RESEARCH ARTICLE

Cardiovascular Risk Trajectories and Risk of Developing Stroke and Dementia

A Community-Based Cohort Study in Taiwan

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Abstract

Background and Objectives

Stroke and dementia share common cardiovascular risk factors, but few studies have evaluated long-term changes in cardiovascular disease (CVD) risk scores, which may better capture cumulative vascular burden. We aimed to investigate whether the longitudinal trajectory of CVD risk was associated with the risk of developing stroke and dementia.

Methods

This prospective cohort study included residents aged 35 years and older from a community in northern Taiwan. We included participants without a history of stroke or dementia and assessed CVD risk at baseline (visit 1) and 3 follow-up visits (visits 2–4) from 1990 to 2000 using the Framingham general CVD risk function. CVD risk trajectories were modeled as linear changes over time using a pattern-mixture approach to account for attrition. Incident stroke and dementia were ascertained through linkage to National Health Insurance claims data starting in 2000. In the primary analysis, Cox proportional hazard models were used to estimate adjusted hazard ratios (HRs) for associations of CVD risk trajectory groups with risk of stroke and dementia. In the secondary analysis, we assessed the associations between baseline CVD risk and these outcomes.

Results

Among 2,335 participants (mean age 52.3 ± 11.2 years; 56.6% women), CVD risk trajectories over 10 years were classified as accelerated increase (29.2%), moderate increase (30.9%), or stable (39.9%). Over a median 21-year follow-up, an accelerated CVD risk trajectory, compared with the stable group, was associated with an increased risk of developing all stroke (HR 1.81, 95% CI 1.40–2.34), ischemic stroke (HR 1.84, 95% CI 1.37–2.48), hemorrhagic stroke (HR 2.38, 95% CI 1.49–3.80), and vascular dementia (HR 2.07, 95% CI 1.03–4.16). The secondary analysis revealed a positive association between baseline CVD risk and risk of developing stroke, but association with vascular dementia was weaker (baseline CVD risk ≥20% vs <10%: for stroke, HR 2.32, 95% CI 1.61–3.33; for vascular dementia, HR 1.84, 95% CI 0.74–4.56). No association was observed with all-cause or nonvascular dementia.

Discussion

Participants with an accelerated CVD risk had an elevated risk of developing stroke and vascular dementia. Our findings suggested that longitudinal trajectories of CVD risk may affect the risk of vascular dementia beyond individual baseline risks.

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Introduction

Stroke and dementia are among the leading causes of death and disability worldwide.[1,2] Cardiovascular conditions, such as atrial fibrillation and myocardial infarction, are established risk

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Glossary

AD = Alzheimer disease; **CVD** = cardiovascular disease; **HR** = hazard ratio; **ICD** = International Classification of Diseases.

factors of stroke and have been linked to cognitive impairment and the development of dementia in epidemiologic studies.[3-5] Stroke and dementia also share common cardiovascular risk factors.[6] While vascular dementia primarily results from cerebrovascular damage, vascular-related factors have also been implicated in the pathogenesis of neurodegeneration and other forms of dementia.[5,7] Neuropathologic studies have reported that vascular pathologies were present in 80% of patients with Alzheimer disease (AD).[8] Compared with patients with normal brains, those with vascular lesions, whether alone or mixed with Alzheimer pathology, were more likely to present with dementia.[9] These observations suggest that targeting modifiable cardiovascular risks could be a practical and promising approach to delaying or preventing both stroke and cognitive outcomes.[6,10,11]

Vascular risk factors typically emerge during midlife and are associated with an increased risk of developing dementia later in life.[12] Previous studies have reported associations of midlife cardiovascular risk factors, composite risk scores,[12,13] and the trajectories of individual risk factors with the risk of dementia.[14,15] However, only few studies have investigated longitudinal changes in multiple cardiovascular risk factors, which could more effectively capture the cumulative and dynamic nature of evolving vascular risks over time.[10] Such evidence may offer valuable insights for public health policies and clinical practice by highlighting the potential role of early and sustained cardiovascular risk management in mitigating dementia risk.

Cardiovascular risk prediction models are tools used to estimate an individual's future risk of cardiovascular disease (CVD) based on multiple risk factors and are recommended to support primary prevention.[16,17] The aim of this study was to evaluate whether the longitudinal trajectory of cardiovascular risk, estimated using a validated prediction model, was associated with subsequent risks of stroke and dementia in a middle-aged and older population. We also assessed the association between baseline CVD risk, measured at a single time point, and these outcomes.

