Vascular cognitive impairment

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VASCULAR COGNITIVE IMPAIRMENT

At the heart of the matter

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VASCULAR COGNITIVE IMPAIRMENT

At the heart of the matter

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert,
volgens het besluit van het College van Decanen,
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**General introduction,
thesis aims, and outline**

GENERAL INTRODUCTION

Worldwide, life expectancy has dramatically increased as a result of an ongoing process of improved general health and reduced mortality from life-threatening diseases.¹ Increases in life expectancy, however, also led to an increased risk of age-related diseases such as cardiovascular disease (CVD) and dementia. Both are highly prevalent, are expected to increase greatly over the next 20 years, and co-exist more often than expected by chance alone. Importantly, CVD is the primary cause of preventable death.²

CVD includes acute events such as stroke or myocardial infarction causing end-organ damage, but also chronic conditions such as atrial fibrillation, coronary heart disease, and angina pectoris. CVD causes more than four million deaths each year across Europe, which accounts for 45 percent of all deaths. Coronary heart disease and cerebrovascular disease were the most common causes of CVD deaths in 2016, accounting for 1.8 million and one million deaths, respectively.² Although CVD is the leading cause of death, mortality rates due to CVD are declining due to advances in health care. As a result, CVD is becoming more and more a chronic disease.

Many survivors of a cardiovascular event are not only confronted with physical disabilities but also with cognitive difficulties. Frequently, these cognitive difficulties worsen over time and lead to significant cognitive impairment, or even develop into vascular dementia in the long run. Worldwide, about 47 million people in the general population were suffering from dementia in 2015, a figure that is expected to triple by 2050.³ Vascular dementia accounts for at least 20 percent of these cases, which makes it the second most common dementia diagnosis after dementia due to Alzheimer's disease.⁴ CVD is increasingly being recognized as an independent contributor to cognitive impairment and vascular dementia, and thereby, prevention of CVD could lead to prevention of dementia.⁴

Vascular cognitive impairment – definition and prevalence

Vascular cognitive impairment (VCI) is an umbrella term covering all forms of cognitive deficits of vascular origin, ranging from a mild form of cognitive impairment to vascular or post-stroke dementia.⁴ Because VCI includes diverse syndromes with varying causes, differences in clinical presentation and course between patients exist.⁵ Cognitive functions are variably affected depending on the pathological substrate and/or strategic lesion location in individual cases, but neuropsychological deficits frequently include impairment of executive functions, such as planning, task structuring and inhibition, as

well as impairment in attention, information processing speed, and motor performance. In contrast, episodic memory can be relatively spared, which is different to the cognitive profile seen in neurodegenerative conditions such as Alzheimer's disease.⁶

Notably, the prevalence of mild forms of VCI (mild cognitive impairment of vascular origin) is higher than that of severe VCI such as vascular dementia.⁴ Mild VCI is considered an intermediate stage between a normal cognitive state and dementia, because being in this stage increases the risk of conversion to dementia, institutionalization, and mortality.⁷ Identification of those who are at-risk could lead to the development of both primary and secondary prevention strategies for the development of VCI.

Predicting VCI

More insight into underlying risk factors or markers that are associated with the onset and progression of VCI might provide new insights into expected disease trajectories of patients and open up new possibilities for selective or indicated prevention that may result in a better functional outcome.

Predicting VCI in heart disease

Although heart disease has been related to cognitive decline, the evidence-base is rather incomplete.⁸ Individual heart diseases have been investigated before, such as meta-analyses for atrial fibrillation, showing that individuals with atrial fibrillation have a 36 percent increased risk of developing cognitive impairment or dementia.⁹ Yet, current guidelines on CVD prevention do not comment on the association between heart disease and cognitive decline.¹⁰ Although coronary heart disease has been shown to be a candidate risk factor for VCI,¹¹ this disease category and, more specifically, myocardial infarction and angina pectoris as the most prevalent diseases in this category, have not been investigated in similar detail yet.

Also, little is still known about the cognitive trajectories of individuals with heart disease and whether these trajectories follow a different course when disease duration and risk exposure differs. Cognitive changes in incident cases may still be modest, which would make them a relevant target group for indicated prevention. Insight into the onset and course of cognitive functions after prevalent and incident CVD could show whether there is a window of opportunity in time to delay or even prevent onset of cognitive decline. Moreover, knowing how much time is needed before cognitive decline becomes observable, is valuable for prevention strategies and for understanding when best to apply these. Also,

the associations between CVD and cognitive decline may be different in middle-aged and older individuals, as has been shown for hypertension¹² and diabetes.¹³

Predicting VCI in stroke

In contrast to heart disease, the association between stroke and cognitive impairment has already been well established.¹⁴ Stroke survivors are prone to develop cognitive impairment, with a frequency of 62.6 percent at three months post-stroke,¹⁵ and persistent long-term functional effects.¹⁶ Both community-based and clinical studies have shown that worse cognition in stroke survivors is related to a higher risk for dementia and increased mortality compared to healthy controls.^{17,18} However, it is less clear whether cognition can also indicate which patients are at most risk. Individual cognitive domains may have good prognostic value, which might allow for a more specific selection of at-risk patients. Cognitive rehabilitation build around these specific cognitive domains may have the most beneficial effect on the long-term outcomes of stroke survivors.

