A Review of literature on Ischemic Heart Disease and Risk of Development of Cognitive Disorders

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ABSTRACT:
Aim: A Review of literature on Ischemic Heart Disease and Risk of Development of Cognitive Disorders
Methods: The literature search was conducted in Medline, Embase, PsycINFO, and CINAHL. The search string consisted of predictor-related terms (e.g. myocardial infarction, angina pectoris), outcome-related terms (e.g. dementia, Alzheimer, cognition), as well as some specific limitations. All publications until 2021 were included if they fulfilled the following eligibility criteria: 1) MI, AP, or a CHD variable that is a combination of MI and AP (e.g. ischemic heart disease (IHD)) as predictor variable; 2) cognition, cognitive impairment or dementia as outcome; 3) population-based study; 4) prospective (≥1 year follow-up), cross-sectional or case-control study design; 5) ≥100 participants; and 6) aged ≥45 years. Reference lists of publications and secondary literature were hand-searched for possible missing articles.
Results: The search yielded 3500 abstracts, of which (number***) were included in this study. This resulted in 5 cross-sectional studies, 3 case-control studies, 6 prospective cohort studies and 1 study with both cross-sectional and prospective analyses (designated as cross-sectional regarding study quality). Quality assessment of all 15 included studies was sufficient (overall mean NOS score = 6.7, SD = 1.30, range = 3–10). Separate analyses for each study design showed similar results for prospective (mean NOS score = 6.92, SD = 1.14, range = 5–9) and cross-sectional studies (mean NOS score = 7.23, SD = 0.98, range = 6–8), but the quality of case-control studies was somewhat lower (mean NOS score = 5.9, SD = 1.93, range = 3–7), mainly due to the effects of one particular study with a score of 3.
Conclusion: We concluded that the CHD was associated with an increased risk of cognitive impairment or dementia in prospective cohort studies. More mechanistic studies are needed that focus on the underlying biological pathways (e.g. left ventricular dysfunction, cerebral small vessel disease, hypoperfusion) and shared risks that link CHD with the occurence of cognitive impairment or dementia.
Keywords: Coronary heart disease (CHD), Atherosclerosis, Cognitive impairments, Dementia, middle age, old age and senile patients, Acute myocardial infarction(AMI), Percutaneous coronary intervention (PCI), Coronary artery bypass grafting (CABG)

INTRODUCTION

The term vascular cognitive impairment was introduced at the beginning of the new millennium and refers to the contribution of vascular pathology to any degree of cognitive impairment, ranging from subjective cognitive decline or mild cognitive impairment to dementia. IHD shares risk factors with cognitive impairment. These factors include age (men over 45 years old, women 55 years old), gender (men), family history of CVD. Common modifiable risk factors include elevated low-density lipoprotein cholesterol, hypertension, metabolic syndrome, diabetes mellitus, smoking, obesity, physical inactivity, mental stress, depression, excessive alcohol consumption. A recent analysis of studies on modifiable risk factors revealed several works on cardiac diseases, most of which reported a higher risk of cognitive impairment or dementia in this category of patients. It has been proven that

individuals with atrial fibrillation have a 36% increased risk of cognitive impairment or dementia.[1]

Coronary heart disease (CHD), heart failure (HF), and dementia are among the leading causes of death and disability[1,2] and often co-occur in the ageing population. The importance of late-life complications of cardiovascular disease has been amplified with the advances in cardiovascular medicine over the decades. Mortality due to CHD has plunged since its peak in the early 1960s, largely due to improvements in acute treatment and secondary prevention.[3] Similarly, the prognosis of HF has improved with better medical treatment and cardiac resynchronization therapy.[3,4] Despite great improvements in health care, these developments now render patients with cardiovascular disease susceptible to diseases that have their incidence peak in late-life, such as dementia. The brain is a highly vascularized organ, receiving 15% of cardiac output and accounting for about 20% of the body's total oxygen consumption despite comprising less than 3% of body weight[5], and it may therefore be particularly vulnerable to impairment in blood flow. The now well-established importance of cardiovascular risk factors in prevention of dementia, including Alzheimer's disease (AD)[6,7] further suggests that patients with manifest cardiovascular disease may be at increased risk of developing dementia years or even decades later. Because of the urgency for timely intervention to prevent dementia[8], this could hold important implications for focused preventive strategies.[9] However, evidence from longitudinal studies linking CHD and HF to dementia is fragmented, with inconsistencies between findings, and study populations are often too small to detect clinically relevant associations.

