent lifestyle-related disorders, such as diabetes, heart diseases, and stroke, which in turn may increase dementia risk [10–12]. However, to our knowledge, no studies have investigated whether lifestyle behaviors can mitigate the increased risk of dementia related to CMDs. Given the high prevalence of CMDs in older adults, CMDs could be an ideal target for interventions to prevent dementia by healthy lifestyle behaviors, if possible.

We hypothesized that comorbid CMDs significantly increase the risk of dementia, but an active lifestyle can help diminish this risk. In the present study, we sought to (1) quantify the magnitude of the association of single and comorbid CMDs with dementia and (2) explore whether an active lifestyle may counteract the risk of dementia associated with CMDs using the 12-year follow-up data from the Swedish National Study on Aging and Care–Kungsholmen (SNAC-K).

2. Methods

2.1. Study population

SNAC-K is a part of the Swedish National Study on Aging and Care, an ongoing longitudinal project on aging and care in Sweden (http://www.snac-k.se/). At baseline (March 2001–June 2004), SNAC-K included 3363 people aged ≥60 years residing in Kungsholmen, an urban area in Stockholm, living at home, or living in institutions [13]. The younger age cohorts (60, 66, and 72 years) were followed up every 6 years until 2016. Because of the relatively high attrition rate and more rapid changes in health condition in older age groups, the older age cohorts (≥78 years) were followed up every 3 years until 2016.

We excluded 322 participants with dementia at baseline, 273 who declined to participate in any follow-up examinations, 90 with missing data on glycated hemoglobin, 16 with schizophrenia or developmental disorders, and 14 with type 1 diabetes. Thus, the final study sample included 2648 dementia-free participants.

During the 12-year follow-up, 291 of the 2648 participants developed dementia, 856 died, and 393 (14.8%) dropped out (moved or declined to participate after baseline) (Supplementary Fig. 1). Medical records and death certificates were available for all participants who died during the three follow-up periods.

SNAC-K was approved by the Karolinska Institutet Ethical Committee and the Regional Ethical Review Board in Stockholm, Sweden. A written informed consent was collected from all participants or a proxy (a close family member or guardian).

2.2. Data collection

All participants underwent comprehensive examination by a physician, a psychologist, and a nurse. Data on sociodemographic variables (age, sex, and education), anthropometrics (body weight and height), vascular risk factors (smoking, alcohol consumption, overweight/obesity, high cholesterol, and hypertension), medical conditions, current medication use, lifestyle behaviors (leisure activities and social network), and cognitive function were collected through structured interviews and clinical examination (http://www.snac.org).

Education was categorized as elementary school, professional school, high school, or university [14]. The body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m^2) and was categorized as underweight (<20.0), normal weight (20–25), overweight (25–30), or obese (≥30). Smoking was dichotomized as never smoked versus former/current smoker. Alcohol consumption was categorized into no/occasional consumption versus regular consumption (including light-to-heavy drinking).

During the physician's examination, the participants' arterial blood pressure was measured twice at a 5-min interval on their left arm while they were seated. Hypertension was identified as blood pressure ≥140/90 mmHg. Peripheral blood samples were collected for laboratory tests. Glycated hemoglobin (HbA1c) and nonfasting cholesterol were measured, and the *APOE* gene was genotyped. High cholesterol was defined as nonfasting total serum cholesterol ≥6.22 mmol/l or use of cholesterol-lowering agents (ATC code C10) [14]. As a measure of functional ability, walking speed was tested by asking the participants to walk 6 meters in their usual pace or 2.4 meters if the participant was reported walking quite slow and was recorded in meters per second [15].

Data on all medical conditions were also available in the Swedish National Patient Register (NPR) system, which covers all inpatient and outpatient care [16]. Codes from the International Classification of Diseases, tenth revision (ICD-10), were used to identify chronic medical conditions. Depression (no vs. yes) was diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) revised criteria. The participants' vital status during the study period was assessed through death certificates from the Swedish Cause of Death Registry and medical records at hospital discharge.

