Cardiometabolic determinants of cognitive function in later life: unravelling the roles of risk factors

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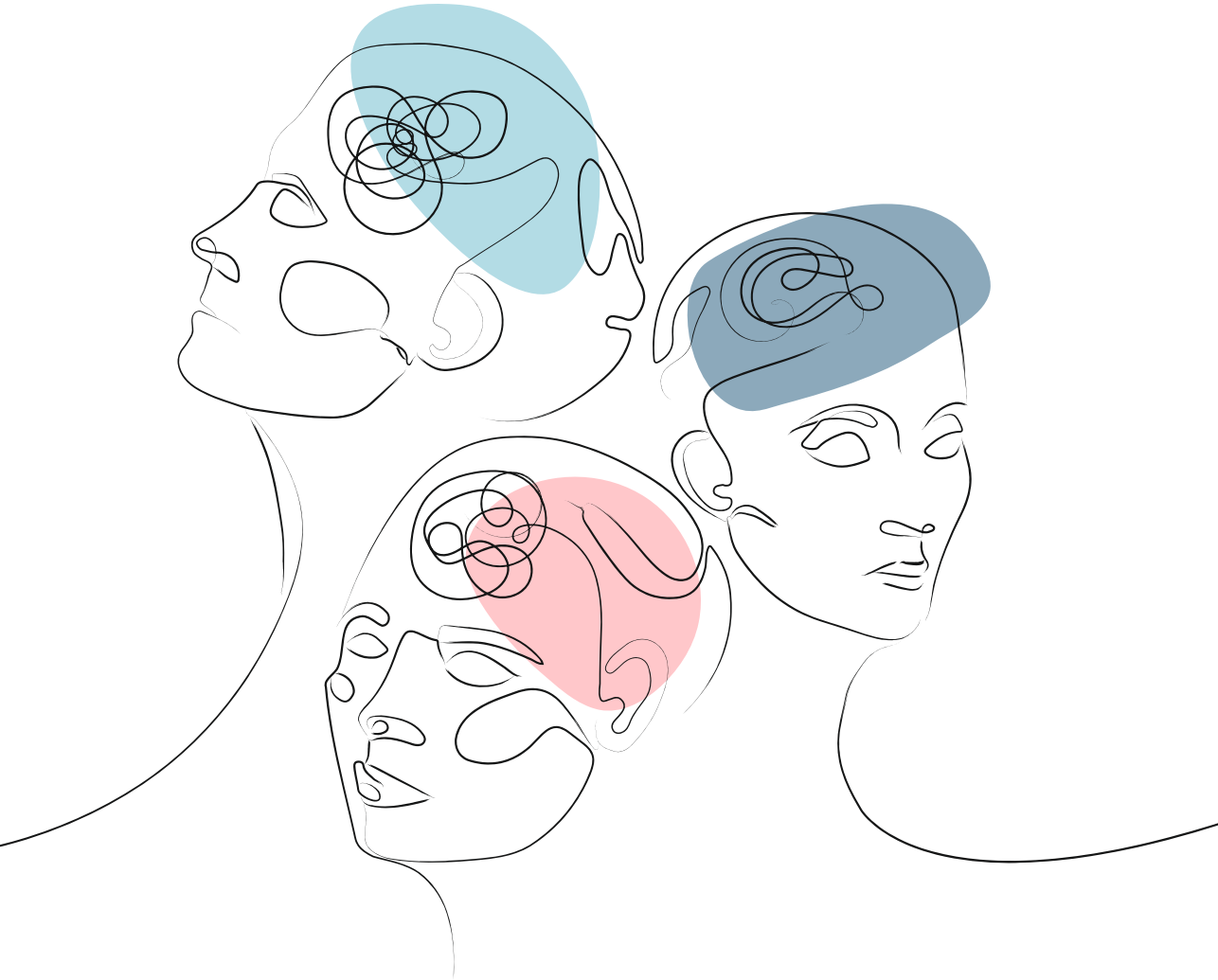

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General discussion

General discussion and summary of the main results

The main objective of this thesis was to study various cardiometabolic risk factors in relation to cognitive function and cognitive decline in older adults. As the prevalence of dementia continues to rise, it is important to explore various potential underlying pathways that can strengthen our understanding of the multifactorial pathophysiology of cognitive decline. Moreover, this can offer guidance to future research into prevention of dementia as well as help identify potential novel treatment targets, as it is currently irreversible and incurable.