MATERIAL AND METHODS

The literature search was conducted on Medline, Embase, PsycINFO, and CINAHL. The search string consisted of predictor-related terms (e.g. myocardial infarction, angina pectoris), outcome-related terms (e.g. dementia, Alzheimer, cognition), as well as some specific limitations (e.g. only studies in human, language restrictions).

All publications until 2021 were included if they fulfilled the following eligibility criteria: 1) MI, AP, or a CHD variable that is a combination of MI and AP (e.g. ischemic heart disease (IHD)) as predictor variable; 2) cognition, cognitive impairment or dementia as outcome; 3) population-based study; 4) prospective (≥1 year follow-up), cross-sectional or case-control study design; 5) ≥100 participants; and 6) aged ≥45 years. Reference lists of publications and secondary literature (review articles, editorials, book chapters, etc.) were hand-searched for possible missing articles.

RESULTS

The search yielded 3500 abstracts, of which *** were included in this study. This resulted in 5 cross-sectional studies, 3 case-control studies, 6 prospective cohort studies and 1 study with both cross-sectional and prospective analyses (designated as cross-sectional regarding study quality). Quality assessment of all 15 included studies was sufficient (overall mean NOS score = 6.7, SD = 1.30, range = 3–10). Separate analyses for each study design showed similar results for prospective (mean NOS score = 6.92, SD = 1.14, range = 5–9) and cross-sectional studies (mean NOS score = 7.23, SD = 0.98, range = 6–8), but the quality of case-control studies was somewhat lower (mean NOS score = 5.9, SD = 1.93, range = 3–7), mainly due to the effects of one particular study with a score of 3. All 15 studies and their details and results are summarized in detail in Tables 1-3

Table 1
Characteristics of prospective cohort studies assessing the relation between angina pectoris, myocardial infarction, coronary heart disease and cognition or dementia.
Authors
Cohort/ sample/age/ follow-up
Outcome/cognitive test, diagnostic criteria
Predictor/ ascertainment of exposure
Adjustment for confounders
Most important results
Aronson et al., 1990[10]
Bronx Aging study; N = 442; mean age: 79.2; FU range = 2–7 years
Dementia; annual exam measures (including cognitive tests), interview with proxy informant, EEG, CT or MRI, psychiatric assessment, assignment of an ischemic score, DSM-III criteria, NINCDS-ADRDA, neuropathological confirmation
MI; medical and laboratory studies (e.g. blood sample, ECG)
Sex, age, word fluency, Blessed IMC error score
Significant association between MI and dementia (HR = 1.8 (1.03–3.2))
Kalmijn et al., 1996[11]
Zuthpen Elderly study; N = 353; mean age: 74.6; 3-year FU
Cognitive decline; drop of >2 points on the MMSE
CHD; diagnosis of MI or AP (self-report verified by medical records, ECGs, hospital discharge data, and notes from GP)
Age, education, baseline MMSE score
No significant association between CHD and cognitive decline (OR = 1.7 (0.8–3.5))
Ross et al., 1999[12]
Honolulu-Asia Aging study; N = 2,916; age range: 71–93; maximum FU = 28 years
VaD; cognitive screening with CASI, additional cognitive testing, interview with proxy-informant, full-dementia examination (interview, neurological examination, neuropsychological test battery), brain CT, laboratory tests, DSM-III-R criteria, expert panel consensus diagnosis
CHD; diagnosis of MI or AP (medical history, ECG)
Age, education, hypertension, diabetes, Western diet preference, use of Vitamin E, 1-hour postprandial glucose at examination 1
Significant association between CHD and VaD (OR = 2.5 (1.35–4.62))
Kivipelto et al., 2002[13]
North Karelia Project and FINMONICA study; N = 1,287; age range: 65–79; mean FU = 21 yearsAD, AD/VaD; 1) screening phase with MMSE; 2) clinical phase where participants (MMSE ≤ 24) underwent neurological, cardiovascular and neuropsychological examinations; 3) differential diagnosis phase (blood test, brain imaging, ECG and cerebrospinal fluid analysis) based on established criteria (DSM-IV, NINCDS-ADRDA)
MI; self-report of a physician diagnosis
Age, sex, education, smoking, alcohol consumption, APOE genotype
MI (as of the late-life visit) was significantly associated with AD (OR = 2.1 (1.1-4-5)) and AD or VaD (OR = 2.5 (1.2–5.4)). MI at midlife was not associated with AD.
Verhaeghen et al., 2003 [14]
Berlin Aging Study; N = 206; mean age >70; FU = 4 years
Cognitive decline; perceptual speed (Digit Letter, Identical Pictures), episodic memory (Paired Associates, Memory for text), fluency (Categories, Word Beginnings), knowledge (Vocabulary, Spot-a-Word), intelligence (composite based on four separate composites)