2.3. Assessment of cardiometabolic diseases

Information on medical conditions was based on clinical examination, medication use, NPR data, and laboratory tests (e.g., HbA1c). CMDs included diabetes, heart diseases (i.e., coronary heart diseases and heart failure codes), and stroke [17]. In addition to the clinical examination, the following

information was used to ascertain each CMDs: (1) NPR data (ICD-10 code E11), use of antidiabetic medication (ATC code A10), or HbA1c $\geq$ 6.5% [18,19] for diabetes; (2) NPR data for coronary heart disease (CHD) (ICD-10 codes: I20-22, I24-25, Z951, and Z955) and heart failure (ICD-10 codes: I110, I130, I132, I27, I280, I42, I43, I50, I515, I517, I528, Z941, and Z943); (3) NPR data (ICD10 codes: G45, I61-I69) for stroke.

The CMD status was categorized as CMD-free, one CMD (any one of the following: diabetes, one or more heart diseases, or stroke), two CMDs (any two of the following: diabetes, heart diseases, or stroke), and three CMDs (diabetes, heart diseases, and stroke).

2.4. Dementia diagnoses

At each wave, the clock-drawing test, the digit span forward and backward test, and orientation, calculation, and judgment tasks were administered [20]. Global cognitive function was measured with the Mini-Mental State Examination (MMSE). All-cause dementia (hereafter, dementia) was diagnosed with the DSM-IV criteria, using a validated three-step procedure, as in a previous study [21]. Two examining physicians independently made preliminary diagnoses of dementia on the basis of the participant's physical, neurological, and cognitive status. In case of disagreement, a third neurologist was consulted to reach concordant diagnoses. For participants who died during the follow-up, one physician made the diagnosis of dementia and its subtypes by referring death certificates and medical records at hospital discharge.

2.5. Assessment of leisure activities and social network

In this study, lifestyle factors included leisure activities and social network, which were measured during the baseline nurse interview.

2.5.1. Leisure activities

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 (Appendix A). Response alternatives for physical activities were daily, weekly, monthly, less frequently, or never. Based on the previous studies [22,23], the activities were categorized as physical, mental, or social.

Physical activities were 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). Engagement in physical activity was coded as 0 (performed $<$1 time/week), 1 (performed 1 time/week), or 2 (performed $\geq$2 time/week).

Mental activities included those activities that were predominantly cognitive in nature and required little to no social engagement (reading books, playing chess/cards, playing a musical instrument, listening to music, using Internet or playing computer games, and painting/drawing/working with clay). Engagement in mental activity was coded as 0 ($\leq$1 activity), 1 (2–3 activities), or 2 ($\geq$4 activities).

Social activities included those with social interactions (sport events, cinema/theater/concerts, museums/art exhibitions, restaurants/bar/cafés, bingo, dancing, church service, traveling, volunteering, study circles/courses, and other social meetings). Engagement in social activities was coded as 0 (no activities), 1 (1 activity), or 2 ($\geq$2 activities).

Finally, the engagement level in these three types of activities was summed into a continuous variable ranging between 0 and 6, which was used as a leisure activity index that categorized participation in leisure activities as low (score 0–1), moderate (score 2–3), or high (score 4–6) [24].

2.5.2. Social network

At baseline, the nurse used a validated 10-item questionnaire to collect data on social network (social connection and social support) [25,26]. Social connection consisted of five items: (1) marital status; (2) living arrangement; (3) the number of living children; (4) frequency of direct and remote contacts with parents, children, relatives, neighbors, and friends; and (5) social network size, defined as the number of people the participants felt they knew well and could talk to about most issues. Social support was assessed on the basis of five items: (1) reported satisfaction with aforementioned contacts; (2) perceived material support; (3) psychological support; (4) sense of affinity with association members, relatives, and residence area; and (5) being part of a group of friends (Appendix B).

Raw scores of the five items on the 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: poor social network [≤ -0.27] or support [≤ -0.10], moderate social network [-0.26 to 0.39] or support [-0.09 to 0.33], and 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 into tertiles by distribution: low (≤ -0.14), moderate (-0.13 to 0.30), or rich (>0.30) [27].

2.6. Statistical analysis

Baseline characteristics of the study participants by CMD status (CMD-free, one CMD, two CMDs, and three CMDs) were described using χ^2 tests for categorical variables and one-way ANOVA followed by Bonferroni correction for continuous variables.

