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Narrative Review

Cardiovascular Disease Burden and Longitudinal Changes in Cognitive Function among Older Adults: A Narrative Review

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Abstract

Cardiovascular diseases (CVD) and cognitive decline both impart a significant burden on the life and livelihood of elderly people. Growing evidence suggests an association between CVD burden with changes in cognitive outcomes. This narrative review aimed to compile, synthesize, compare, and critique findings from articles of the last 10 years regarding the temporal relationship between CVD burden and cognitive function among older adults. Electronic databases of PubMed and Google Scholar were searched for prospective cohort studies that estimated CVD burden in the form of the presence of CVDs, or assessment of health through CVD risk models and determined temporal change in cognitive function by either detailing cognitive decline or incident dementia/cognitive impairment. Seventeen original articles met with eligibility criteria during the screening process and were included. The follow-up period of the prospective cohort studies ranged from 24 months- 41 years. Framingham General CVD Risk Score and Atrial Fibrillation were the most frequently found CVD risk model and cardiovascular diseases associated with cognitive change, respectively. Incidence of dementia/cognitive impairment in various studies ranged from 4.2-14.9%. All but one of the studies had shown a positive longitudinal association between CVD burden and cognitive decline among the study participants. Consistent findings of the temporal relationship between CVD risk models and cognitive decline in the review pave the way for operationalizing preventive strategies that act on multiple cardiovascular risk factors before old age. Strategic reform and capacity building in pre-existing CVD health infrastructures could effectively reduce the dementia burden of any specific country.

Keywords: Cardiovascular Diseases, Cognitive Dysfunction, Dementia, Elderly

Introduction

Cognitive Function is a broad term that refers to mental processes involved in the acquisition of knowledge, manipulation of information, and reasoning.[1] Cognitive functions include domains of perception, visuospatial and executive function, memory, attention, decision-making, abstract thinking, and language abilities. Dementia, a leading global disease burden, is the irreversible end-point of the cognitive function spectrum. Diagnostic and Statistical Manual of Mental Disorders (DSM-V) refers to dementia, along with mild cognitive impairment (MCI) as 'neurocognitive disorders' which is characterized by a decline from a previously attained level of cognitive functioning.[2] The massive burden of neurocognitive disorders is reflected in the fact that around 60 million people are living with dementia, which is projected to be 152 million within 2050, among which about 60% of the cases come from low-to-middle income countries.[3]

While age is the strongest known predictor of cognitive decline, recent shreds of evidence have established an association between certain medical conditions and some lifestyle-related factors with the development of MCI and dementia. Cardiovascular co-morbidities like ischemic heart disease, cerebrovascular diseases, arterial fibrillation, etc., are documented to be associated with the development of dementia, whereas modification of cardiovascular risk factors like hyper-tension, obesity, diabetes, and physical inactivity is estimated to reduce 8.3% of the global Alzheimer's disease prevalence by 2050.[4] Cardiovascular/vascular risk models (like Framingham General CVD Risk Score (FGCRS), CAIDE, QRISK-1&2, WHO/ISH, ASSIGN-SCORE, etc.) contain multiple risk factors and predict overall cardiovascular health status in an individual.[5-9] Cardiovascular risk models along with the cardiovascular comorbidities comprise the overall

cardiovascular disease burden of an elderly individual, which in turn is an important predictor of cognitive function or incident dementia/cognitive impairment. The rationale for determining the temporal relationship of cardiovascular disease (CVD) burden with cognitive decline is that if substantial pieces of evidence were generated, identifying CVD burden, which is usually common among middle-aged or late working-group population, it could provide clinicians a therapeutic window to manage various neurocognitive disorders. Also, interventions to reduce the CVD burden would in turn delay the process of cognitive decline in the geriatric population. Although many studies focus on the association of cardiovascular disease and cognitive impairment in a cross-sectional manner, there is a glaring scarcity of systematic reviews on the temporal relationship of CVD burden and cognitive function in the existing literature, and gathering evidence regarding the issue would catalyze the policymakers to prioritize research efforts and implement resource-based focused interventions.

In this review, an effort was made to compile, synthesize, compare, and critique findings from research works of the last 10 years from around the world regarding the temporal relationship or longitudinal association of cardiovascular disease burden with cognitive function, i.e., cognitive decline and/or incident dementia/cognitive impairment among elderly people.

Materials and Methods

This research work is a narrative review, such as the articles were reported as narrative results and no meta-analysis could be performed due to the wide variability of the articles in the primary and secondary outcomes, and methodology applied. The period of the study was from July 2021 to February 2022.

Information Sources and Search Strategy

The review was undertaken conforming with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[10] Electronic databases of MEDLINE/PubMed (https://www.ncbi.nlm.nih.gov) and Google Scholar (https://scholar.google.com) were searched for pre-print and published literature from January 1, 2011, until December 31, 2021. A combination of the following terms was included in the initial field search: "Cardiovascular risk," "Cardiovascular health", "Cardiovascular comorbidities", "Cardiovascular disease", "Cardiovascular abnormalities", "Cognit", "Neurocognitive disorder", "Delirium, Dementia, Amnestic, Cognitive Disorders", "Elderly", "Older adults", "MCI", "Vascular risk", and "Stroke risk". Boolean operators such as "AND" and "OR" were used in the search engines. Any stop words like adverbs, prepositions, and conjunction were avoided. The keywords for the advanced search were constructed after analysis of MeSH and entry terms as per the PICO format of the research question (for MEDLINE) (Supplementary 1: sample search strategy). Additionally, reference lists from the index articles selected through electronic database search were searched manually for articles. Database search was done in two phases, at first in July 2021, where a search strategy was developed and initial analysis conducted; and finally in January 2022 to accommodate articles identified from forward and backward reference search and the ones published recently.