CHD; typical angina, Stenocardia, nitrate therapy, family doctor's diagnosis, ECG abnormalities

Age, sex, SES, dementia status

CHD was not associated with cognitive decline

Newman et al., 2005[15]

Cardiovascular Health study; N = 2,539; median age: 74; mean FU = 5.4 years

Dementia, AD with or without VaD, AD with no VaD; annual measures of cognition, detailed neurological and neuropsychological examinations, medical records, physician questionnaires, proxy-informant interviews, brain MRI, expert panel consensus diagnosis, several diagnostic criteria (e.g. NINCDS-ADRDA)

MI, AP; self-report confirmed by medical records, test results (e.g. ECG), or medication use at study entry (e.g. nitroglycerin)

Age at baseline, education, race, income, APOE genotype, modified MMSE score at time of brain MRI

The incidence of dementia was higher in those with MI or AP. In adjusted models, these associations were no longer or borderline significant (e.g. dementia: HR = 1.3 (1.0–1.9))

Hayden et al., 2006[16]

Cache County study; N = 3,264; mean age: 74; mean FU = 3.2 years

Dementia, AD, VaD; multi-stage cognitive screening procedure (e.g. cognitive test, proxy-informant questionnaires), full clinical assessment (neurological and neuropsychological assessment, laboratory tests, brain-imaging, expert panel consensus diagnosis, several diagnostic criteria (DSM-III-R, NINCDS-ADRDA, NINDS-AIREN)

MI; self-report or proxy-informant-report of a physician diagnosis together with self-reported treatment

Age, sex, education, hypertension, high cholesterol, diabetes, obesity, stroke, CABG, APOE genotype

MI was not significantly associated with dementia (HR = 1.13 (0.59–2.03))

Ikram et al., 2008[17]

Rotterdam study; N = 5,578; mean age > 68; maximum FU = 15 years

Dementia; cognitive screening tests, CAMDEX, neuropsychological assessment, imaging data, record linkage, expert panel consensus diagnosis, several diagnostic criteria (DSM-III-R, NINCDS-ADRDA, NINDS-AIREN)

MI (recognized); based on Q-wave (self-reported MI confirmed by ECG abnormalities) and non-Q-wave MI (self-reported MI confirmed by only clinical data)

Unrecognized MI; no self-reported or documented MI, but based on only ECG abnormalities

Age, sex, systolic blood pressure, diastolic blood pressure, BMI, atrial fibrillation, diabetes, current smoking, intima media thickness, total cholesterol, HDL-cholesterol, APOE genotype

Recognized MI was not significantly associated with dementia risk (HR = 1.12 (0.77–164)). Unrecognized MI was associated with an increased risk of dementia, but only in men (HR = 2.14 (1.37–3.35))

Chen et al., 2011[18]

Anhui cohort study; N = 1,307; mean age> 65; median FU = 3.9 years

Dementia; GMS-AGECAT diagnosis, death register (for cases who died in the FU before re-interviewing), psychiatrist's diagnosis (for patients from case-control study)

AP; doctor's diagnosis

Age, sex, education, main occupation, annual income, urban rurality, BMI, smoking habits, hobby's (e.g. playing chess, pet), relationship with others, living with others, worrying, hypochondriasis, anything severely upsetting, horrifying experience

AP was significantly associated with incident dementia (OR = 2.58 (1.01–6.59))

Haring et al., 2013[19]

Women's Health Initiative Memory study; N = 6,455; age range: 65–79; median FU = 8.4 years

Possible dementia, MCI, possible dementia or MCI; cognitive screening (3MSE), CERAD battery of neuropsychological tests and standardized interviews, interview with proxy-informant, review meeting with local physician (medical history, neuropsychiatric evaluation), brain CT, laboratory tests, expert panel consensus diagnosis, several diagnostic criteria (DSM-IV, CERAD)