Methods

Study Design and Participants

The Chin-Shan Community Cardiovascular Cohort Study is a prospective, longitudinal study of middle-aged and older adults recruited in 1990–1991 from a suburban township in northern Taipei, Taiwan.[18,19] Study recruitment was conducted with the assistance of local population authorities to identify all households with noninstitutionalized residents aged 35 years and older. Eligible residents were contacted by mailing invitation letters to their registered addresses, and those who agreed to participate were invited to complete baseline assessments in 1990–1991 (visit 1) at the Chin-Shan Community Health Center. Participants were invited for in-person follow-up assessments approximately every 2–5 years through 1999–2000, including visit 2 (1992–1993), visit 3 (1994–1995), and visit 4 (1999–2000) (Figure 1). For this analysis, participants were excluded if they (1) had a history of CVD, including coronary heart disease and stroke, at visit 1; (2) had a history of stroke or dementia or died before 2000; (3) had insufficient data to calculate the Framingham CVD risk trajectory; or (4) could not be successfully linked to National Health Insurance claims data for outcome ascertainment (Figure 1 and eFigure 1).

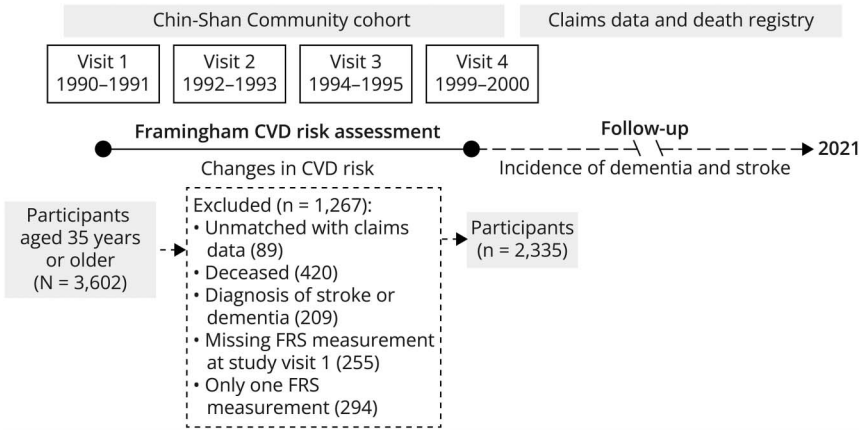
Framingham CVD Risk Trajectory

Detailed information about data collection procedures, including interviews, physical examinations, and laboratory measurements, has been described elsewhere.[19] In brief, at each study visit (1990–1991, 1992–1993, 1994–1995, and 1999–2000), data on demographics and lifestyle variables were collected through questionnaires. Information on CVD history such as hypertension, stroke, and coronary heart disease and anthropometric measurements were also collected. Overnight fasting blood and urine samples were obtained and stored at −70°C at National Taiwan University Hospital until analysis. Laboratory testing, including measurements of fasting glucose, lipids, and serum creatinine, was conducted at the hospital's central laboratory.[19] Details of the covariates used in this study are described in eMethods.

At each of the 4 study visits, we assessed CVD risk using the Framingham general CVD risk function, which provides an individual's predicted risk (probability) of developing CVD events within a 10-year time frame (Figure 1).[20] The risk was calculated separately for men and women by incorporating conventional CVD risk factors, including systolic blood pressure, antihypertensive medication use, total and high-density lipoprotein cholesterol levels, current smoking status, and diabetes status. Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dL (7.0 mmol/L) and/or a documented history of antidiabetic medication or insulin injections.

We classified participants into distinct longitudinal trajectories using the predicted CVD risk values calculated at the 4 study visits. Details of the approach are described in eMethods. In brief, the rate of change for each participant was estimated using a linear model that regressed Framingham CVD risk on time. The overall average rate of change in CVD risk was estimated using a pattern-mixture modeling approach with random coefficients to account for attrition bias caused by nonignorable dropout.[21] This method estimates individual CVD risks and applies age-specific dropout-pattern weights

Figure 1 Study Timeline and Participants



CVD = cardiovascular disease.

when computing the overall average risks. Participants whose predicted final CVD risk, which incorporated both baseline risk and the rate of change, was at least 1 SD above or below the overall average were classified into accelerated or stable trajectory groups, respectively.[10,21] All remaining participants were categorized into the moderate group.

Outcome Measure

The primary outcomes were incident stroke and incident dementia. Stroke was classified into ischemic and hemorrhagic types, and dementia was classified into vascular and nonvascular dementia. All outcomes were defined using the International Classification of Diseases (ICD), Ninth and Tenth Revision Clinical Modification diagnosis codes, identified through linkage to National Health Insurance claims data containing encrypted personal identifiers (eTable 1 gives ICD codes). Taiwan's National Health Insurance program is a compulsory social insurance system covering more than 99% of the population, and the claims data have been extensively used in research.[22,23] Stroke was defined as a hospital admission with corresponding diagnosis codes. Dementia was identified using relevant ICD codes assigned by a psychiatrist or neurologist, documented in at least 3 outpatient visits or 1 hospital admission.