Eligibility Criteria and Study Selection

The selection of articles was restricted to human studies and articles published in English. Original research findings based on primary data were explored and included if found suitable. After completing the literature search, merging the search results from different sources and removal of duplicate studies were done by manual checking. All titles and abstracts were examined to remove irrelevant studies or documents. In the next step, the available full texts of the selected studies were retrieved by filtering the abstract-only papers. Articles were included in the review based on the following criteria:

i) The article must have examined the cardiovascular disease burden of the study participants (presence of cardiovascular diseases, assessment of health by various cardiovascular risk models, or combination of those two)
ii) Details of cognitive decline (or change) through various cognitive tests were available and/or incidences of dementia/cognitive impairment were reported over time, and finally,
iii) Prospective cohort studies

There was a list of definitive exclusion criteria which were applied during the article screening process. They were as follows: a) Articles not in English languages, b) non-human studies, c) Studies where there was no

reported temporal association between cardiovascular disease burden and cognitive outcome, d) study participants' age less than 50 years during follow-up assessment, e) protocols of cohort studies.

Additional filters of date of publications were applied upon exclusion criteria.

Data Extraction and Charting

Data extraction was done from individual full-text studies in two separate structured extraction sheets in Microsoft Excel. In one sheet, information like author name, journal, year of publication, study setting, length to follow-up period, participant characteristics, and source of data was extracted. In another sheet, relevant output data of each full-text study in the form of influence of CVD burden on cognition was extracted along with the type of CVD burden measured, cognitive outcome diagnostic criteria, statistics used, confounders present in the outcome findings, and the status of cognitive decline/incident dementia.

The search strategy was first developed and completed by BC. To validate the process, BP and RD independently reviewed a proportion of the documents included for full-text review, and any discrepancies with regards to inclusion were discussed by BC, BP, and RD to reach consensus.

- *Framingham General Cardiovascular disease risk score/Framingham Coronary Heart Disease Risk Score (FGCVDRS): [Kaffashian et.al.] [Yaffe et.al.]*

It provides an estimate of the risk of CVD over a 10-year period. Components are: Age, HDL cholesterol, total cholesterol, systolic blood pressure, cigarette smoking, and diabetes. FGCRS>10 is denoted as high 10-year CVD risk.

- *The Framingham Stroke Risk Score (FSRS): [Dregan et.al.] [Unverzagt et.al.]*

It combines stroke risk factors (age, sex, systolic blood pressure, use of antihypertensives, presence/absence of left ventricular hypertrophy on ECG, prevalent cardiovascular disease, current smoking status, current/previous atrial fibrillation, and diabetes mellitus) to predict 10-year probability of stroke

- *PATHrisk: [Anstey et.al.]*

Score of 0 to 6. Six Components: Diabetes + smoking + hypertension + depression + insufficient physical activity + High BMI.

- *Absolute CVD risk score (%): [Makino et.al.]*

Derived by region-specific estimation of WHO CVD-risk charts. Includes: age, sex, current history of diabetes mellitus, smoking status, systolic blood pressure, and total cholesterol. Stratification of risk: - Low= <10%, moderate=10-20%, high= >20%.

- *AHA Cardiovascular Health Score: [Samieri et.al.]*

A CVD risk model developed to ascertain Cardiovascular health status by categorizing 7 metrics into optimal, intermediate, and poor level (assigning 2,1,0 points respectively): Smoking, Physical activity, Healthy Diet, BMI, Total Cholesterol, Blood pressure and Fasting Plasma Glucose.

- *VRF: [Carmasin et.al.]*

A vascular risk-factor index, whose components are- diabetes, cardiovascular disease, high blood pressure, history of heart attack, angina, circulation problems, and history of stroke.

Figure 1. Selected Cardiovascular Risk Model Definitions.

Data Items and Operational Definition

The review aimed to critique the evidence of the influence of CVD burdens on cognitive function among elderly people. During the final follow-up assessment of any of the individual studies, when cognitive outcomes were measured, any person who was 50 years or above was considered elderly. The reason for the apparent age-threshold reduction compared to the conventional definitions of older adults was to incorporate midlife cardiovascular risks which impart significant influence in late-life cognitive decline.

CVD burden was operationalized as three of the following conditions measured in individual studies, in any combinations, namely: i) cardiovascular diseases like coronary artery diseases, arrhythmia, cerebrovascular diseases, and ii) cardiovascular disease risk models like Framingham Coronary Heart Disease Risk, FGCRS, PATHrisk, Framingham Stroke Risk Score (FSRS), Absolute CVD risk, CAIDE model, etc.[5,6,11-14]

Definition of Few of the cardiovascular risk models mentioned here are briefed in Figure 1.

Results

Main Search

The main systematic literature search resulted in 1088 records for review. Additionally, 21 records were identified from reference lists and expert recommend-dations. Out of them, 268 were duplicates, and hence, removed. After reviewing titles/abstracts for eligibility, 221 records were retained for full-text evaluation. In total, 17 articles met the eligibility (inclusion and exclusion) criteria and were finally included in the review. The primary reasons for exclusions were that the designs of the studies were not longitudinal or outcomes were not appropriate for the review objectives. Figure 2 demonstrates the number of records in each phase of the screening procedure as per a PRISMA flowchart.