MI; based on self-report or evolving Q-wave (ECG) AP; self-report

Age, education, race, HTR arm, baseline 3MSE, alcohol intake, smoking, physical activity, diabetes, sleep hours, hypertension, BMI, depression, waist-hip ratio, hypercholesterolemia, aspirin use

MI was significantly associated with for possible dementia or MCI (HR = 2.10 (1.40–3.15))

AP was moderately associated with possible dementia or MCI (HR = 1.45 (1.05–2.01))

Lipnicki et al., 2013[20]

Sydney Memory and Ageing study; N = 660*; mean age: 78.59; mean FU = 23 months, 12 days

Decline to MCI or dementia; MCI: participant or informant cognitive complaint, cognitive impairment on objective testing, no dementia diagnosis, normal function or minimal impairment in instrumental activities of daily living, expert panel consensus diagnosis, diagnostic criteria; dementia: expert panel consensus diagnosis, diagnostic criteria (DSM-IV)

MI; self-report of a physician diagnosis

AP; doctor's diagnosis

CHD; combination of MI and AP

Age, sex

No significant associations between MI (OR = 1.12 (0.58–2.19)), AP (OR = 0.98 (0.51–1.88)) or CHD (OR = 0.97 (0.55–1.71)) [a]

3MSE, Modified Mini-Mental State Examination; AD, Alzheimer's disease; APOE, apolipoprotein E; AP, angina pectoris; Blessed IMC, Blessed Test of Information, Memory, and Concentration; BMI, body mass index; CABG, coronary artery bypass graft surgery; CAMDEX, Cambridge Examination for Mental Disorders in the Elderly; CASI, Cognitive Abilities Screening Instrument; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CHD, coronary heart disease; CT, computer tomography; DSM-III, Diagnostic and Statistical Manual of Mental Disorders (third edition); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (fourth edition); ECG, electrocardiography; EEG, electroencephalography; FU, follow-up; GMS-AGECAT, Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy; GP, general practitioner; HDL, high-density lipoprotein; HR, hazard ratio; HTR-arm, Women's Health Initiative Hormone Trial Randomization assignment; MCI, mild cognitive impairment; MI, myocardial infarction; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; HR, hazard ratio; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Strokes—Alzheimer's Disease and Related Disorders Association criteria; NINDS-AIREN, National Institute of Neurological Disorders and Strokes—Association International pour la Recherché l'enseignement en Neurosciences criteria; OR, odds ratio; VaD, vascular dementia.

[a] Number of participants and ORs obtained after contact with corresponding author.

Table 2
Characteristics of case-control studies assessing the relation between angina pectoris, myocardial infarction, coronary heart disease and cognition or dementia.
Authors

Cohort/sample (cases and controls), age
Outcome/cognitive test, diagnostic criteria
Predictor/ ascertainment of exposure
Adjustment for confounders
Most important results
Brayne et al., 1998[21]
The Cambridge City over -75s Cohort study (CC75C); N = 376 (36 cases; 340 controls); mean age >77
Dementia, AD; CAMDEX interview
MI; self-report or proxy-informant-reported history of MI
Age, sex
History of MI associated with dementia risk (OR = 2.94 (1.2–7.21))
Massaia et al., 2001[22]
Persons visiting the Geriatric Institute of the University of Torino, Italy; N = 456 (228 cases; 228 controls); mean age > 74
AD; DSM-III and NINCDS-ADRDA criteria
MI; not described
Not applicable
No significant difference between cases and controls with regard to MI
Bursi et al., 2006[23]
Rochester Epidemiology Project; N = 1,832 (916 cases; 916 controls); median age cases: 82 years
Dementia; record linkage, screening of medical records, confirmation by neurologist, DSM-IV criteria
MI; record linkage, screening of medical records based on discharge diagnosis codes, validation of diagnosis based on standardized criteria
None
No significant association between MI and dementia (OR = 1.0 (0.62–1.62))
Hughes et al., 2010[24]
HARMONY study; N = 3,779 (355 cases; 3,424 controls); mean age: 79.81
Dementia, AD; telephonic cognitive screening, in-person clinical evaluation including neurological and neuropsychological examination, several diagnostic criteria, expert panel consensus diagnosis
AP; self-reported
Not applicable
No significant association between AP and dementia (OR = 0.86 (0.66–1.13)) or AD (OR = 0.80 (0.58–1.11))[a]
Takahashi et al., 2012 [25]
Subjects living in Olmsted County, USA; N = 410 (205 cases; 205 controls); mean age: 81.9
VaD; medical history, neuroimaging studies, clinical diagnosis from medical records, NINDS-AIREN criteria
MI, AP; medical records including physician notes, laboratory data, letters, non-visit care information, hospitalizations and dismissal diagnoses
None
No significant association between dementia risk and MI (OR = 1.11 (0.66–1.87)) or AP (OR = 1.22 (0.79–1.88))