The follow-up period began on the date of study visit 4 in 2000 and continued until the first occurrence of outcomes (stroke or dementia), death, or the end of the study on December 31, 2021. Stroke, dementia, and their major types were analyzed separately. Participants diagnosed with both vascular and nonvascular dementia (i.e., mixed dementia) were included in both the vascular and nonvascular dementia analyses. Survival status and dates of death were ascertained through the National Death Registry. We considered the likelihood of loss to follow-up to be minimal, given Taiwan's universal health coverage and the mandatory death registration system.[22,23] All data linkage and analysis were conducted at the Health and Welfare Data Center, Ministry of Health and Welfare, Taiwan, to ensure data confidentiality and security.

Statistical Analysis

In the primary analysis, we first plotted the mean predicted Framingham CVD risk and corresponding 95% CIs at the 4 study visits for each of the 3 trajectory groups, accelerated, moderate, and stable, to illustrate longitudinal changes in CVD risk. Cox proportional hazard models were used to estimate the hazard ratios (HRs) for stroke (all, ischemic, and hemorrhagic stroke) and dementia (all, vascular, and nonvascular dementia) associated with the CVD risk trajectories, with the stable group serving as the reference category. The models were applied separately for each outcome and adjusted for age, sex, educational level, occupation, alcohol consumption, and estimated glomerular filtration rate collected at study visit 1. In the multivariable-adjusted models for stroke, body mass index was included as an additional covariate based on evidence indicating a positive association between body mass index and stroke risk.[24] Participants with missing covariate data were excluded from the adjusted models. We did not perform multiple imputation because only 2 participants had missing values for alcohol consumption and 1 had missing values for body mass index. The proportional hazard assumption was tested by including interaction terms with the log of follow-up time and examining Schoenfeld residuals. No violations of the assumption were identified.

We performed a secondary analysis to evaluate the association between Framingham CVD risk measured at study visit 1 (baseline risk) and the risk of developing stroke and dementia. Participants were categorized into low-risk, intermediate-risk, and high-risk groups, with estimated baseline CVD risk values of <10%, ≥10%–<20%, and ≥20%, respectively.[20,25] We repeated the Cox proportional hazard models used in the primary analysis to estimate HRs for the

intermediate and high baseline CVD risk groups compared with the low-risk group.

Three sensitivity analyses were performed. First, death was considered a competing event for both stroke and dementia. In the primary analysis, we used the cause-specific hazard model, which is recommended for investigating etiologic associations in the presence of competing risk.[26,27] To provide a more comprehensive interpretation of the results, we also applied the Fine-Gray subdistribution hazard model to account for competing risk as a sensitivity analysis. Second, in the models for both stroke and dementia, we further adjusted for the average annual number of outpatient visits during the 2 years preceding the end of the CVD risk trajectory period (1998–2000) to evaluate the potential impact of detection bias.[28] Third, in the secondary analysis, a 10-year lag between baseline CVD risk and dementia ascertainment resulted in a 10-year period of immortal person-time for all participants. To evaluate the impact of this, we conducted an additional analysis using Framingham CVD risk measured at visit 4 (1999–2000), with follow-up beginning in 2000.

Data analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was determined using a p value with $\alpha = 0.05$.

Standard Protocol Approvals, Registrations, and Participant Consents

The institutional review board at China Medical University Hospital approved the study (CRREC-109-047), and informed consent was obtained from study participants.

Data Availability

Anonymized data are available on reasonable request from the corresponding author.

Results

Study Population

Of the 4,349 eligible residents invited to participate, 3,602 completed the baseline assessment (visit 1) between 1990 and 1991, yielding a response rate of 82.8%. Of the original cohort, 5.9% dropped out at visit 2 (1992–1993); 5.7% of those remaining dropped out at visit 3 (1994–1995), and 17.2% of those remaining dropped out at visit 4 (1999–2000). Participants who dropped out but remained alive were not excluded from this study. After applying exclusion criteria, 2,335 participants were included in the final analysis (Figure 1 and eFigure 1). Excluded participants were older and had a less favorable cardiovascular risk profile at visit 1 than those included (eTable 2).

Table 1 summarizes participant characteristics at visit 1. The mean age of all participants was 52.3 (SD = 11.2) years, and 56.6% of the participants were women. A total of 932 participants (39.9%) were classified into the stable group, 682 (29.2%) into the accelerated group, and 721 (30.9%) into the moderate group. Figure 2 shows the mean Framingham CVD risk (10-year probability) and the corresponding 95% CIs at the 4 study visits by trajectory group. At visit 1, the CVD risk was higher in the stable group than in the moderate group (mean CVD risk: 11.4%, 7.2%, and 17.7% in the stable, moderate, and accelerated groups, respectively). The moderate group exhibited a steady increase in CVD risk, whereas the accelerated group showed a marked progression. Boxplots of the CVD risk distribution at each visit are presented in eFigure 2.