Incidence rates and 95% confidence intervals (95% CIs) of dementia per 1000 person-years were calculated for each CMD, leisure activities, and social network. Cox

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proportional hazards models were applied to estimate the hazard ratios (HRs) and 95% CIs of dementia associated with CMDs, leisure activities, and social network. Follow-up time was calculated as the time from study entry to dementia diagnosis, death, or last examination. The basic models were adjusted for age, sex, and education. The multi-adjusted models were further adjusted for MMSE, smoking, alcohol consumption, BMI, hypertension, high cholesterol, depression, and *APOE* ε4. The models did not violate the assumption of proportionality.

The joint exposure of CMDs (no vs. yes) with leisure activities (moderate-to-high vs. low) and social network (moderate-to-rich vs. low) was assessed by creating a four-category dummy variable: (1) CMD-free active: CMD-free with at least one active leisure activity or rich social network (reference group); (2) CMD-free inactive: CMD-free with low leisure activity and poor social network; (3) CMDs inactive: CMDs with low leisure activity and poor social network; and (4) CMDs active: CMDs with at least one active leisure activity or rich social network. Statistical interactions between CMDs and each active lifestyle and social network indicators in predicting dementia were examined in separate Cox regression models. We calculated the attributable fraction for the population and 95% CI for dementia associated with active lifestyle of participants with any CMDs.

In sensitivity analyses, multiple imputation by chained equations (MICE) was performed for missing values to obtain five data sets, which were pooled together using Rubin's rule to obtain valid statistical inferences. All analyses were performed with Stata SE, version 15.0, (StataCorp LP, College Station, Texas).

3. Results

3.1. Characteristics of study population

Table 1 shows the sociodemographic, clinical, and lifestyle characteristics of 2648 participants (mean age, 73.6 years; standard deviation [SD], 10.5 years; range,

Table 1
Baseline characteristics of the study population (N = 2648) by cardiometabolic diseases (CMDs)

Characteristics	CMD-free (n = 1910)	One CMD (n = 576)	Two CMDs (n = 145)	Three CMDs (n = 17)	*P*
Age of cohorts, years	71.4 ± 9.8	79.1 ± 10.3*	79.0 ± 9.0*	80.0 ± 8.5*	<.001
60 and 66	943 (49.4)	119 (20.7)	20 (13.8)	1 (5.9)	<.001
72 and 78	562 (29.4)	179 (31.1)	64 (44.1)	8 (47.1)	
81, 84, and 87	295 (15.5)	151 (26.2)	37 (25.5)	5 (29.4)	
90+	110 (5.8)	127 (22.1)	24 (16.6)	3 (17.7)	
Women	1243 (65.1)	337 (58.5)	79 (54.5)	8 (47.1)	.002
Education					
Elementary school	251 (13.2)	116 (20.1)	31 (21.5)	4 (23.5)	<.001
Professional school	787 (41.3)	266 (46.2)	71 (49.3)	10 (58.8)	
High school	186 (9.8)	66 (11.5)	12 (8.3)	1 (5.9)	
University	684 (35.9)	128 (22.2)	30 (20.8)	2 (11.8)	
Current smoking	1015 (53.4)	297 (52.0)	79 (54.5)	10 (58.8)	.882
Alcohol consumption	1366 (71.8)	323 (56.6)	74 (51.0)	5 (29.4)	<.001
BMI, kg/m^2	25.5 ± 3.7	25.5 ± 4.4	26.0 ± 4.5	27.0 ± 5.5	.149
Underweight (<20)	95 (5.0)	49 (8.5)	11 (7.6)	1 (5.9)	<.001
Normal weight (20–25)	853 (44.7)	236 (41.0)	56 (38.6)	7 (41.2)	
Overweight (25–30)	755 (39.5)	210 (36.5)	50 (34.5)	4 (23.5)	
Obese (≥30)	207 (10.8)	81 (14.7)	28 (19.3)	5 (29.4)	
Hypertension	1291 (67.6)	444 (77.1)	107 (73.8)	14 (82.4)	<.001
High cholesterol	942 (49.5)	284 (49.6)	87 (61.3)	8 (53.3)	.057
HbA1c, %	5.5 ± 0.3	5.9 ± 0.9*	6.7 ± 1.3*	7.6 ± 1.5*	<.001
Any *APOE* ε4 allele	541 (29.4)	147 (28.1)	32 (23.7)	4 (30.8)	.538
MMSE score	29.0 ± 1.3	28.4 ± 1.6*	28.2 ± 1.9*	27.8 ± 1.8*	<.001
Depression	79 (4.1)	44 (7.6)	10 (6.9)	0 (0.0)	<.001
Leisure activities index					
Low	462 (26.9)	174 (38.2)	47 (46.1)	6 (54.6)	<.001
Moderate	793 (46.2)	192 (42.1)	46 (45.1)	5 (45.5)	
High	462 (26.9)	90 (19.7)	9 (8.8)	0 (0.0)	
Social network index					
Poor	496 (27.1)	209 (39.1)	47 (37.0)	13 (81.3)	<.001
Moderate	640 (35.0)	174 (32.6)	44 (34.7)	2 (12.5)	
Rich	693 (37.9)	15 (28.3)	36 (28.4)	1 (6.3)	