AD, Alzheimer's disease; AP, angina pectoris; CAMDEX, Cambridge Examination for Mental Disorders in the Elderly; DSM-III, Diagnostic and Statistical Manual of Mental Disorders (third edition); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders

(fourth edition); MI, myocardial infarction; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Strokes—Alzheimer's Disease and Related Disorders Association criteria; NINDS-AIREN, National Institute of Neurological Disorders and Strokes—Association International pour la Recherché l'enseignement en Neurosciences criteria; OR, odds ratio; USA, United Stated of America; VaD, vascular dementia.

[a] Crude OR calculated based on numbers reported in Table 1 of the article.

Table 3
Characteristics of cross-sectional studies assessing the relation between angina pectoris, myocardial infarction, coronary heart disease and cognition or dementia.

Authors
Cohort/sample/ age
Outcome/ cognitive test, diagnostic criteria
Predictor/ ascertainment of exposure
Adjustment for confounders
Most important results
Breteler et al., 1994[26]
Rotterdam study; N = 4,971; age range: 55–94
Cognitive function; MMSE
MI; ECG abnormalities reviewed by a cardiologist
Age, sex, education, smoking
History of MI was associated with lower cognitive scores
Petrovitch et al., 1998[27]
Honolulu-Asia Aging study; N = 341; mean age >77
Cognitive function; CASI (poor cognitive performance was defined as a score of < 74)
MI; diagnosis of MI (chest pain with ECG changes or cardiac enzyme elevation, temporal ECG changes considered to be diagnostic of interim MI) based on several sources (e.g. surveillance of all hospital discharge records, death certificates) and subjected to standardized review and classification by a consensus diagnosis committee
Age, years of education, and years of childhood spent in Japan
No significant association between MI and cognitive performance (OR = 1.3 (0.8–1,9)
Elwood et al., 2002[28]
Caerphilly study; N ≈ 1,500; age range: 55–69
Cognitive function; AH4-1 test, CAMCOG, MMSE and CRT
MI; questionnaire on vascular events, admission lists of local hospitals, hospital and GP notes, chest ECG
AP; questionnaire on vascular events, admission lists of local hospitals, hospital and GP notes, chest ECG
Age, social class, (mood)
Significant associations between cognitive function and past MI or the presence of AP
Singh-Manoux et al., 2003[29]
Whitehall II study; N = 5,812; age range: 46–68
Cognitive function; memory test, AH4-1 test, Mill Hill Vocabulary test, phonemic and semantic fluency
MI, AP; validated diagnosis based on clinical test abnormality or physician confirmation
CHD; validated MI or AP and doctor-diagnosed CHD
Age, employment grade, (hypertension, cholesterol, cigarette smoking)
MI, AP and CHD were associated with poor cognitive function
Verhaeghen et al., 2003[14]

Berlin Aging Study; N = 516; mean age >70

Cognitive function; perceptual speed (Digit Letter, Identical Pictures), episodic memory (Paired Associates, Memory for text), fluency (Categories, Word Beginnings), knowledge (Vocabulary, Spot-a-Word), intelligence (composite based on four separate composites)

MI; case history, interview with general physician, ECG abnormalities CHD; typical angina, stenocardia, nitrate therapy, family doctor's diagnosis, ECG abnormalities

Age, sex, SES, dementia diagnosis

MI was negatively associated with fluency, knowledge and intelligence composite[a]

CHD was negatively associated with cognition

Singh-Manoux et al., 2008[30]

Whitehall II study; N = 5,837; mean age: 61.0

Cognitive function; memory test, AH4-1 test (reasoning), Mill Hill Vocabulary test, phonemic and semantic fluency, MMSE