Cardiovascular Risk Trajectory and Incident Stroke

A total of 371 participants developed stroke over a median follow-up of 21.4 years (interquartile range 11.4–22.0 years; total of 38,751 person-years). The mean age at stroke diagnosis was 76.2 (SD = 10.0) years (eTable 3). The incidence rates of overall stroke, ischemic stroke, and hemorrhagic stroke were higher in the accelerated group than in the stable or moderate groups (accelerated vs stable group, per 1,000 person-years: 15.5 vs 7.6 for overall stroke, 11.7 vs 5.7 for ischemic stroke, and 5.7 vs 2.1 for hemorrhagic stroke; Table 2). In multivariable-adjusted models, the HR for developing stroke was 1.46 (95% CI 1.11–1.92) in the moderate group and 1.81 (95% CI 1.40–2.34) in the accelerated group, compared with the stable group (p for trend, 0.061). Similarly, the risks of both ischemic and hemorrhagic stroke increased with worsening cardiovascular risk trajectories (p for trend <0.001 for both). For ischemic stroke, the HRs were 1.58 (95% CI 1.16–2.16) in the moderate group and 1.84 (95% CI 1.37–2.48) in the accelerated group, compared with the stable group. For hemorrhagic stroke, the corresponding HRs were 1.43 (95% CI 0.86–2.40) and 2.38 (95% CI 1.49–3.80), respectively.

Cardiovascular Risk Trajectory and Incident Dementia

During a median follow-up of 21.4 years (interquartile range: 12.5–22.0; total of 39,302 person-years), 319 participants had a new diagnosis of dementia recorded in our claims data (Table 3). The mean age at dementia diagnosis was 78.7 (SD = 8.4) years (eTable 3). The incidence rates of all-cause dementia and nonvascular dementia were higher in the stable group than in the moderate or accelerated groups (per 1,000 person-years, accelerated group vs stable: 8.4 vs 9.1 for all-cause dementia and 5.7 vs 8.4 for nonvascular dementia). By contrast, the incidence of vascular dementia increased progressively across the stable, moderate, and accelerated trajectory groups (1.0, 1.4, and 1.9 per 1,000 person-years, respectively). After controlling for potential baseline confounders, the HR for vascular dementia was 1.84 (95% CI 0.92–3.68) in the moderate group and 2.07 (95% CI 1.03–4.16) in the accelerated group, compared with that in the stable group (p for trend = 0.039). No association was observed between CVD risk trajectory and all-cause dementia (HR 1.08, 95% CI 0.82–1.41 for the moderate group; HR

Table 1 Characteristics of Participants According to the Longitudinal Trajectories of Framingham CVD Risk Over 10 Years

Characteristics[a]	Overall (n = 2,335)	CVD risk trajectory		
		Stable (n = 932)	Moderate (n = 721)	Accelerated (n = 682)
Age, y, mean (SD)	52.3 (11.2)	53.8 (10.9)	47.6 (10.5)	55.3 (10.6)
Women, n (%)	1,321 (56.6)	698 (74.9)	424 (58.8)	199 (29.2)
Education ≥9 y, n (%)	155 (6.6)	39 (4.2)	56 (7.8)	60 (8.8)
Occupation, n (%)				
Clerical	431 (18.5)	158 (17.0)	155 (21.5)	118 (17.3)
Labor	830 (35.6)	261 (28.0)	281 (39.0)	288 (42.2)
Others or unemployed	1,074 (46.0)	513 (55.0)	285 (39.5)	276 (40.5)
Regular exercise, n (%)[b]				
No	1,948 (85.3)	765 (82.1)	607 (84.2)	576 (84.5)
Yes	336 (14.7)	142 (15.2)	101 (14.0)	93 (13.6)
Alcohol drinking, n (%)[c]				
Never	1,687 (72.3)	757 (81.2)	508 (70.5)	422 (61.9)
Former	97 (4.2)	38 (4.1)	20 (2.8)	39 (5.7)
Current	549 (23.5)	136 (14.6)	193 (26.8)	220 (32.3)
Smoking, n (%)				
Never	1,560 (66.8)	732 (78.5)	525 (72.8)	303 (44.4)
Former	97 (4.2)	21 (2.3)	26 (3.6)	50 (7.3)
Current	678 (29.0)	179 (19.2)	170 (23.6)	329 (48.2)
Body mass index, kg/m^2, mean (SD)[d]	23.51 (3.3)	23.2 (3.2)	23.3 (3.1)	24.2 (3.5)
eGFR, mL/min/1.73 m^2				
Mean (SD)	98.5 (33.9)	96.4 (35.7)	101.1 (32.5)	98.7 (32.6)
eGFR ≤60	169 (7.2)	81 (8.7)	41 (5.7)	47 (6.9)
eGFR >60	2,166 (92.8)	851 (91.3)	680 (94.3)	635 (93.1)
Diabetes, n (%)	256 (11.0)	103 (11.1)	45 (6.2)	108 (15.8)
Antihypertensive medication, n (%)	101 (4.3)	42 (4.5)	17 (2.4)	42 (6.2)
Total cholesterol, mg/dL, mean (SD)	196.7 (44.3)	198.9 (44.8)	192.2 (43.3)	198.5 (44.4)
High-density lipoprotein cholesterol, mg/dL, mean (SD)	47.8 (12.1)	50.2 (12.7)	48 (11.1)	44.2 (11.6)
Systolic blood pressure, mm Hg, mean (SD)	121.7 (17.6)	121.7 (18.4)	117.3 (14.6)	126.2 (18.3)
Length of follow-up, y, mean (median)				
Stroke	16.6 (21.4)	16.8 (21.4)	18.2 (21.4)	14.6 (16.9)
Dementia	16.8 (21.4)	16.6 (20.9)	18.5 (21.4)	15.3 (18.4)