In this chapter, the main findings of this thesis will be summarized and placed into the context of current knowledge in the literature. Cardiac and metabolic determinants will be discussed separately. Furthermore, the implications and future perspectives in the field of cardiovascular disease and dementia will be outlined and placed specifically within a clinical framework.

Summary of the main findings

Cardiovascular determinants of cognitive function

The connection between cardiovascular disease and cognitive impairment (preceding the diagnosis of dementia) is well-established [1-3]. Several epidemiological studies have identified various cardiac function markers such as heart-rate variability, QRS-T angle and higher serum concentrations of cardiac troponin to be associated with worse cognitive function measures [4-8]. In **Chapter 2,** we assessed the association between various ECG-based intervals, cognitive function and MRI-based structural status in a population of older adults at higher risk of developing cardiovascular disease. We found that a longer JT interval, reflecting ventricular repolarization, was strongly associated with worse cognitive function. Although in line with previous findings, our study was performed in older adults free of dementia at baseline, whereas other prior studies were primarily conducted in individuals with already established cognitive impairment or dementia. This means that subclinical changes in cardiac function may exist before cognitive dysfunction becomes apparent. Thus, prolonged ventricular depolarization and repolarization may potentially precede (sub) clinical cognitive dysfunction.

Increasing evidence suggest that higher plasma troponin is associated with accelerated cognitive decline and an increased risk of dementia [7, 9, 10]. In **Chapter 3,** we performed a systematic review of cohort studies investigating the association between serum troponin concentration, cognitive function and/or dementia. The twelve population-based cohort studies that were included reported that higher cardiac troponin levels are associated with higher risk of cognitive impairment, but not with incident dementia nor with incident Alzheimer's Disease. Higher cardiac troponin levels were also associated with worse global cognitive function and attention, both cross-sectionally and prospectively, although effect sizes were modest. This was the first systematic review on the association between cardiac

troponin and cognition, and sheds light on the possibility of troponin functioning as a risk marker of future cognitive vulnerability.

In line with the findings in **Chapter 3**, we continued exploring the (causal) contributions of different cardiac biomarkers in blood, including troponin, to dementia in **Chapter 4**. Though multiple observational cohort studies have identified significant associations between cardiac blood biomarkers such as troponin T, troponin I, N-terminal pro B-type natriuretic peptide (NT-proBNP), and growth-differentiation factor 15 (GDF15) with cognitive function and dementia, it was unknown whether this association could potentially be causal. This is because the findings from multivariable-adjusted cohort analyses might be harmed by residual confounding and/or reverse causation. Mendelian Randomization (MR) analysis has the ability of overcoming limitations such as confounding and reverse causation by using genetic variations as instrumental variables from previously performed genome-wide association studies [11]. We have performed the first MR study using the previously mentioned cardiac biomarkers, and dementia and cognitive function, however we did not find evidence that these cardiac biomarkers causally influence dementia risk, although this might be in part due to the low number of instrumental variables causing lower statistical power. Nevertheless, based on our findings, we suggest that underlying pathways leading to cognitive changes are more likely to employ mechanisms other than biomarkers of cardiac (dys)function.

Our research shows that a longer ventricular depolarization interval as well as higher troponin are associated with worse cognitive function in various domains. We did not find clear evidence of a causal association between higher troponin and other cardiac biomarkers like NT-proBNP with risk of dementia. Thus, cardiac function changes as measured by an ECG as well as higher levels of serum blood troponin (although not causal), may signal preclinical cognitive (dys)function. Patients with diagnosed cardiovascular disease may therefore be at higher risk of cognitive impairment.

Metabolic determinants of cognitive function

Adjacent to the rapid growing number of older people, the problem of obesity is also on the rise as a result of our changing lifestyle [12]. Obesity, defined as a body mass index (BMI) above 30 kg/m^2, is a modifiable risk factor for several adverse health outcomes, including type 2 diabetes mellitus, cardiovascular disease and dementia [12]. Currently, the pathways in which body composition can affect the brain are not well understood. Thus, the second part of this thesis aimed to further elucidate the relationship between measurements of weight and underlying metabolic changes with cognitive function and MRI-based structural volumes of the brain.