CHD; non-fatal MI (questionnaire data, study and hospital ECGs, cardiac enzymes and physician records) and definite AP (self-report of symptoms corroborated by information from medical records for nitrate medication or abnormalities on ECG, exercise ECG or coronary angiogram)

Age, education, marital status, use of medication for cardiovascular disease

In both men and women, CHD was associated with lower cognitive scores on reasoning, vocabulary and the MMSE. In women, CHD was also associated with lower scores on phonemic and semantic verbal fluency

Roberts et al., 2010[31]

Mayo Clinic Study of Ageing; N = 1,969; median age: 80.4

MCI; cognitive concern by a physician, patient, or nurse, impairment in ≥1 cognitive domains (executive function, memory, language visuospatial skills), essentially normal functional activities, no dementia diagnosis a-MCI: MCI with memory impairment na-MCI: MCI with no memory impairment

MI (definite); three sources: 1) self-report of a physician diagnosis; 2) ICD-codes based on information from the medical index of the Rochester Epidemiology Project; 3) validated diagnoses from a separate surveillance study AP (probable); two sources: 1) self-report of a physician diagnosis with or without self-report of treatment with nitrates, beta-blockers, or calcium channel blockers specifically stated as treatment for angina; 2) ICD-codes from the medical records-linkage system

Age, sex, and years of education, diabetes, hypertension, stroke, BMI, depression, dyslipidemia, APOE genotype

MI and AP were not significantly associated with MCI, a-MCI or na-MCI

Arntzen et al., 2011[32]

Tromsø study; N = 5,033; mean age: 58.8 (men)/ 58.2 (women)

Cognitive function; twelve word memory test, digit-symbol coding test, tapping test Cognitive impairment; lowest quintile on cognitive test scores

CHD; self-reported MI or AP

Age, education, physical activity, depression, current smoking, hypertension, hypercholesterolemia, low HDL-cholesterol, obesity, diabetes

No significant associations between CHD and any of the cognitive tests

Heath et al., 2015[33]

UK National Health Service; N = 616,245; age range: 40–64

Dementia; the presence ever of one of a specified set of GP codes for dementia or the prescription ever of an anti-cholinesterase inhibitor

IHD[b]; GP codes for MI or AP

Age, sex, SES, presence of neurodegenerative disorder or learning disability
Significant association between IHD and dementia (OR = 1.9 (1.5–2.4))

AH4-1, Alice Heim 4–1; a-MCI, amnestic mild cognitive impairment; AP, angina pectoris; APOE, apolipoprotein E; BMI, body mass index; CASI, Cognitive Abilities Screening Instrument; CAMCOG, Cambridge Cognitive Examination; CHD, coronary heart disease; CRT, Choice Reaction Time test; ECG, electrocardiography; GP, general practitioner; HDL, high-density lipoprotein; ICD, International Classification of Diseases; IHD, ischemic heart disease; MCI, mild cognitive impairment; MI, myocardial infarction; MMSE, Mini-Mental State Examination; na-MCI, non-amnestic mild cognitive impairment; OR, odds ratio; SES, socioeconomic status; UK, United Kingdom.

[a] More specific results were obtained after contact with the corresponding author.
[b] Definition of IHD was obtained after contact with the corresponding author.

DISCUSSION

The incidence of coronary heart disease and the presence of cognitive impairments and dementia increase with age and have common risk factors. Furthermore, the established fact is interesting as the biology of ageing and the pathophysiology of CVD partially coincide, which leads to the coexistence and synergy of these two health concerns in modern medicine. IHD is the leading cause of death worldwide. The main etiological factor affecting the vascular system is the atherosclerotic process that disrupts the arterial bed by the formation of atheromatous plaques.

The results of the meta-analysis in the prospective cohort studies indicate that individuals with CHD have, on an average, a 45% increased risk of cognitive impairment or dementia. Separate meta-analyses of prospective cohort studies for the individual predictors (MI, AP) showed similar significant results. In contrast, meta-analyses of cross-sectional and case-control studies yielded no significant results, possibly due to the low number of studies included within these analyses and the moderate to substantial heterogeneity among these studies. It has to be noted that, for cross-sectional studies, those studies that could not be included in the meta-analysis (those using different continuous outcome measures of cognitive functioning), notably discovered lower cognitive abilities in CHD. The literature on CHD is mixed in general, with the majority of prospective and cross-sectional studies demonstrating a significant association with cognition or dementia, and most of the case-control studies showed no association.