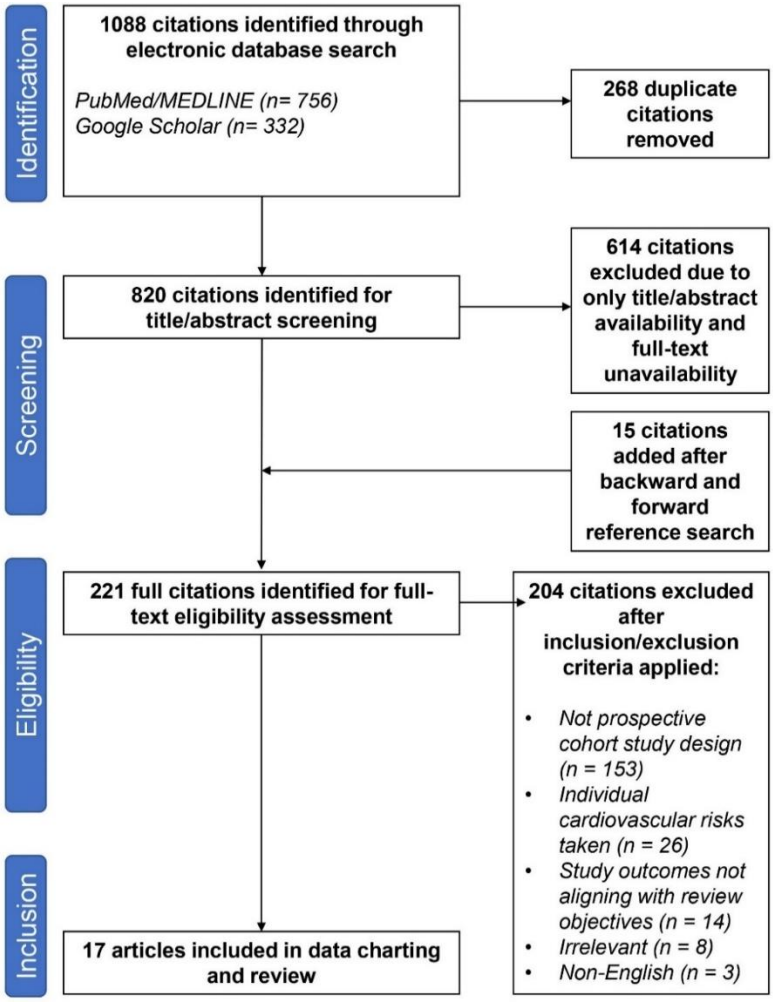

Figure 2. PRISMA flow Diagram for Identification, Screening, Eligibility Testing, and Inclusion Process of Selected Studies in the Narrative Review.

Study Characteristics

After the comprehensive selection process, 17 original articles with a prospective cohort study design were included for analysis in the review.[15-31] The included studies added up to around 1,30,000 elderly persons recruited from all around the world: the USA, the UK, Scandinavian Countries Sweden and Finland, Germany, France, Australia, Japan, Korea, South Africa, Brazil, China, India, etc. (Supplementary 2: Geographical Heatmap of countries as the study settings of the included studies). The length of the follow-up period ranged from 24 months to 41 years. The mean age of the study participants at baseline ranged from 40 to 85 years. All but one study were gender-neutral; the Women's Health Initiative Memory Study (WHIMS) by Haring et al.,[27] was a female-only study. Out of the included studies, only four were institution-based, one was conducted through telephonic interviews, rest of them were population-based studies in the community setting. Table 1 shows a detailed summary of included studies according to specific parameters like author and journal names, year of publication, source of data length to follow-up, and sample characteristics.

Table 1. Summary of Studies Included in the Review (Author, Year of Publication, Study Design, Study Setting, Follow-up Period, Sample Characteristics) (n = 17)

Name of Author (year of publication) and Data Source	Study Setting	Follow-up Period	Sample Characteristics
Covello et al. (2021)[15] HRS: Health and Retirement Study	USA Clinic-based	8 years	Adults aged more than 65 years Exposed cohort: Incident CVD group- 1305 Non-exposed cohort: age- and gender-matched control group- 2610
Makino et al. (2021)[16] NGCC-SGS, Japanese National Cohort study	Obu City, Aichi Prefecture Community-based	48 ± 2 months	Non-hospitalized Adults aged more than 65 years: 5104 completed baseline assessment 2783 cognitively intact participants without CVD 1641 completed follow-up assessment
Yaffe et al. (2020)[17] CARDIA (The Coronary Artery Risk Development in Young Adults) Study	4 US Cities: Birmingham (AL), Chicago (IL), Minneapolis (MN) {Community-based}, and Oakland (CA) {Health-care settings}	5 years	The final analytic cohort consisted of 2675 people Mean age: 50.2 ± 36 57% female, 45% black population.
Song et al. (2020)[18] Rush Memory and Aging Project (MAP)	Northeastern Illinois; Community-based study	Participants were annually followedup for 21 years	1588 dementia-free participants Mean age: 79.5 years
Schubert et al. (2019)[19] BDOS (Beaver Dam Offspring Study) Epidemiology of hearing loss study	Beaver Dam, Wisconsin, USA. Population-based	5-year, and 10-year follow-up	2556 participants without cognitive impairment at baseline. Mean age: 50 years
Ding et al. (2018)[20] SNAC-K: Swedish National Study on Aging and Care	Kungsholmen, Stockholm, Sweden; Population-based study	10 years	Dementia-free persons of age 60 and above living at home or institutions selected from 11 agecohorts. 3,363 attended baseline investigation (73.3% response) 2,263 in the final analytical sample
Samieri et al. (2018)[21]	Three French Cities: Bordeaux	Mean follow-up duration: 8.5 years	6626 participants aged 65 years or above without a history of CVD or dementia at