In **Chapter 5**, we investigated the association between BMI and serum leptin levels with cognition, cognitive decline and various brain volumes. More specifically, we aimed to assess the mutual independence of effects of BMI and circulating leptin, as adipose tissue is the largest endocrine organ in the human body secreting leptin [13]. We found that higher leptin was associated with increased volume of the amygdala, independent of BMI. Furthermore, a BMI above 30 kg/m^2 was associated with worse executive functioning, with higher volumes

of the amygdala and of the hippocampus, independent of leptin. Unlike previous studies, our results suggest it is unlikely that leptin functions as a mediator, implying distinct biological mechanisms between BMI and leptin cognitive function [14, 15].

Next to a high BMI, we were also interested in other measurements of body weight, including loss of body weight and weight variability. In **Chapter 6**, we examined weight loss and variability in relation to cognitive function and functional independence. We found that during 2.5-years of follow-up, individuals with a higher variability of body weight and loss ≥5% of baseline body weight scored significantly lower in four domains of cognitive function, but were not more functionally dependent than those who did not lose weight or had a low body weight variability. Unlike other studies whom employed a delta of weight loss [16-18], we calculated an average slope of weight change during follow-up, therefore taking into account more data points, and demonstrated that these findings were independent of incident disease states such as cancer or heart failure, use of diuretics or antidepressants, and cardiovascular risk-factors. Weight loss and higher variability of body weight may signify an early manifestation of cognitive decline.

Finally, in **Chapter 7**, we studied the role of metabolomics, the analysis of small blood serum metabolites, in light of cognitive impairment. Although individual metabolites have been associated with dementia before [19, 20], we assessed the association between the MetaboHealth score, composed of 14 different metabolites and used to predict disease-specific mortality, with cognitive function and functional independence [21]. Our results showed that a higher MetaboHealth score was associated with worse neurocognitive test scores, cognitive decline and lower functional capacity. This suggests that metabolite-based scores predicting mortality may also be used to identify individuals at higher risk of future cognitive decline.

We found that a higher BMI independent of serum leptin, higher variability in body weight and higher loss of body weight, as well as a higher MetaboHealth score were independently associated with worse cognitive function. Thus, substantial changes in body weight may be a risk factor for worse cognitive function in older patients. The results emphasize the importance of maintaining a healthy and stable weight, which could potentially be a preventative measure of cognitive decline in an older population at higher risk for cardiovascular disease.

Study limitations

Nevertheless, it is important to take into account the limitations of the studies. The follow-up time of PROSPER was 3.2-years, which is relatively short and may not be sufficient to capture cognitive decline in all study participants. In addition, the study participants included were either at higher risk for cardiovascular disease, or had a history of cardiovascular disease, which may lower the generalizability of the findings. Our results may also be nuanced by the fact that the study participants were free of dementia at baseline. Moreover, relatively few studies were included in the systematic review and we could therefore not perform a meta-analysis. In line, only relatively few genetic instruments associated with cardiac biomarkers were available for the MR study, preventing further sensitivity analyses addressing the

common pleiotropy issue in MR studies. However, in spite of these limitations, we found robust associations that strongly suggest an interaction between different cardiometabolic determinants and cognitive function, and thereby gained a deeper understanding of the pathophysiology.

Future perspectives

Shifts in the demography of dementia – the role of improved prevention of cardiovascular disease

The results described in this thesis, in which we examined multiple cardiovascular and cardiometabolic risk factors, contribute to the knowledge on potential constituent pathways leading to cognitive impairment: the phase preceding the clinical manifestation of dementia. The prevalence of dementia is projected to rise in the future, mainly due to the aging of the population [22]. Although there is an increase in the number of older individuals, multiple studies have established that the *relative incidence* of dementia is in fact decreasing [22, 23]. To illustrate; a population-based cohort study using data from the Rotterdam Study found that the incidence of dementia was 25% lower in the subcohort initiated in 2000, compared to the counterpart that was initiated in 1990 [22]. Similarly, a large observational study including more than 21,000 American (US) adults above the age of 65 years, report a decline in prevalence of dementia, from 11.6% in 2000 to 8.8% in 2012 [24]. In line, the Framingham Heart Study also describe a decline of approximately 20% per decade between 1977 and 2008 in incidence of dementia among older participants [25].