The exact biological mechanism by which CHD is related to the risk of development of cognitive impairment or dementia is still unestablished, but several candidate pathways are known to exist. Common risk factors shared by CHD and dementia are obesity, type-2 diabetes, smoking, hypertension, physical inactivity, and hypercholesterolemia. Post-hoc meta-regression analyses showed that there were no differences between studies (n = 3) that corrected for cardiovascular risk factors (diabetes, hypertension, high cholesterol) and studies that did not correct for these factors. In other words, the association between CHD and dementia risk cannot be solely explained by shared cardiovascular risk factors. Additionally, CHD can be associated with cardiac complications (atrial fibrillation, heart failure), whose association with cognitive impairment or dementia is well-established.[34] Additionally, CHD and accompanying vascular insufficiency can lead to cerebrovascular changes such as reduced cerebral blood flow (which can lead to hypoperfusion)[35], white matter lesions and brain infarctions, which in turn are associated with reduced cognitive functioning and risk of dementia. CHD might however not be causally linked to cognition on its own, but the effects on brain(e.g. cognitive impairment with vascular[36,37] origin) might be due to underlying atherosclerosis, which increases the risk of CHD and dementia[38,39]

SimilarlyPolicy makers and health workers must become more aware of the fact that identification of individuals at high risk for CHD or dementia is essential to intervene at an early stage by targeting the shared modifiable risk factors (e.g. obesity, hypercholesterolemia, physical inactivity, hypertension, smoking).

Studies have shown that targeting these modifiable risk factors can be effective in scaling down incidence rates and disease burden. Concerted actions focusing on the heart-brain connection might be key to fostering healthy ageing. Future public health campaigns focusing on preventing CHD and dementia should join forces and consider placing a greater emphasis on targeting shared risk factors.[40]

The strengths of this study include the use of large population-based studies with different study designs and the use of risk estimates that were pre-adjusted for confounding variables. Nevertheless, a number of limitations have to be mentioned. First, some studies based the ascertainment of the predictors on self-report or proxy-report, which can be prone to recall bias and underreporting, given the relative older age of the included cohorts. This is particularly problematic in case-control studies, in which differential reporting bias may lead to exposure misclassification or diluted and biased estimates. Fortunately, the majority of the included studies used validated or combined (e.g. self-report verified by validated) measurements to establish the exposure status. Related to this, is the underreporting of CHD events whereby stronger association might be distorted. This particularly applies to AP since AP is often missed, especially in comorbidity with atrial fibrillation. However, as shown by the separate meta-analyses of prospective cohort studies for MI and AP, there were no large differences between the different exposures. Second, substantial heterogeneity was observed in both cross-sectional and case-control studies. This can be related to differences in methodology across studies (e.g. assessment of dementia or cognitive functioning, ascertainment of exposure, variation between cohorts (e.g. gender specific) selection of study participants, follow-up duration and adjustment for important covariates). While meta-regression analyses did not identify any statistically significant source of heterogeneity (e.g. mean age at baseline, outcome measurement, follow-up duration), other methodological differences not included in the analyses might explain the differences between studies in effect estimates. By using a random-effects meta-analysis we have tried to account for variability within and between studies. The above mentioned issues related to cross-sectional and case-control studies might have led to the inconsistent findings between study designs. As prospective cohort studies are generally considered superior study designs to test the association between CHD exposure and dementia risk, we based our conclusion mainly on the results of prospective cohort studies, whilst not ignoring the findings of the other study designs. Third, the observed effects could probably be attributed to residual confounding in the original studies, although we used the most fully adjusted models. Fourth, studies were excluded if their CHD exposure was not a combination of purely MI and AP. For instance, studies reporting on IHD based on the the International Classification of Diseases and Related Health Problems (ICD-10) codes for IHD (I20-I25) were excluded because some of the codes also include coronary atherosclerosis and coronary artery aneurysm which are more causes of IHD.

CONCLUSION

We concluded that CHD was associated with an increased risk of cognitive impairment or dementia in prospective cohort studies. More mechanistic studies are needed that focus on the underlying biological pathways (e.g. left ventricular dysfunction, cerebral small vessel disease, hypoperfusion) and shared risks that link CHD with the occurence of cognitive impairment or dementia.

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