Three-City Study (3C)	Dijon Montpellier Population-based study		baseline were selected Mean age of 73.7 years, 63.4% are women
Bleckwenn et al. (2017)[22] AgeCoDe	Clinic-based; Registries of 138 GPs in Six Cities in Germany: Bonn, Dusseldorf, Hamburg, Leipzig, Mannheim, Munich	Patients were followed-up in 6 monthly intervals up to 4.5 years	118 patients with probable mild-to-moderate AD or mixed dementia. Mean age: 85.6 ± 3.4 years
Gardener et al. (2016)[23] NOMAS (Northern Manhattan Study)	Urban population of New York City	Mean time from baseline assessment and first assessment of neuropsychiatric test: 7.2±2.4 years, from Neuropsychiatric I to II: 6±2 years	1091 people clinically stroke-free, >50 years of age, with no contraindication to MRI were included. Mean age at initial cognitive assessment: 72±8 years.
Carmasin et al. (2014)[24] BSBA: The Baltimore Study of Black Aging	Baltimore, MD, USA. Community-based study	Follow-up after 2.5 years of baseline assessment	435 community-dwelling, African American, older adults residing in Baltimore were included. Mean age: 68.8 ± 9.0 years
Anstey et al. (2014)[12] PATH Through Life Project	Canberra and the neighboring town of Queanbeyan, NSW, Australia Community-based study	8-year follow-up with cognitive assessment in a 4-yearly interval	A mid-life cohort of Australian Citizens. Wave 1: n= 2530 Wave 2: n= 2354 Wave 3: n= 2182 Age 40-44 at baseline
Rusanen et al. (2014)[25] CAIDE Study	Towns of Kuopio and Joensuu in Eastern Finland. Population-based	The mean follow-up time from midlife was 25.5 ± 6.3 years and from late-life (first re-examination) 7.8 ± 1.0 years	The analytical cohort includes 1510 participants of the CAIDE study aged 65 to 79 years, undergoing first re-examination of cognitive status and not diagnosed dementia in it
Haring et al. (2013)[26] WHIMS (The Women's Health Initiative Memory Study)	USA Clinic-based, study population selected from 39 clinical centers	Median follow-up: 8.4 years	7479 post-menopausal women, aged >65 years and free from dementia during enrollment are selected Analytic cohort: 6455
Hazzouri et al. (2013)[27] SALSA (Sacramento Area Latino Study on Aging)	Sacramento, CA, USA Community-based	Every 12 to 15 months, biological and clinical data were collected on participants in-home visits for a maximum of 6 follow-ups	1116 community-dwelling older Mexican American aged 60-101 years
Dregan et al. (2012)[28] ELSA (English Longitudinal Study of Ageing)	England. Community-based	Cognitive outcomes at 4-year and 8-year follow-ups were estimated	8780 persons (>50 years of age) residing in a private household Mean age: 66.93 years, 55% female
Unverzagt et al. (2011)[29] REGARDS (The Reasons for Geographic and Racial Differences in Stroke)	USA Population-based	Mean follow-up 4.1 years	23,752 participants aged 45 years or above, without stroke at baseline is selected Mean age: 64.3 ± 9.2 years, 44% men
Kaffashian et al. (2011)[30] Whitehall-II study	England Community-based	Measures of cognitive function assessed three times over 10	The study sample consists of 3486 men and 1341 women. Mean age: 55 ± 6.0 years

		years from baseline data	

Cardiovascular Disease Burden

There was a large variability within the studies in employing cardiovascular burden to estimate its longitudinal association with cognitive decline/ incident dementia. Out of the 17 studies, five[15,20,22,25,26] estimated association with specific cardiovascular diseases, eleven[12,16-18,21,23,24,27-30] estimated temporal relationship of cognitive function with various CVD risk models, while only one[19] of them employed a combination of risk factors models and diseases. Framingham General CVD Risk Score was the most frequent cardiovascular risk model used among the included studies. Studies by Samieri et al.,[21] and Gardener et al.,[23] used cardio-protective models which were based on optimal cardiovascular health metrics, such as ideal diet, no smoking, BMI< 25kg/m^2, etc. Among the different cardiovascular diseases measured in the articles of the review, atrial fibrillation was found to be most frequently associated with cognitive decline or incident dementia.[20,25] Table 2 illustrates a detailed account of individual studies with their CVD disease burdens taken, cognitive outcome measurements, and statistical methods applied with adjusted covariates for the prospective cohorts.

Table 2. Summary of Studies in the Review Regarding Cardiovascular Disease Burden Observed, Cognitive Diagnostic Criteria, Outcome Statistics Employed, and Adjusted Covariates (n = 17)