Despite the contribution of various factors such as improved educational attainment to the expected decrease in incidence [24], it is often also attributed to improved prevention of cardiovascular disease. This is also relevant to the findings of this thesis, as the various cardiometabolic determinants investigated here are risk-factors that can be targeted in the prevention of dementia. Studies also report more frequent use of lipid-lowering drugs (which were introduced in the late 90s) and antithrombotic drugs, suggesting that treatment and improved prevention of cardiovascular disease may also effectively contribute to lowering vascular-related risk of future dementia [22, 24, 25]. In line, the results in **Chapter 5** and **6** of this thesis suggest that better management of risk factors like change in body weight, may help prevent cognitive (dys)function.

Studies have also shown that better management of diagnosed cardiovascular disease in patients may already lead to (short-term) improvements in cognitive function [26]. For example, reduced cardiac ejection fraction has been associated with impaired cognition [27]. A study examined whether patients whom underwent cardiac resynchronization therapy (CRT), aimed at ameliorating left ventricular ejection fraction (LVEF), also improved in neuropsychological performance [27]. They found that patients with improved LVEF also scored better on measures of overall cognitive function, executive functioning, and visuospatial function, compared to patients whom did not show LVEF improvement. These findings are corroborated by other studies, whom found improved attention and processing

speed three months post-CRT [28]. A recent population-based study investigated cognitive function in patients with atrial fibrillation (AF) at baseline or during follow-up, compared to healthy counterparts. They found AF was significantly associated with a faster decline in cognitive function and an increased risk of developing all-cause dementia during nine years of follow-up [26]. Interestingly, among patients with either prevalent or incident AF, use of anticoagulation drugs was associated with a 60% decreased risk of dementia [26]. Although a recent MR study did not find evidence of a causal association between AF and Alzheimer's Disease, another MR study demonstrated genetic predisposition for AF was causally associated with lower gray matter volume [29, 30]. This association was attenuated after adjusting for ischemic stroke, suggesting that the pathway between AF and cognitive function may be mediated by stroke [30]. As demonstrated in **Chapter 2, 3** and **4**, patients exhibiting an increase in other markers of cardiac dysfunction like prolonged ventricular depolarization and higher troponin could potentially in the future be considered for cardiac improvement therapy. Improved treatment of existing cardiac conditions may have an effect on the risk of future cognitive decline.

In line, a recent large, randomized controlled trial demonstrated the impact of better management of cardiovascular risk factors on cognitive function. In this study, a multidomain approach (including physical function, polypharmacy, cognition, dependency in activities of daily living) was designed to prevent cognitive decline in older adults at higher risk of cardiovascular disease in the general Finnish population, without severe cognitive impairment [31]. The intervention group received a dietary intervention, physical exercise regime, cognitive training and vascular-risk monitoring, whereas the control group received general health advice [32]. After 2-years, the intervention group scored higher on the neuropsychological test battery compared to the controls, suggesting early interventions during the pre-symptomatic stages may contribute to maintaining or improving cognitive function in a subcohort of the general population at higher risk of cardiovascular disease [32].

These results can be extrapolated to the participants of the PROSPER study. Our participants had a similar cardiovascular disease risk to the participants of the general Finnish population, also without cognitive dysfunction at baseline. The cardiometabolic determinants that we investigated in this thesis are risk factors for (pre)clinical cognitive decline. Therefore, in addition to treatment of established clinical cardiovascular disease, tackling risk factors such as those presented in the present thesis may be of benefit to future cognitive changes.

The future of cognitive screening in cardiac patients

Various studies have been initiated to further investigate the complex interaction between vascular health and brain functioning. The Heart-Brain Study, a part of the larger Heart-Brain Connection Consortium, is a multicenter cohort study in the Netherlands of nearly 700 participants with either heart failure, carotid occlusive disease, or vascular cognitive impairment. This study was designed to examine to what extent hemodynamic changes contribute to vascular cognitive impairment, and what mechanisms are involved [33, 34]. The first results after 2-years of follow-up demonstrate progression of white matter

hyperintensities in patients with increased diastolic blood pressure variability [35]. Moreover, participants with heart failure and carotid occlusive disease scored lower on multiple domains of cognitive function such as memory, executive functioning, attention, global cognition, compared to healthy counterparts [36]. The next steps of the consortium include multidisciplinary collaborations between cardiology, geriatrics and internal medicine departments in order to screen patients with cardiovascular disease for memory and cognitive deficits.