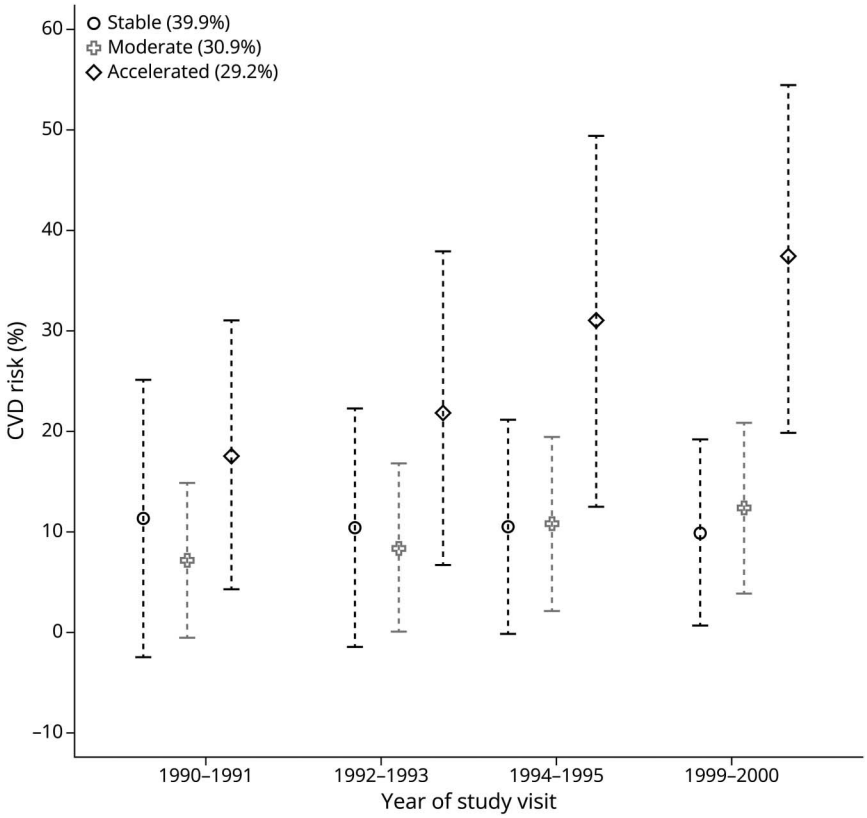
Abbreviations: CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.
[a] All information is from the baseline survey (1990–1991) unless otherwise indicated.
[b] Participants with missing values for regular exercise, n = 51.
[c] Participants with missing values for alcohol drinking, n = 2.
[d] Participants with missing values for body mass index, n = 1.

1.07, 95% CI 0.80–1.42 for the accelerated group, compared with the stable group; Table 3) or nonvascular dementia (HR 1.03, 95% CI 0.78–1.38 for the moderate group; HR 0.92, 95% CI 0.68–1.25 for the accelerated group; Table 3).

Baseline CVD Risk and Incident Stroke and Dementia

In the secondary analysis, the incidence rates of stroke among participants with low, intermediate, and high baseline CVD

Figure 2 CVD Risk Assessed Using the Framingham General CVD Model at 4 Visits in Accelerated, Moderate, and Stable CVD Risk Trajectory Groups



The figure illustrates the mean CVD risk (predicted probability of CVD within 10 years) for participants in each trajectory group at each study visit. Shaded areas indicate 95% CIs. CVD = cardiovascular disease.

risk were 5.1, 16.1, and 25.2 per 1,000 person-years (eTable 4). Compared with the low-risk group, adjusted HRs for overall stroke were 1.89 (95% CI 1.41–2.55) and 2.32 (95% CI 1.61–3.33) in the intermediate-risk and high-risk groups, respectively. A similar pattern was observed for ischemic stroke (HR 1.91, 95% CI 1.36–2.68 for the intermediate-risk group; HR 2.36, 95% CI 1.56–3.56 for the high-risk group; eTable 4). For hemorrhagic stroke, the risk was also elevated, but HRs were comparable between the intermediate-risk and high-risk groups (2.16 [95% CI 1.30–3.62] and 1.99 [95% CI 1.04–3.83], respectively).