Author	CVD Burden Used	Cognitive Outcome Measurement	Outcome Statistics; Adjusted Covariates
Studies that assessed cardiovascular diseases as CVD burden			
Covello et.al.[15]	CVD: Included self-reported CHD, angina, heart failure, MI, or other heart conditions	Incidence of Cognitive Impairment: Using Cumulative Incidence Function (CIF) CI was defined as a score < 11 on the 27-point Modified version of Telephone Interview for Cognitive Status	Effect of CVD and Covariates on Incidence of Cognitive Impairment per Sub-distribution Hazard Regression Model Competing risk of death
Ding et.al.[20]	Atrial Fibrillation (AF): Ascertained by clinical examination, ECG, and patient registry	Global Cognitive Function: MMSE Incident Dementia: DSM-IV for dementia NINDS-AIREN for vascular dementia NINCDS-ADRDA for Alzheimer's disease	Multiple linear mixed-effects and Cox regression models Education, smoking, alcohol consumption, physical activity, HTN, DM, high cholesterol,
Bleckwenn et.al.[22]	Presence of Coronary Heart Disease (CHD), as diagnosed by family physicians	Cognitive Decline: Measured by the change in MMSE score Cognitive-functional ability: Measured by Clinical Dementia Rating-Sum of Boxes. (CDR-SoB)	The association of prevalent CHD at baseline with patients' cognitive capacity was examined by latent variable growth curve modeling (LGCM) Age, Sex, education. Time since dementia diagnosis
Rusanen et.al.[25]	Mid-life and late-life AF, Heart Failure, Coronary artery disease (CAD)	Incident dementia: Dementia diagnosis by DSM-IV criteria AD diagnosis by NINCDS-ADRDA criteria	Flexible parametric survival models for dementia-free survival time were fitted to investigate the association between midlife and late-life AF, HF, CAD, or any heart disease combined and the later risk of dementia and AD Gender, education, mid-life vascular factors, APOE- ε4 carrier status
Haring et.al.[26]	CVD: The composite variable of any CVD was coded as positive if the participant reported a history of MI, angina pectoris, AF, HF, PAD, coronary bypass surgery, angioplasty, or carotid endarterectomy at enrollment	Incident Mild Cognitive Impairment or Possible Dementia: MMSE, CERAD battery of neuropsychological tests and standardized interviews, brain CT, Expert panel consensus diagnosis by DSM-IV criteria	Cox's proportional hazard model Age, race, education level, baseline MMSE, smoking, alcohol, physical activity, sleep hours, diabetes, HTN, BMI, Hypercholesterolemia, Depression, aspirin use
Studies that assessed cardiovascular risk models as CVD burden			

Makino et.al.[16]	Absolute CVD Risk (%)	Cognitive Impairment (≥1.5 SD below age and education-specific means in ≥1 cognitive test) NCGG-FAT: Word list memory- I & II Trail-making test- Part A (TMT-A) Trail-making test- Part B (TMT-B) Speed processing: Digit Symbol Substitution Test (DSST)	Multivariable (adjusted) logistic regression Education, BMI, medication, alcohol consumption habits, living arrangement, employment status, history of pulmonary diseases, depression
Yaffe et.al.[17]	Framingham Coronary Heart Disease Risk Score (FCHDR)	Cognitive Decline: Difference in composite cognitive z-score assessed by three tests: DSST, Stroop Test, Rey Auditory Verbal Learning Test (RAVLT) Accelerated cognitive decline: race-specific decline ≥1.5 SD from the mean change on a composite cognitive score	Logistic regression model Age, sex, race, physical activity, alcohol use, depression, APOE ε4
Song et.al.[18]	Framingham General Cardiovascular risk score (FGCRS) Categorized into tertiles: Lowest Middle Highest	Cognitive decline: Measured by a difference in z-scores of global cognitions (composite score), and domains like: episodic, semantic, working memory, visuospatial ability, and perceptual speed. Assessed by a battery of 19 tests.	β-coefficients from the linear mixed-Effects model for the longitudinal association of FGCRS with changes in global cognition and cognitive function in different domains over follow-up time. Age, sex, education, BMI, stroke, alcohol consumption, PA
Samieri et.al.[21]	AHA Cardiovascular Health score (0 to 14) No. of cardiovascular Health metrics on a recommended optimal level	Incident dementia: Diagnosed by neurologists by a 3-step procedure, supplemented by the DSM-IV criteria Cognitive Decline: Changes in the composite score (mean of z-scores from 4 cognitive assessment tests) of globalcognition MMSE, Isac's Set Test for verbal semantic fluency, Benton Visual Retention test, and TMT-A	Hazard ratios (HRs) of dementia per each additional metric at recommended optimal level and a per 1-point increase in the cardiovascular health score was estimated using Cox proportional hazardmodels with delayed entry and taking age as a time scale.
Gardener et.al.[23]	No. of Ideal Cardiovascular factors (Ideal CVD Metrics): from the AHA cardiovascular health score	Cognitive Domains: Domain-specific z-scores were derived for episodic memory, semantic memory, executive function, and Processing speed, based on initial performance and decline over time. Assessment by, several neuropsychological tests	Linear regression model. Socio-demographic variables and MRI brain markers
Carmasin et.al.[24]	VRF**:** 7 vascular risk factors: - diabetes, CVD, high BP, history of heart attack, angina, circulation problems, and history of stroke. Dichotomous If multiple (two or more) are present: The patient is a high risk	Mini-mental state examinationfor measuring cognitive change over a 2.5-year follow-up period The Wechsler Adult Intelligence Scale-Revised Digital Symbol Task: Measure for processing speed	Path Analysis Model: Exogenous variable: VRF (dichotomous) at baseline Endogenous: both baseline and 2.5-year follow-up versions of MMSE and digit symbol
Anstey et.al.[12]	PATHrisk score:A summary cardiovascular risk score (Range 0 to 6)	Domain-specific Cognitive function: Verbal ability: STW Processing Speed: SDMT Delayed and immediate recall: CVLT Working memory: DSB Reaction time: SRT and CRT Global cognitive score by averaging domain scores	Cognitive test scores are converted into z-scores. A linear mixed model (with random effects for intercept and time) using restricted maximum likelihood estimation was used