The results in the present thesis reiterate the fact that cardiometabolic disease can play a considerable role in the development of dementia. However, it is important to note that this is currently not included in the biological definition of Alzheimer's Disease. A recent review was published as a response to the National Institute on Aging and Alzheimer's Association Research Framework titled "Towards a Biological Definition of Alzheimer's Disease", arguing adding vascular biomarkers to the proposed amyloid-beta, tau and neurodegeneration biomarker system definition [37]. For example, a large autopsy-based neuropathological study demonstrated the presence of vascular pathology such as cerebral microbleeds, intracranial atherosclerosis and cortical infarcts in 80% of patients diagnosed with Alzheimer's disease [38]. It is also argued that epidemiological research should expand beyond classical clinical vascular risk factors to include risk factors stemming from other novel pathways contributing to the development of Alzheimer's Disease, in line with the implications described in **Chapters 2, 3** and **4** of this thesis like prolonged ventricular depolarization and troponin [37].

In addition, there is growing interest in the contribution of frailty to cardiovascular disease and its treatment in older patients. Frailty, which can be described as an accumulation of deficits including geriatric syndromes like cognitive impairment and co-morbidities such as cardiovascular disease, is associated with reduced functional reserve [39]. A meta-analysis including almost 7000 patients from 26 studies reported nearly half of all patients with heart failure to be frail [40]. Recent major heart failure guidelines recognize the impact of frailty on prognosis, therefore recommending an overall holistic approach by screening for frailty in order to optimize treatment [41-43], as it has been shown that impairment in the cognitive domain in HF patients was significantly associated with a higher 1-year mortality risk [44]. The latter result is reemphasized by the findings in this thesis. We found significant associations between various cardiovascular and metabolic determinants, including domains of frailty like weight loss, with cognitive function, strongly suggesting the approach to cognitive decline and dementia ought to be multidimensional.

Recommendations for the future

The results of this thesis emphasize the fact that cognitive decline has a multifactorial origin and that both cardiac and metabolic risk factors play a role. The pathways leading from metabolic and cardiovascular imbalance to cognitive impairment are complex, as no single mechanism can describe the intricate pathophysiology. In line with the 2021 European Society of Cardiology (ESC) guidelines on cardiovascular disease prevention in clinical practice, attention should be directed towards optimizing treatment of conditions like

heart failure and atrial fibrillation in order to decrease the risk of cognitive decline or even reverse damage [43]. Future research could perhaps target whether long-term treatment of for example hypertension may in fact prevent cognitive dysfunction, as this is currently unknown.

Moreover, continuing prevention of cardiovascular disease from middle-age onwards will be paramount to supporting the decline of dementia incidence and sustaining current health care systems, as highlighted in for example the 2018 Dutch National Prevention Pact. The Pact focuses on three themes: smoking, obesity and problematic alcohol use, each strongly associated with cardiovascular disease [45]. In general, the aim is to prevent children and young adults from taking up unhealthy habits, which will impact future development of various (additional overlapping) risk factors related to cardiovascular disease and dementia, such as described in this thesis [45].

It is evident that different components of cardiovascular disease are strongly associated with cognitive dysfunction, however it remains challenging to prove direct causality. As an alternative to expensive and lengthy randomized controlled trials, MR analyses may be a useful technique to identify vascular risk factors that have a causal relationship with the brain, using data from large populations. Although the U.S. Food and Drug Administration recently approved the use of Lecanemab, a humanized IgG1 monoclonal antibody that reduces markers of amyloid in early Alzheimer's Disease, no clear effects on restoring lost cognitive capacity have been found [46]. The ability to regenerate cognitive function using medication has not been demonstrated yet, therefore research should primarily be focused on *prevention*. Thus, identifying *vascular* drug targets using MR can also be instrumental to treating dementia, as vascular dementia is the second-most common form of dementia and accounts for 20% of all dementia cases [47].

In conclusion, we studied several cardiometabolic risk factors and their relationship to cognitive function in older adults. The results described in this thesis reiterate the complex multifaceted interaction between the cardiometabolic system and the brain, and highlight different pathways that may contribute to cognitive decline. This calls for further research into optimizing treatment of cardiometabolic health to positively influence dementia risk. Moreover, this stresses the importance of long-term prevention and understanding the cardiometabolic components of cognitive impairment.