NOTE. Data are presented as mean ± standard deviations or number (proportion %). Missing data: Education = 3, Smoking = 14, Alcohol consumption = 12, *APOE* ε4 = 134, MMSE = 129, Leisure activities index = 362, Social network index = 142.

Abbreviations: *APOE* ε4, apolipoprotein ε4 allele; BMI, body mass index; HbA1c, glycated hemoglobin; MMSE, Mini-Mental State Examination.

*Pairwise means comparison using the Bonferroni correction: $P < .05$ (reference group = baseline CMD-free participants).

60–102 years). At baseline, 738 people (27.8%) had at least one CMD. Those with one, two, or three CMDs were more likely to be older; male; to have an elementary or professional school education; to not consume alcohol regularly; to be obese; and to have hypertension, a lower MMSE score, a lower level of leisure activities, and a poor social network than those with no CMDs.

3.2. Relationship between dementia and CMDs, leisure activities, and social network

During the entire follow-up (median 11.0 years [interquartile range, IQR 5.7–11.7 years], accounting for 23,101 person-years), 291 participants (1.3% per year) were diagnosed with incident dementia.

In basic and multiadjusted Cox models, diabetes, heart disease, and stroke were individually associated with an approximately 50%–70% increased dementia risk, whereas moderate and high levels of leisure activities (vs. low levels), and moderate and rich social networks (vs. poor social networks), were related to an approximately 20%–60% decreased risk of dementia (Table 2). Therefore, in subsequent analyses, the leisure activity categories "moderate" and "high" were merged into "moderate to high," and the social network categories "moderate" and "rich" were merged into "moderate to rich."

Table 3 presents incidence rates of dementia in people with one, two, or three CMDs and the adjusted HRs of dementia by the number of CMDs. The HR (95% CI) of dementia in people who had one or more CMDs was 1.62 (1.27–2.08). The multiadjusted HR of dementia was 1.41 (1.07–1.86) for one, 2.38 (1.58–3.59) for two, and 4.76 (2.04–11.13) for three CMDs (reference: no CMD). The number of CMDs was dose-dependently associated with increased risk for dementia (P for trend $<.001$) (Table 3).

3.3. Joint effect of CMDs and leisure activities or social network on dementia risk

In the joint effect analysis, the HRs of dementia were 3.06 (95% CI 2.06–4.56) for those with CMDs and a low level of leisure activities and 1.25 (95% CI 0.82–1.91) for those with CMDs and a moderate to high level of leisure activities (reference: those without CMDs who had a moderate to high level of leisure activities). The HRs of dementia were 1.95 (95% CI 1.28–2.96) for those with CMDs and a poor social network and 1.23 (95% CI 0.85–1.77) for those with CMDs and a moderate to rich social network (reference: those without CMDs who had a moderate to rich social network) (Table 4). These results suggested that a moderate to high level of leisure activities reduced the CMD-related risk of dementia by approximately 80%, and a moderate to rich social network reduced the CMD-related risk by about 75%.