Hazzouri et.al.[27]	Framingham CVD Scores (Percentile)	Dementia and Cognitive Impairment, not dementia (CNID) incidence: Diagnosis through a multistage screening process by neurologists with the help of DSM-IV and NINCDS-ADRDA criteria. Cognitive decline: By change in cognitive score through MMSE and Spanish-English Verbal Learning Test	Cox's proportional Hazard model (Hazard ratio) for incident dementia and CVD risk. β-coefficient in a linear mixed-effects model for cognitive scores
Dregan et.al.[28]	Framingham Stroke Risk (FSR) Score: Quartiles Modified; Left-ventricular hypertrophy excluded 10-year Framingham Cardiovascular Disease Risk (FCVDR): Quartiles	Memory Index Executive Functioning index Cognitive Index (global cognition): summing up z-scores of memories and an executive function index	Linear regression analysis model used Age, sex, education
Unverzagt et.al.[29]	Framingham Stroke Risk Profile	Incident CI: Decline from a baseline score of 5 or 6 (of possible 6 points) to a score of ≤4 in the latest follow-up score on the Six-item Screener (SIS)	A multivariable logistic regression model Sex, Race, Region, and Education
Kaffashian et.al.[30]	Framingham CVD Score Raw scores were calculated and converted to 10-year risk or predicted probability of incident CVD (%)	Changes in the cognitive score: Measured by Alice Heim 4-1 (reasoning), test for memory, phonetic and semantic fluency, and vocabulary (Mill-Hill)	Regression analysis: β-coefficient Age, ethnicity, marital status, education
Studies that assessed a combination of cardiovascular diseases and cardiovascular risk models as CVD burden			
Schubert et.al.[19]	CVD (cardiovascular disease) and CVRF (cardiovascular disease-related risk factors)	10-y Cumulative Incidence of CI: MMSE<24/self-reported/MCI or dementia: Memory concerns and impairment in 1(MCI) or more (dementia) domains best on test performance (TMTA, TMTB, DSST, AVLT, VFT) 10-y decline in cognitive function	Cox's proportional Hazards model used Age, sex, education, head injury

Cognitive Outcome Measurement

While most of the articles included in the review assessed for change in cognitive function and/or incident cognitive impairment or dementia, the operational definitions and modes of assessment of cognitive function in the individual studies varied largely. Out of the 17 articles, seven delineated the level of incident dementia or cognitive impairment at the end of their respective follow-up periods. Ding et al., found the incidence of dementia at the end of a 9-year follow-up period to be 14.9%, the highest among the articles.[20] Seven articles used Mini-Mental State Examination (MMSE) to measure global cognition or cognitive decline,[19-22,24,26,27] whereas, the definition of DSM-IV and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria were majorly used for the diagnosis of dementia, with six and three articles respectively adopting the criteria. Yaffe et al., in their CARDIA longitudinal study computed a composite cognitive function score by a battery of three cognitive tests at baseline and the end of follow-up and used the mean change in composite cognitive z-scores to measure cognitive decline.[17] Use of a composite z-score from a battery of neuropsychiatric assessment tools for determining cognitive decline was also reported by another five articles.[16,18,21,23,28]

Covariate Adjustment and Analysis Method

Age, sex, race, education, marital status, Apo-lipoprotein E- ε4 (APOE- ε4) carrier status, lifestyle factors like physical activity, smoking, alcohol, head injury, baseline cognitive status, etc. were few of the most common covariates adjusted for in the articles to assert a temporal relationship between CVD burden and cognitive decline.

Five articles adopted Cox's Proportional Hazard model (Hazard ratios) to associate cardiovascular risks with incident dementia or cognitive impairment longitudinally.[19-21,26,27] A multiple linear mixed-effects regression model was used by four articles where cognitive scores were elicited at the end of the follow-up.[18,25,27,30] Bleckwenn et al., examined the association of baseline coronary heart disease with a patient's cognitive ability over time through latent variable growth curve monitoring,[22] while, Carmasin et al., incorporated the Path Analysis model to observe the influence of vascular risk factors on cognitive outcome in older individuals.[24]

Association of CVD Burden with Cognitive Decline

Table 3 gives a detailed account of the relevant findings of the longitudinal influence of CVD burden on the cognitive function, of each of the articles within the review.

Some of the studies found a longitudinal association of cardiovascular burden with change in all domains of cognitive function, while others only found an association with only some of the domains. For example, Gardener et al., found less decline in only specific domains of processing speed, executive function, and episodic memory with an increasing number of ideal Cardiovascular health factors.[23] Higher FGCRS scores, both absolute value or as percentile/tertiles, resulted in a faster decline in global cognitive functions, as reported by multiple articles.[17,18,27]