References

1. Eggermont LHP, de Boer K, Muller M, Jaschke AC, Kamp O, Scherder EJA. Cardiac disease and cognitive impairment: a systematic review. Heart. 2012;98(18):1334-40.
2. van der Velpen IF, Yancy CW, Sorond FA, Sabayan B. Impaired Cardiac Function and Cognitive Brain Aging. Can J Cardiol. 2017;33(12):1587-96.
3. Hooghiemstra AM, Leeuwis AE, Bertens AS, Biessels GJ, Bots ML, Brunner-La Rocca HP, et al. Frequent Cognitive Impairment in Patients With Disorders Along the Heart-Brain Axis. Stroke. 2019;50(12):3369-75.
4. Mahinrad S, Ferguson I, Macfarlane PW, Clark EN, Stott DJ, Ford I, et al. Spatial QRS-T Angle and Cognitive Decline in Older Subjects. Journal of Alzheimer's disease : JAD. 2019;67(1):279-89.
5. Mahinrad S, Jukema JW, van Heemst D, Macfarlane PW, Clark EN, de Craen AJ, et al. 10-Second heart rate variability and cognitive function in old age. Neurology. 2016;86(12):1120-7.
6. Wijsman LW, De Craen AJM, Muller M, Trompet S, Jukema JW, Sabayan B, et al. High-sensitivity cardiac troponin T is associated with cognitive decline in older adults at high cardiovascular risk. European Journal of Preventive Cardiology. 2016;23(13):1383-92.
7. Bertens AS, Sabayan B, de Craen AJM, Van der Mast RC, Gussekloo J. High Sensitivity Cardiac Troponin T and Cognitive Function in the Oldest Old: The Leiden 85-Plus Study. Journal of Alzheimers Disease. 2017;60(1):235-42.
8. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA. 2010;304(22):2494-502.
9. Broersen LHA, Siegerink B, Von Rennenberg R, Liman TG, Piper SK, Sperber PS, et al. High-Sensitivity Cardiac Troponin T and Cognitive Function in Patients with Ischemic Stroke. Stroke. 2020:1604-7.
10. von Rennenberg R, Liman T, Nolte CH, Nave AH, Scheitz JF, Düzel S, et al. High-Sensitivity Cardiac Troponin T and Cognitive Decline in Older Adults: Results of the Berlin Aging Study II. Gerontology. 2022.
11. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. JAMA. 2021;326(16):1614-21.
12. Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288-98.
13. Scheja L, Heeren J. The endocrine function of adipose tissues in health and cardiometabolic disease. Nat Rev Endocrinol. 2019;15(9):507-24.
14. Gilbert T, Roche S, Blond E, Bar JY, Drai J, Cuerq C, et al. Association between Peripheral Leptin and Adiponectin Levels and Cognitive Decline in Patients with Neurocognitive Disorders >/=65 Years. Journal of Alzheimer's disease : JAD. 2018;66(3):1255-64.
15. Santos T, Fonseca LC, Tedrus G, Delbue JL. Alzheimer's disease: nutritional status and cognitive aspects associated with disease severity. Nutricion hospitalaria. 2018;35(6):1298-304.
16. Ravona-Springer R, Schnaider-Beeri M, Goldbourt U. Body weight variability in midlife and risk for dementia in old age. Neurology. 2013;80(18):1677-83.
17. Park S, Jeon SM, Jung SY, Hwang J, Kwon JW. Effect of late-life weight change on dementia incidence: a 10-year cohort study using claim data in Korea. BMJ Open. 2019;9(5):e021739.
18. Giudici KV, Guyonnet S, Rolland Y, Vellas B, de Souto Barreto P, Nourhashemi F. Body Weight Variation Patterns as Predictors of Cognitive Decline over a 5 Year Follow-Up among Community-Dwelling Elderly (MAPT Study). Nutrients. 2019;11(6).
19. Calice-Silva V, Suemoto CK, Brunoni AR, Bensenor IM, Lotufo PA. Association Between GlycA and Cognitive Function: Cross-Sectional Results From the ELSA-Brasil Study. Alzheimer Dis Assoc Disord. 2021;35(2):128-34.
20. Larsson SC, Markus HS. Branched-chain amino acids and Alzheimer's disease: a Mendelian randomization analysis. Sci Rep. 2017;7(1):13604.