The incidence of all-cause, vascular, and nonvascular dementia increased across the low, intermediate, and high baseline CVD risk groups (all-cause dementia: 6.5, 10.8, and 12.8 per 1,000 person-years; eTable 5). The associations of baseline CVD risk with both all-cause and nonvascular dementia no longer existed after adjusting for baseline covariates. The association with vascular dementia also attenuated substantially; the HR for high vs low CVD risk decreased from 3.55 (95% CI 1.86–6.77) in the unadjusted model to 1.84 (95% CI 0.74–4.56) after adjustment.

Sensitivity Analysis

In the Fine-Gray subdistribution hazard model, a positive association remained between the CVD risk trajectory and the incidence of overall stroke, ischemic stroke, and hemorrhagic stroke (eTable 6). No significant associations were observed between CVD risk trajectory and the incidence of all-cause or nonvascular dementia (eTable 7). Although not statistically significant, a positive association between CVD risk trajectory and vascular dementia was suggested. In the adjusted models, the subdistribution HR for vascular dementia was 1.62 (95% CI 0.80–3.26) in the moderate group and 1.84 (95% CI 0.92–3.70) in the accelerated group, compared with the stable group (p for trend 0.074).

Adjusting for the average annual number of outpatient visits yielded results consistent with the primary analyses for both stroke and dementia (eTable 8). In analysis using CVD risk measured at visit 4 as the baseline, the results were consistent with those of the main analysis (eTables 9 and 10).

Discussion

Our analysis linked the Framingham CVD risk trajectory to the risk of developing both stroke and dementia within the same cohort, considering the increasing global focus on their combined prevention.[3,6,11] We found that in a community-based cohort of middle-aged and older adults, a 10-year increase in individual CVD risk was associated with an

Table 2 Hazard Ratios of Developing Stroke Associated With Trajectories of Framingham CVD Risk

Trajectories of CVD risk	Person-years at risk	No. of events	Incidence[a] (95% CI)[b]	HR (95% CI)	
				Unadjusted	Adjusted
Overall stroke					
Stable	15,624	118	7.55 (6.25–9.04)	Ref.	Ref.
Moderate	13,116	99	7.55 (6.14–9.19)	1.00 (0.77–1.31)	1.46 (1.11–1.92)
Accelerated	9,954	154	15.47 (13.12–18.12)	2.04 (1.60–2.59)	1.81 (1.40–2.34)
Test for trend				<0.001	0.061
Ischemic stroke					
Stable	15,624	89	5.70 (4.58–7.01)	Ref.	Ref.
Moderate	13,116	80	6.10 (4.84–7.59)	1.07 (0.79–1.45)	1.58 (1.16–2.16)
Accelerated	9,954	116	11.65 (9.63–13.98)	2.04 (1.55–2.69)	1.84 (1.37–2.48)
Test for trend				<0.001	<0.001
Hemorrhagic stroke					
Stable	15,624	32	2.05 (1.40–2.89)	Ref.	Ref.
Moderate	13,116	30	2.29 (1.54–3.27)	1.11 (0.67–1.82)	1.43 (0.86–2.40)
Accelerated	9,954	57	5.73 (4.34–7.42)	2.84 (1.84–4.37)	2.38 (1.49–3.80)
Test for trend				<0.001	<0.001

Abbreviations: CVD = cardiovascular disease; HR = hazard ratio.
Models were adjusted for the following baseline covariates (1990–1991): age, sex, education level, occupation, alcohol drinking, estimated glomerular filtration rate, and body mass index (n = 2,332).
[a] Per 1,000 person-years
[b] Byar approximation of the exact Poisson distribution.

elevated risk of developing stroke (including all stroke, ischemic stroke, and hemorrhagic stroke) and vascular dementia later in life. Furthermore, participants with moderately elevated CVD risk exhibited an increased risk of developing stroke and vascular dementia compared with the stable group, despite having a lower baseline CVD risk than the stable group.

Dementia is a progressive and long-term pathologic process. Assessing long-term trajectories of CVD profiles, rather than relying solely on single time-point measurements, may provide a more comprehensive understanding of the cumulative CVD-associated risk of cognitive decline and dementia.[10,14] In our analysis, both baseline Framingham CVD risk and its trajectory were strongly associated with stroke; however, the association between the CVD risk trajectory and vascular dementia was stronger than that of baseline CVD risk. These findings underscore the significance of cumulative vascular burden over time, rather than baseline risk alone, in the development of vascular dementia. In addition, although the classification of CVD risk trajectory groups in our analysis accounted for both baseline CVD risk and changes over time, we did not evaluate the interaction between baseline CVD risk and trajectory groups. Future investigations examining potential interactions between baseline CVD risk and longitudinal changes may provide further insights for refining risk stratification and guiding intervention strategies.