Author	Relevant findings on the longitudinal association of CVD Burden with Cognitive function change/incident dementia or cognitive impairment
Covello et al.[15]	The cumulative incidence analysis showed no significant difference in the likelihood of cognitive impairment between the CVD and control groups (29.7% vs. 30.6%, absolute difference − 0.9, 95% confidence interval − 5.6 to 3.7%)
Ding et al.[20]	As a time-varying variable, AF was significantly associated with a faster annual cognitive decline (MMSE) (β coefficient = −0.24, 95% CI: −0.31 to −0.16) and an increased hazard ratio (HR) of all-cause dementia (HR = 1.40, 95% CI: 1.11–1.77) and vascular and mixed dementia (HR = 1.88, 95% CI: 1.09–3.23)
Bleckwenn et al.[22]	The presence of CHD accelerated cognitive decline (MMSE, P<0.05) by about 66%, and reduced cognitive-functional ability (CDR-SoB, P<0.05) by about 83%
Rusanen et al.[25]	AF in latelife was an independent risk factor for dementia (HR 2.61, 95% CI 1.05–6.47) and AD (HR 2.54, 95% CI 1.04–6.16) in the fully adjusted analyses. The association was even stronger among the apolipoprotein E(APOE)- ε4 non-carriers
Haring et al.[26]	Women with CVD tended to be at increased risk for cognitive decline compared with those free of CVD (HR 1.29; 95% CI: 1.00, 1.67). Women with MI or other vascular diseases were at the highest risk (HR, 2.10; 95% CI: 1.40, 3.15 or HR, 1.97; 95% CI: 1.34, 2.87). Angina pectoris was moderately associated with cognitive decline (HR 1.45; 95% CI: 1.05, 2.01)
Makino et al.[16]	Cognitive Impairment is significantly associated with High (AOR=2.21,95% CI:1.24-3.95) and moderate (AOR=1.56,95% CI:1.02-2.38) CVD risk with low-risk as reference. After adjusting for potential confounding factors, the absolute CVD risk level was significantly associated with non-amnestic impairment but not with amnestic impairment
Yaffe et al.[17]	In the multivariable model, Smoking (AOR=1.65, 95%CI 1.02-2.71), Hypertension (AOR=1.87. 95% CI 1.26-2.75), and diabetes (AOR=2.45, 95%CI 1.54-3.88) associated with increased likelihood of accelerated cognitive decline The likelihood of accelerated cognitive decline increased with FCHDR score ≥ 10 (AOR=2.29, 95% CI 1.21-4.34)
Song et al.[18]	Compared with the lowest tertile of FGCRS, the highest tertile was associated with a faster decline in global cognition (β= -0.019, 95% CI: -0.035 to -0.003), episodic memory, working memory, and perceptual speed.
Samieri et al.[21]	In multivariable models, the hazard ratios for dementia were 0.90 (95%CI, 0.84-0.97) per additional optimal metric and 0.92 (95%CI, 0.89-0.96) per additional point on the global score. So, increased numbers of optimal cardiovascular health metrics and a higher cardiovascular health score were associated with lower rates of incident dementia and cognitive decline

Gardener et al.[23]	An increasing number of ideal CVH factors was associated with better processing speed at initial assessment and less decline. Among those with better cognitive performance at initial assessment, positive associations were observed between the number of ideal CVH factors and less decline in the domains of Executive Function and Episodic Memory.
Carmasin et al.[24]	Baseline VRF high risk was associated with baseline lower scores on MMSE and Digit symbol. VRF had a small, but direct negative effect (-0.16) on the 2.5-year follow-up Digit Symbol score, indicating baseline vascular risk factors predicted a change in processing speed. No effect on MMSE score over the 2.5-year follow-up period
Anstey et al.[12]	A Higher PATHrisk score was associated with poorerperformance on all cognitive tests, except for Reaction Time (RT). Participants with higher PATHrisk scores had greater slowing on choice RT over 8 years
Hazzouri et al.[27]	The annual decrease in the SEVLT score was- 0.09 points for women at the 25th percentile of CVD risk, 0.10 points at the 50th percentile, and 0.12 points at the 75th percentile (P value: CVD risk-time=0.02). From adjusted Cox models in women, compared with having <6 years of education, having 12+ years of education was associated with a 76% lower hazard of dementia/CIND (95% CI, 0.08 to 0.71) at the 25th percentile of CVD risk and with a 45% lower hazard (95% CI, 0.28 to 1.07) at the 75th percentile
Dregan et al.[28]	Participants in the highest quartile of FSR had lower global cognition (β = −0.73, CI: −1.37, −0.10), memory (β = −0.56, CI: −0.99, −0.12), and executive (β = −0.37, CI: −0.74, −0.01) scores at 4-year follow-up compared with those in the lower quartile. Similar findings with FCVDR scores also. Systolic BP≥160 mmHg was associated with lower global cognitive (b = −1.26, CI: −2.52, −0.01) and specific memory (b = −1.16, CI: −1.94, −0.37) scores at 8-year follow-up
Unverzagt et al.[29]	Higher FSRS was associated with incident CI (AOR=1.41, 95%CI= 1.37-1.46) Among the individual risk factors within the FSRP model, only Left Ventricular Hypertrophy at baseline was significantly associated with incident CI (AOR= 1.29, 95%CI= 1.05-1.58)
Kaffashian et al.[30]	In the multivariable model, 10% higher cardiovascular risk was associated with greater overall 10-year cognitive decline in men, reasoning in particular. (β= -0.47; 95% CI: -0.81 to -0.11)
Schubert et al.[19]	In the multivariable model, CVD (hazard ratio = 2.37, 95% confidence interval=1.24 - 4.52) was found to be associated with a 10-year cumulative incidence of cognitive impairment. Current smoking and diabetes were associated with increased risk, and exercise with decreased risk, of a 10-year decline in cognitive function

All but one article found results that agreed with the hypothesis of CVD burdens influencing cognitive function over time. The exceptional study was by Covello et al., which through cumulative incidence analysis showed no significant difference in the likelihood of cognitive impairment between people with cardiovascular diseases and without it (29.7% vs. 30.6%, absolute difference − 0.9, 95% confidence interval − 5.6 to 3.7%).[15]