21. Deelen J, Kettunen J, Fischer K, van der Spek A, Trompet S, Kastenmüller G, et al. A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. Nat Commun. 2019;10(1):3346.
22. Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology. 2012;78(19):1456-63.
23. Brück CC, Wolters FJ, Ikram MA, de Kok I. Projected prevalence and incidence of dementia accounting for secular trends and birth cohort effects: a population-based microsimulation study. Eur J Epidemiol. 2022;37(8):807-14.
24. Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. JAMA Intern Med. 2017;177(1):51-8.
25. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med. 2016;374(6):523-32.
26. Ding M, Fratiglioni L, Johnell K, Santoni G, Fastbom J, Ljungman P, et al. Atrial fibrillation, antithrombotic treatment, and cognitive aging: A population-based study. Neurology. 2018;91(19):e1732-e40.
27. Hoth KF, Poppas A, Ellison KE, Paul RH, Sokobin A, Cho Y, et al. Link between change in cognition and left ventricular function following cardiac resynchronization therapy. J Cardiopulm Rehabil Prev. 2010;30(6):401-8.
28. Dixit NK, Vazquez LD, Cross NJ, Kuhl EA, Serber ER, Kovacs A, et al. Cardiac resynchronization therapy: a pilot study examining cognitive change in patients before and after treatment. Clinical cardiology. 2010;33(2):84-8.
29. Pan Y, Wang Y, Wang Y. Investigation of Causal Effect of Atrial Fibrillation on Alzheimer Disease: A Mendelian Randomization Study. J Am Heart Assoc. 2020;9(2):e014889.
30. Park S, Lee S, Kim Y, Cho S, Kim K, Kim YC, et al. Causal effects of atrial fibrillation on brain white and gray matter volume: a Mendelian randomization study. BMC Med. 2021;19(1):274.
31. Kivipelto M, Solomon A, Ahtiluoto S, Ngandu T, Lehtisalo J, Antikainen R, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2013;9(6):657-65.
32. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385(9984):2255-63.
33. Hooghiemstra AM, Bertens AS, Leeuwis AE, Bron EE, Bots ML, Brunner-La Rocca HP, et al. The Missing Link in the Pathophysiology of Vascular Cognitive Impairment: Design of the Heart-Brain Study. Cerebrovasc Dis Extra. 2017;7(3):140-52.
34. van Buchem MA, Biessels GJ, Brunner la Rocca HP, de Craen AJ, van der Flier WM, Ikram MA, et al. The heart-brain connection: a multidisciplinary approach targeting a missing link in the pathophysiology of vascular cognitive impairment. Journal of Alzheimer's disease : JAD. 2014;42 Suppl 4:S443-51.
35. Starmans NL, Wolters FJ, Leeuwis AE, Bron EE, Brunner La Rocca HP, Staals J, et al. Twenty-four hour blood pressure variability and the prevalence and the progression of cerebral white matter hyperintensities. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 2023:271678x221149937.
36. Hooghiemstra AM, Leeuwis AE, Bertens AS, Biessels GJ, Bots ML, Rocca H-PB-L, et al. Frequent Cognitive Impairment in Patients With Disorders Along the Heart-Brain Axis. Stroke. 2019;50(12):3369-75.
37. Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC, et al. Vascular dysfunction-The disregarded partner of Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2019;15(1):158-67.
38. Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. Brain. 2013;136(Pt 9):2697-706.

39. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. Cmaj. 2005;173(5):489-95.
40. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: A systematic review and meta-analysis. Int J Cardiol. 2017;236:283-9.
41. Boureau AS, Annweiler C, Belmin J, Bouleti C, Chacornac M, Chuzeville M, et al. Practical management of frailty in older patients with heart failure: Statement from a panel of multidisciplinary experts on behalf the Heart Failure Working Group of the French Society of Cardiology and on behalf French Society of Geriatrics and Gerontology. ESC Heart Fail. 2022;9(6):4053-63.
42. Wiersinga JHI, Rhodius-Meester HFM, Kleipool EEF, Handoko L, van Rossum AC, Liem SS, et al. Managing older patients with heart failure calls for a holistic approach. ESC Heart Fail. 2021;8(3):2111-9.
43. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). European Heart Journal. 2021;42(34):3227-337.
44. Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. Stroke. 2010;41(4):600-6.
45. Rijksoverheid. Nationaal Preventieakkoord 2018 [Available from: https://www.rijksoverheid.nl/onderwerpen/gezondheid-en-preventie/documenten/convenanten/2018/11/23/nationaal-preventieakkoord.
46. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023;388(1):9-21.
47. Wolters FJ, Ikram MA. Epidemiology of Vascular Dementia. Arteriosclerosis, Thrombosis, and Vascular Biology. 2019;39(8):1542-9.