Fig. 1 shows the combined effect of CMDs and an active lifestyle (i.e., having moderate to high levels of leisure activities and/or a moderate to rich social network, otherwise as an inactive lifestyle) on dementia risk. The multiadjusted HRs (95% CIs) of dementia were 3.36 (2.14–5.30) for participants with CMDs and an inactive lifestyle and 1.32 (0.95–1.84) for those with CMDs and an active lifestyle (reference:

Table 2
Incidence rate (IR) per 1000 person-years and hazard ratio (HR) with 95% confidence interval (CI) of all-cause dementia in relation to individual cardiometabolic diseases (CMDs), leisure activities, and social network (results of separate Cox regression models)

			Dementia (n = 291)	
Factors	No. of events/person-year	IR (95% CI)	HR (95% CI)*	HR (95% CI)†
Diabetes				
No	252/21,283	11.8 (10.5–13.4)	Reference	Reference
Yes	39/1818	21.4 (15.7–29.4)	1.60 (1.14–2.25)	1.64 (1.15–2.36)
Heart diseases				
No	263/19,779	10.3 (8.9–11.8)	Reference	Reference
Yes	88/3322	26.5 (21.5–32.6)	1.49 (1.16–1.93)	1.55 (1.18–2.04)
Stroke				
No	253/21,918	11.5 (10.2–13.1)	Reference	Reference
Yes	38/1183	32.1 (23.4–44.1)	1.74 (1.24–2.46)	1.53 (1.07–2.19)
Leisure activities				
Low	110/5363	20.5 (17.0–24.7)	Reference	Reference
Moderate	78/9727	8.0 (6.4–10.0)	0.62 (0.46–0.85)	0.56 (0.42–0.76)
High	26/5810	4.5 (3.0–6.6)	0.46 (0.29–0.74)	0.41 (0.27–0.65)
Social network				
Poor	113/5621	20.1 (16.7–24.2)	Reference	Reference
Moderate	88/7831	11.2 (9.1–13.8)	0.69 (0.51–0.93)	0.79 (0.59–1.06)
Rich	62/8689	7.1 (5.6–9.2)	0.57 (0.41–0.80)	0.70 (0.50–0.97)

Abbreviations: BMI, body mass index; IR, incidence rate; MMSE, Mini-Mental State Examination.

*Adjusted for baseline age, sex, and education.

†Adjusted for baseline age, sex, education, MMSE score, smoking, alcohol consumption, BMI, hypertension, high cholesterol, depression, and *APOE* ε4, as well as diabetes, stroke, and heart diseases, if applicable.

Table 3
Incidence rate (IR) per 1000 person-years and hazard ratio (HR) with 95% confidence interval (CI) of all-cause dementia (n = 291) by cardiometabolic diseases (CMDs) status during the 12-year follow-up (results of separate Cox regression models)

		Dementia			
CMDs status	No. of participants	No. of cases	IR	Basic-adjusted HR (95% CI)*	Multiadjusted HR (95% CI)†
No	1910	169	9.5	1.0 (Ref.)	1.0 (Ref.)
Yes	738	291	23.3	1.49 (1.18–1.90)	1.62 (1.27–2.08)
Only one	576	85	20.1	1.29 (0.99–1.68)‡	1.41 (1.07–1.86)
Diabetes	131	11	9.9	0.86 (0.47–1.58)	1.02 (0.55–1.90)
Heart diseases	349	53	22.2	1.27 (0.93–1.75)	1.44 (1.05–1.99)
Stroke	96	21	28.5	1.79 (1.14–2.83)	1.65 (1.03–2.65)
Any two	145	31	33.2	2.12 (1.44–3.12)	2.38 (1.58–3.59)
Diabetes + heart diseases	85	20	35.6	2.70 (1.69–4.31)	3.29 (2.01–5.39)
Diabetes + stroke	10	2	28.8	2.40 (0.59–9.74)	1.43 (0.18–11.16)
Heart diseases + stroke	50	9	29.8	1.42 (0.72–2.78)	1.59 (0.81–3.14)
Three (diabetes + heart disease + stroke)	17	6	80.1	6.57 (2.89–14.97)	4.76 (2.04–11.13)
P for trend				<.001	<.001

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination.
*Adjusted for baseline age, sex, and education.
†Adjusted for baseline age, sex, education, smoking, alcohol consumption, BMI, hypertension, MMSE score, high cholesterol, depression, and *APOE* ε4, as well as for diabetes, heart diseases, and stroke when applicable.
‡Showing borderline significance.

those without CMDs who had an active lifestyle) (Supplementary Table 1).