Discussion

The narrative review of Seventeen longitudinal studies found that a variety of cardiovascular risk factor prediction models and diseases have been associated with cognitive decline over time. Evidence gathered from the review also pointed out a clear relationship between a higher amount of cardiovascular disease burden at baseline with increased risk of incident cognitive impairment or dementia. On the other hand, the presence of health-protective cardio- vascular factors was also found to be associated with less decline in cognitive function. These observations are in unison with WHO guidelines for risk reduction of cognitive decline and dementia, where they have recommended the management of CVD risk factors like hypertension, dyslipidemia, diabetes mellitus, etc.[31]

A systematic review and meta-analysis combining modifiable cardiovascular risk factors with the risk of dementia reported a consistent increased risk of dementia with increasing risk factors. (Pooled relative risk for dementia of 1.20, 1.65, and 2.21 for one, two, and more than two risk factors respectively).[32] Another systematic review by Harrison et al., observed a strong positive association between different cardiovascular risk models and future cognitive decline or incident dementia.[33] In this review, there was, however, large variability in studies concerning the cognitive outcome assessed and the pattern of associations observed with

cardiovascular disease burdens. Although a conclusion could be drawn on the directionality of association, variability of risk factor measurement and outcome statistics constrained the scope of performing a meta-analysis from this review, henceforth, the dose-response relationship could not be elicited.

The strength of the study lies in the fact that it incorporates evidence from studies that assessed not only individual cardiovascular risk factors, or only risk models, but in addition, cardiovascular diseases, and studies that found an association of change in future cognition with any combination of CVD burdens. In this review, all but one of the studies that assessed CVD Risk models in baseline reported significant cognitive decline after the follow-up period. This finding has an important clinical implication that even apparently well and cardiovascular disease-free individuals could be at future risk of dementia if cardiovascular risks are present.

This review inevitably has a few limitations. This review only entails a fragmented picture of the association of cardiovascular risk and cognitive decline all over the world, while this review is skewed by its Western studies, under-representation from studies from the Indian subcontinent and other parts of the world is visible. Large variability in study design, CVD burden assessment, and cognitive measures used made the generation of meaningful aggregates difficult.

Conclusion

Evidence gathered from the individual studies in the narrative review suggests that the presence of cardiovascular disease burden, in the form of diseases, and risk models, is associated with future cognitive decline or incident dementia in older individuals. The consistent relation of cognitive decline with higher CVD risk model scores offers an advantage in operationalizing prevention strategies on models, rather than individual risk factors, as cardiovascular multi morbidity is highly prevalent in old age. Hopefully, the findings from this review would catalyse clinicians, public health professionals, and organizations in early life detection of cardiovascular disease burdens in apparently healthy individuals who could potentially develop dementia in their later life.

Countries need to develop and implement their health policies keeping in mind the rising trend of preventable dementia. Countries like India, which do not have any national health program solely designated to dementia, could benefit from building capacity in the already existent managerial structure of the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS). Under NPCDCS, training human resources within public settings, about the potential CVD risk factors could in turn decrease the cognitive burden of the nation. With the exponential rise of people with dementia and cognitive impairment all around the world, future research work should be developed to synthesize evidence regarding the longitudinal association between specific cardiovascular disease burdens and specific-cause dementias, to reduce variability.

Conflict of Interest

The authors declare no conflicts of interest.

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Supplementary 1. Sample Search Strategy for MEDLINE

1. "Cardiovascular Diseases"[MeSH Major Topic:noexp] OR "cardiovascular disease*"[Title/Abstract] OR "cardiovascular abnormalit*"[Title/Abstract] OR "Cardiovascular Abnormalities"[MeSH Major Topic:noexp]
2. "Heart Disease Risk Factors"[MeSH Major Topic:noexp] OR "cardiovascular risk factor*"[Title/Abstract] OR "risk factors for heart disease"[Title/Abstract] OR "Risk Factors for Cardiovascular Disease"[Title/Abstract] OR "cardiovascular risk score*"[Title/Abstract] OR "cardiovascular risk"[Title/Abstract] OR "cardiovascular risks"[Title/Abstract] OR "residual cardiovascular risk*"[Title/Abstract]
3. 1 OR 2
4. "Cognitive Dysfunction"[MeSH Major Topic:noexp] OR "cognitive dysfunction*"[Title/Abstract] OR "cognitive impairment*"[Title/Abstract] OR "mild cognitive impairment*"[Title/Abstract] OR "mild neurocognitive disorder*"[Title/Abstract] OR "cognitive decline*"[Title/Abstract] OR "mental deterioration*"[Title/Abstract]
5. "Dementia"[MeSH Major Topic:noexp] OR "Alzheimer Disease"[MeSH Major Topic:noexp] OR "Alzheimer's Diseases"[Title/Abstract] OR "Alzheimer's Disease"[Title/Abstract] OR "alzheimer dementia*"[Title/Abstract] OR "Neurocognitive Disorders"[MeSH Major Topic:noexp] OR "delirium dementia amnestic cognitive disorders"[Title/Abstract] OR "neurocognitive disorder*"[Title/Abstract]
6. 4 OR 5
7. "Aged"[MeSH Major Topic:noexp] OR "elderly"[Title/Abstract] OR "Frail Elderly"[MeSH Major Topic:noexp] OR "frail elder*"[Title/Abstract] OR "older adult*"[Title/Abstract]
8. 3 AND 6 AND 7
9. Limit 8 to Publications in English, Human Studies, and from 01.01.2011 to 31.12.2021

Supplementary 2. Heatmap Showing Geographical Distribution of Study Setting of Studies Included in the Review