Research examining the relationship between CVD risk trajectories and the incidence of dementia remains limited. In a Swedish cohort study, accelerated Framingham CVD risk was associated with increased risk of AD, vascular dementia, and memory decline.[10] Although not explicitly reported, the authors suggested a likely association with all-cause dementia, given the similar results for both AD and vascular dementia.[10] Their findings for vascular dementia are consistent with ours; however, we did not observe an association with overall or nonvascular dementia. These discrepancies may reflect differences in study populations, designs, and methods of dementia ascertainment. In the Swedish study, dementia was diagnosed through clinical assessments mainly based on DSM-IV criteria, and the associations with CVD risk trajectories were assessed from midlife to late life using a multistate survival analysis.[10] By contrast, we used diagnosis codes from administrative claims data to define dementia and focused on the long-term impact of early vascular risk exposure on later life dementia risk in a population predominantly of Han Chinese ethnicity. It is important to note that dementia remains clinically difficult to diagnose, and definitive diagnosis and characterization of neuropathology still require

Table 3 Hazard Ratios of Developing Dementia Associated With Trajectories of Framingham CVD Risk

Trajectories of CVD risk	Person-years at risk	No. of events	Incidence[a] (95% CI)[b]	HR (95% CI)	
				Unadjusted	Adjusted
All-cause dementia					
Stable	15,510	141	9.09 (7.65–10.72)	Ref.	Ref.
Moderate	13,311	90	6.76 (5.44–8.31)	0.71 (0.55–0.93)	1.08 (0.82–1.41)
Accelerated	10,426	88	8.44 (6.77–10.40)	0.96 (0.73–1.25)	1.07 (0.80–1.42)
Test for trend				0.015	0.59
Vascular dementia					
Stable	15,510	16	1.03 (0.59–1.68)	Ref.	Ref.
Moderate	13,311	18	1.35 (0.80–2.14)	1.25 (0.64–2.46)	1.84 (0.92–3.68)
Accelerated	10,426	20	1.92 (1.17–2.96)	1.92 (0.99–3.70)	2.07 (1.03–4.16)
Test for trend				0.053	0.039
Nonvascular dementia					
Stable	15,510	131	8.45 (7.06–10.02)	Ref.	Ref.
Moderate	13,311	80	6.01 (4.77–7.48)	0.68 (0.52–0.90)	1.03 (0.78–1.38)
Accelerated	10,426	70	6.71 (5.23–8.48)	0.82 (0.61–1.10)	0.92 (0.68–1.25)
Test for trend				0.007	0.87

Abbreviations: CVD = cardiovascular disease; HR = hazard ratio.
Models were adjusted for the following baseline covariates (1990–1991): age, sex, education level, occupation, alcohol drinking, and estimated glomerular filtration rate (n = 2,333).
[a] Per 1,000 person-years
[b] Byar approximation of the exact Poisson distribution.

autopsy.[29,30] Thus, differences in diagnostic practices and variations in case identification and classification may contribute to inconsistencies across studies.

Previous studies linking trajectories of individual cardiovascular risk factors to dementia risk support the importance of cumulative exposure burden.[14,31] A detailed example is the Framingham Offspring Cohort study, which showed that midlife systolic hypertension (mean age 55 years), persistent systolic hypertension from midlife to late life (mean age 69 years), and the cumulative burden of systolic blood pressure over time were all associated with an elevated risk of subsequent dementia.[31] In that study, blood pressure was measured repeatedly over a period of up to 18 years, which is considerably longer than the 10-year trajectory assessed in our study, highlighting the significance of long-term exposure. Future studies that examine trajectories of individual risk factors and overall cardiovascular risk across the life course and at different ages (e.g., midlife and late life) may provide deeper insight into these associations.

Although previous studies have linked a high baseline Framingham CVD risk score to accelerated cognitive decline[32,33] and to increased risk of progression from mild cognitive impairment to dementia,[13] we did not find evidence of an association between baseline CVD risk and incident dementia after covariate adjustment. One possible explanation is the difference in follow-up time. Previous studies had mean or median follow-up periods of less than 6 years. During the prolonged preclinical phase of dementia, behavior and physiologic changes may already be influenced by early neuropathologic processes, rather than serving as causal risk factors.[12] Thus, in studies with relatively short follow-up and no lag between exposure measurement and dementia ascertainment, exposures assessed a few years before dementia onset may already be influenced by preclinical disease process, potentially leading to reverse causation. Supporting this, studies with long follow-up have shown that the observed associations attenuated or disappeared after excluding dementia cases diagnosed within the first decade after baseline exposure assessment.[12,34,35] In our analysis, incident cases of dementia were identified 10 years after the baseline CVD risk assessment and the median follow-up was 21 years. This design may help mitigate the potential for reverse causation.