The HR for the statistical interaction between an active lifestyle and CMDs on dementia was 0.44 (95% CI 0.23–0.84, $P = .014$) after adjustment for age, sex, education, smoking, alcohol consumption, BMI, hypertension, MMSE, high cholesterol, depression, and *APOE* ε4. Our results suggest that an active lifestyle may significantly diminish the risk of dementia related to CMDs.

In participants with CMDs, the proportion of dementia cases attributable to an active lifestyle was 0.67 (95% CI 0.43–0.90). Thus, if all older adults with CMDs have an active lifestyle, about 67% of CMDs-related dementia cases could be prevented.

In Kaplan-Meier survival analysis, the median time from baseline to dementia occurrence was 11.44 years (IQR 7.69–11.69) in people without CMDs and active lifestyle, and 7.53 years (IQR 4.33–11.45) in people without CMDs plus inactive lifestyle, 8.74 years (IQR 4.94–11.66) in people with CMDs plus active lifestyle, and 5.24 years (IQR 2.37–8.56) in people with CMDs plus inactive lifestyle. Thus, an active lifestyle may delay dementia onset by 3.50 years in people with CMDs (Fig. 2).

Table 4
Hazard ratio (HR) and 95% confidence interval (CI) of dementia in relation to the joint exposure of active lifestyle and cardiometabolic diseases (CMDs)

Joint exposure		n	Dementia HR (95% CI)*	*P*
Leisure activities index	CMDs			
Moderate to high	No	1255	Reference	
Low	No	462	1.60 (1.11–2.31)	.012
Moderate to high	Yes	342	1.25 (0.82–1.91)	.306
Low	Yes	227	3.06 (2.06–4.56)	<.001
Social network index				
Moderate to rich	No	1333	Reference	
Poor	No	496	0.84 (0.57–1.25)	.392
Moderate to rich	Yes	408	1.23 (0.85–1.77)	.283
Poor	Yes	269	1.95 (1.28–2.96)	.002

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination.
*Adjusted for baseline age, sex, education, smoking, alcohol consumption, BMI, hypertension, MMSE, high cholesterol, depression, and *APOE* ε4, as well as leisure activities and social network if applicable.

3.4. Sensitivity analysis

The results were not much altered compared with those from the initial analysis when sensitivity analyses were performed (see details in Appendix C).

4. Discussion

In this large population-based cohort study, we found that (1) CMDs were associated with increased dementia risk, and the risk was dose-dependently related to the number of CMDs, (2) about 67% of CMDs-related dementia cases could be prevented if all older adults with CMDs have an active lifestyle (i.e., having moderate to high levels of leisure activities and/or a moderate to rich social network), and (3) an active lifestyle may delay dementia onset by 3.50 years in people with CMDs.

In recent decades, many prospective epidemiological studies have confirmed the association between individual CMDs, such as diabetes, heart disease, or stroke, and increased dementia risk. Researchers have found that

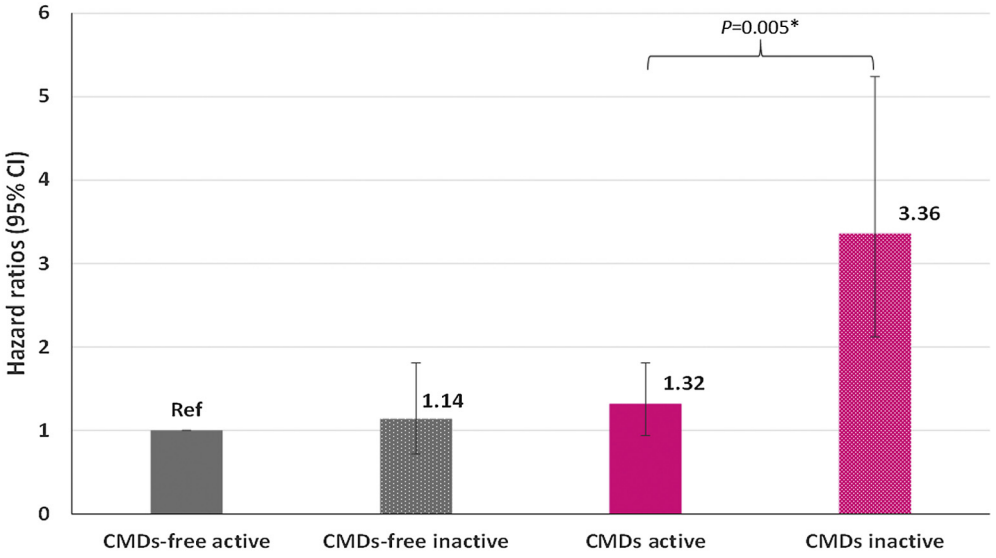

Fig. 1. Joint effect of cardiometabolic diseases (CMDs) and lifestyle (leisure activities and social network) on dementia. Multiadjusted hazard ratio (95% confidence interval) of dementia in relation to joint exposure of CMDs and lifestyle (adjusted for baseline age, sex, education, MMSE score, smoking, alcohol consumption, BMI, hypertension, high cholesterol, depression, and *APOE* ε4 allele). "Inactive" refers to low in both leisure activities and social network. "Active" refers to a moderate to high score on the leisure activities and/or a moderate to rich score on the social network index. *P value = .005 refers to the difference in the risk of dementia between participants with ≥1 CMD who were inactive versus those with ≥1 CMD who were active.

diabetes confers a 60% increased risk of dementia [28]; coronary heart disease, a 1.3-fold greater risk of dementia; and heart failure, a 1.8-fold greater risk [6]. A recent large meta-analysis showed that both prevalent and incident strokes double the risk of dementia [29]. In line with previous studies, we also observed that diabetes, heart diseases, and stroke confer a 1.6- to 2.0-fold greater risk of dementia.

However, given the clustering of different CMDs, it is important to address the combined contribution of CMDs to cognitive deterioration and dementia. One previous cross-sectional study described dose-dependent associations between CMDs and poor cognitive performance in reasoning tasks [30]. A prospective case-control study that investigated the trajectories of people with cardiometabolic risk factors (BMI, blood pressure, cholesterol, and blood glucose) found that the presence of such risk factors was

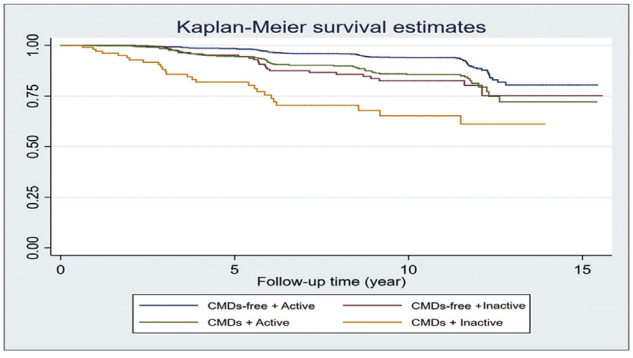

Fig. 2. Kaplan-Meier survival estimates from baseline to dementia occurrence by cardiometabolic diseases (CMDs; yes vs. no) and lifestyle (active vs. inactive) after adjustment for age, sex, and education.

associated with dementia [31]. To the best of our knowledge, our study is the first to provide evidence that comorbid CMDs predispose people to future dementia in a dose-response fashion.

Currently, there is no pharmacological cure for dementia. It is therefore important to identify protective lifestyle behaviors that can help postpone the clinical onset of dementia. Although some studies have reported a lack of associations between physically and/or socially stimulating leisure activities and decreased risk of dementia [32,33], many population-based studies show that being engaged in physically, mentally, and socially stimulating leisure activities was associated with lower dementia risk in older adults [34,35]. Moreover, social integration and social support have been related to better mental and physical health [36]. Having larger social networks of friends is associated with better cognitive performance in older adults [37]. However, these studies have focused on the effect of lifestyle behaviors on dementia risk, regardless of the role of CMDs. In the present study, we found that although CMDs significantly increase dementia risk, a high level of engagement in stimulating leisure activities and/or a rich social network could diminish this risk substantially. To our knowledge, this is the first study to provide the evidence of compensatory effect of an active lifestyle on dementia risk related to CMDs.

Interestingly, we also found that moderate to rich social network seemed to decrease the risk for dementia only among people with CMDs, but not those without CMDs. As a major part of the care for CMDs is carried out at home and by the family, social network can be a vital

component in the management of CMDs [38]. Our finding underscores the importance of social network among patients with CMDs for dementia prevention.