The Framingham general CVD risk function has been well validated across various ethnic populations, including Asians, for primary CVD prevention.[25,36] Our findings are supported by a recent study demonstrating that major CVDs, such as heart failure, peripheral arterial disease, stroke, and

myocardial infarction, which are end points of the Framingham model, have a substantially stronger association with vascular dementia than with AD.[4] Furthermore, a review integrating evidence from observational studies, Mendelian randomization studies, and randomized clinical trials indicates that midlife hypertension and diabetes are significant risk factors of both AD and vascular dementia, whereas findings regarding other risk factors such as lipids and smoking remain inconsistent.[37] These observations highlight the need for further research to clarify the pathogenesis of dementia and identify potential shared causal risk factors between CVD and dementia.[7]

In the presence of competing risks, the cause-specific hazard model and the Fine-Gray subdistribution hazard model are 2 commonly used approaches, which differ in their focus and interpretation.[26] The former estimates the effect of exposure on the cause-specific hazard for the outcome of interest by treating competing events (e.g., death) as censored, whereas the latter retains individuals who have experienced competing events in the risk set and models the cumulative incidence of the outcome. Consequently, the Fine-Gray method captures both the direct effect of exposure on the outcome and the indirect effect through competing risks.[38] In our analyses, associations between CVD risk trajectory and the outcomes were attenuated when using the Fine-Gray method, particularly for vascular dementia, although the overall trends remained consistent with the cause-specific model. This attenuation may, at least in part, reflect an indirect effect of CVD risk trajectory on vascular dementia through death: an accelerated CVD risk trajectory increases mortality, thereby precluding the occurrence of vascular dementia. The competing risk of death may have a greater impact on vascular dementia than on stroke because vascular dementia typically occurs at older ages. In this study, the mean age at diagnosis was 79.2 years for vascular dementia and 76.2 years for stroke (eTable 3). Our findings highlight the importance of appropriately accounting for the competing risk of death when aiming to estimate the absolute risk of vascular dementia, such as in the development of prediction models, for which the Fine-Gray model is generally recommended.[26,39]

Strengths of this study include an extended follow-up duration, which facilitates a clear temporal sequence between the assessment of CVD risk trajectory and dementia diagnosis. Minimal loss to follow-up was achieved by linking to claims data from a national health insurance program that provides health care coverage to over 99% of the population in Taiwan.[23] We used a pattern-mixture modeling approach to address nonignorable dropout and missing data regarding CVD risk predicted values in the analysis of CVD risk trajectory.[10,21]

There are some limitations to this study. First, the outcome assessment based on health insurance claims data may have resulted in misclassification, particularly concerning dementia, as the ICD codes have not yet been validated. To enhance the likelihood of identifying true cases, dementia was defined based on diagnosis codes assigned by a neurologist or psychiatrist, with documentation from at least 3 outpatient visits or 1 hospital admission. Additional analysis revealed that 83.3% of participants with vascular dementia had been diagnosed with either a stroke or coronary heart disease during the follow-up period, which supports the expected clinical profile of vascular dementia. Second, survivor selection bias may have occurred because only participants who survived until study visit 4 (1999–2000) were included in the analysis.[40] Competing risk of death during follow-up could have also introduced bias.[41] Strategies to mitigate these biases include extending the follow-up period, conducting competing risk analyses, and including younger individuals in the study.[7,40,41] In this study, most participants (74.7%) were younger than 65 years at visit 1. Furthermore, competing risk analysis using the Fine-Gray methods yielded results consistent with the main analyses, suggesting that biases did not substantially influence our main findings. Third, residual confounding remains possible because of the observational nature of this study. Fourth, the generalizability of our findings to other ethnic groups may be limited because the study participants were predominantly of Han Chinese ethnicity. Fifth, participants included in this analysis had more favorable cardiovascular risk profiles at baseline than those excluded from the analysis (eTable 2). This non-representativeness may have led to an underestimation of the associations between accelerated CVD risk trajectories and adverse outcomes.[42] Sixth, some residual bias may remain if the dropout mechanism was not fully captured by the model. Because participants who remained in follow-up generally had more favorable cardiovascular profiles, ignoring attrition would probably underestimate both the increase in CVD risk and its association with subsequent outcomes. Seventh, participants in the accelerated CVD risk group may have been more likely to receive a dementia diagnosis because of more frequent interactions with the health care encounters, potentially introducing detection bias.[28] Sensitivity analysis adjusting for the average annual number of outpatient visits did not materially change the results, suggesting that detection bias may not have substantially influenced our findings (eTable 8).

In conclusion, in this community-based cohort study conducted in Taiwan, an accelerated CVD risk trajectory was associated with an increased risk of stroke and vascular dementia later in life. Furthermore, longitudinal CVD risk trajectories may affect the risk of vascular dementia beyond individual baseline risks. Our observation of no association between CVD risk trajectory and all-cause or nonvascular dementia suggests that other underlying pathologic mechanisms and potential shared pathways between stroke and nonvascular dementia warrant further investigation.

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Author Contributions

P.-C. Chen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. T.-C. Su: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. Y.-Y. Chen: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. Y.-T. Lee: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. K.-L. Chien: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design.

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Disclosure

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