The counteracting effects of being engaged in leisure activities and having rich social networks on CMD-related dementia could be explained by two main hypotheses: the vascular hypothesis and the cognitive reserve hypothesis. First, long-term diabetes and cardiac vascular disease may induce systemic atherosclerosis including atherosclerotic lesions. Atherothrombotic stroke often reflects more severe cerebral atherosclerosis. Heart failure may affect cerebral blood flow. Brain hypoxia is a common consequence of both cerebral atherosclerotic lesions and chronic hypoperfusion, which eventually leads to dementia [39]. However, an active lifestyle may improve the person's cardiovascular and cerebrovascular health, thus modulating the processes linked to neuronal injury and neurodegeneration and delaying the clinical onset of dementia [40]. Second, according to the cognitive reserve hypothesis, engagement in physically, mentally, and socially stimulating activities provides an accumulation of neural resources, which can be used to compensate for the effects of CMDs on cognitive decline [41]. Furthermore, rich social networks motivate older adults to interact and be socially active, and therefore maintaining cognitive functioning. As a result, older people with CMDs but with an active and socially integrated lifestyle will maintain their brain capacity by activating compensatory networks to cope with underlying neurodegenerative processes [42].

The strengths of this study are the population-based study design with long follow-up and integration of data from multiple sources. Some limitations should also be mentioned. First, CMDs included only cardiovascular diseases [4,17] but not other vascular risk factors, such as overweight/obesity, high cholesterol, and hypertension, as they were not associated with increased risk of dementia. Second, selection bias may have occurred because of dropouts and deaths during follow-up. However, the proportion of people who declined to take part in follow-up examinations was low (14.8%). Compared with those who dropped out or died, the participants were more likely to be healthier. This might have led to an underestimation of the magnitude of the observed associations. Third, measurement errors might have occurred because of the use of self-reported questionnaires on leisure activities and social network. Although we ascertained information about the frequency of participation, we do not know to what extent the subjects participated in these activities. Because of the small number of participants in each subgroups, we could not determine the effect of any particular activity on dementia related to CMDs. Furthermore, information on social network sites was collected at baseline, and we do not have any information about the past social life of the participants. Thus, we cannot exclude the possibility that the higher incidence of dementia found among those persons with a poor/limited social network was the result of an abrupt change from a previously more extensive network. We therefore performed sensitivity analysis by excluding participants with a baseline MMSE score of $\leq$27 and incident dementia cases over 3 years of follow-up, which showed the results that were similar to those from initial analysis (Supplementary Table 2). In addition, leisure activity and social network could be correlated. Therefore, we mutually adjusted for leisure activity and social network in Cox models, and the results remained significant. Fourth, the diagnosis of anxiety was not available, although it could be partially included in depression diagnosis. Finally, although the statistical models included several potential confounders, there might be residual confounding due to unmeasured variables. Thus, our results can be generalized only to populations with characteristics similar to those of the SNAC-K population.

In conclusion, this is the first study to show that not only are CMDs associated with increased dementia risk, but also the risk increases in a dose-dependent fashion. However, an active lifestyle (i.e., having moderate to high levels of leisure activities and/or a moderate to rich social network) may significantly offset the risk of dementia related to CMDs. Our findings suggest that older adults with CMDs, especially multiple CMDs, warrant closer clinical monitoring for cognitive function.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.09.003.

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RESEARCH IN CONTEXT

1. Systematic review: PubMed and Web of Science databases were searched, and titles and abstracts were screened. Evidence about the magnitude of dementia risk in older adults who have more than one cardiometabolic disease (CMD) remains sparse. So far, no studies have investigated whether lifestyle behaviors can counteract or compensate the increased risk of dementia related to CMDs.
2. Interpretation: In this population-based longitudinal study, we found that CMDs were associated with increased dementia risk, and the risk was dose-dependently related to the number of CMDs. However, about 67% of CMD-related dementia cases could be prevented if all older adults with CMDs have an active lifestyle (i.e., having moderate to high levels of leisure activities and/or a moderate to rich social network). An active lifestyle may delay dementia onset by 3.50 years in people with CMDs.
3. Future directions: Future research should confirm the mitigating effect of active lifestyle on dementia related to CMDs and explore the mechanisms whereby active lifestyle may counteract the risk of dementia in people with CMDs.

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