Cognitive decline or impairment after stroke may result directly from the stroke itself or from pre-existing brain pathology, such as cerebral small vessel disease or brain atrophy.¹⁹ Such pre-existing brain pathologies can be visualised with magnetic resonance imaging (MRI). Assessment of MRI markers of pre-existing brain pathology in stroke survivors may clarify their predictive value for the development of VCI, besides the effect of the stroke. These predictors, if deemed relevant, could also be used in a clinical setting.

THESIS AIMS AND OUTLINE

The general aim of this thesis is to gain more insight into predictors and consequences of VCI in patients with manifest CVD and stroke. The research described in the following chapters is based on the following research questions:

1) Does the current literature suggest a robust association between coronary heart disease and cognitive impairment or dementia on a population level?

Chapter two provides a systematic literature review and meta-analysis summarizing the findings of all available population-based studies investigating the relation between coronary heart disease (i.e. angina pectoris and myocardial infarction) and risk for cognitive impairment or dementia.

2) Are prevalent and incident CVD predictive of long-term cognitive functioning and what are their cognitive trajectories?

In **chapter three** we study the temporal association between prevalent and incident CVD on cognitive change over 12 years in participants of the Maastricht Aging Study. This is a prospective cohort study on determinants of cognitive aging.²⁰ 1,823 Randomly assigned, cognitively healthy participants underwent assessments of blood pressure, medical history, lifestyle, anthropomorphic and neurocognitive measures at six and 12 years after the baseline measurement.

3) What is the prognostic value of domain-specific cognitive functions after stroke with regard to long-term outcomes of dementia and mortality?

In **chapter four** we aim to get more insight into domain-specific cognitive functions that can serve as prognostic predictors among stroke survivors. For this, we used data from the Sydney Stroke Study. This is a prospective clinical cohort study of cognitive, medical, psychiatric, and brain imaging changes after stroke.²¹ Community-dwelling stroke and transient ischemic attack (TIA) patients underwent repeated assessments that took place between three and six months after the index stroke/TIA events and at three and five years after baseline. Mortality data were available up to ten years after the index event.

4) What is the added prognostic value of vascular and degenerative imaging markers, besides stroke lesion volume, with regard to cognitive functioning after stroke?

In **chapter six** we describe a study on the associations between vascular and degenerative MRI measures and cognitive performance at baseline (three months after stroke) and at follow-up (12 months after baseline) within the Cognition and Affect after Stroke: a Prospective Evaluation of Risks (CASPER) cohort. Imaging measures at baseline included volumes of the stroke lesion, white matter hyperintensity, the hippocampus, and global brain atrophy. **Chapter five** describes the design of the CASPER study; a prospective clinical cohort study into stroke-specific, vascular, neurodegenerative, inflammatory, and genetic markers of the development of VCI, depression, and apathy after stroke.²² At baseline (three months post-stroke), a neuropsychological assessment, neuropsychiatric interview, venepuncture, and MRI are conducted. Assessment of neurocognitive and neuropsychiatric status are repeated six and 12 months later. The three-year follow-up is still ongoing.

Chapter seven provides a general discussion, including a summary of the main results, and considers implications for clinical practice and ideas for future research.

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2

Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis

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ABSTRACT

Aims/Hypothesis: Accumulating evidence suggests an association between coronary heart disease and risk for cognitive impairment or dementia, but no study has systematically reviewed this association. Therefore, we summarized the available evidence on the association between coronary heart disease and risk for cognitive impairment or dementia.

Methods: Medline, Embase, PsycINFO, and CINAHL were searched for all publications until 8 January 2016. Articles were included if they fulfilled the inclusion criteria: (1) myocardial infarction, angina pectoris or coronary heart disease (combination of both) 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. Two reviewers independently screened all abstracts and extracted information from potential relevant full-text articles using a standardized data collection form. Study quality was assessed with the Newcastle-Ottawa Scale. We pooled estimates from the most fully adjusted model using random-effects meta-analysis.

Results: We identified 6,132 abstracts, of which 24 studies were included. A meta-analysis of 10 prospective cohort studies showed that coronary heart disease was associated with increased risk of cognitive impairment or dementia (OR = 1.45, 95%CI = 1.21-1.74, $p < 0.001$). Between-study heterogeneity was low ($I^2 = 25.7\%$, 95%CI = 0-64, $p = 0.207$). Similar significant associations were found in separate meta-analyses of prospective cohort studies for the individual predictors (myocardial infarction, angina pectoris). In contrast, meta-analyses of cross-sectional and case-control studies were inconclusive.

Conclusion/Interpretation: This meta-analysis suggests that coronary heart disease is prospectively associated with increased odds of developing cognitive impairment or dementia. Given the projected worldwide increase in the number of people affected by coronary heart disease and dementia, insight into causal mechanisms or common pathways underlying the heart-brain connection is needed.

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death worldwide.¹ An estimated 7.4 million people died from CHD in 2012.² CHD is a broad disease category and consists of several conditions with myocardial infarction (MI) and angina pectoris (AP) being the most prevalent ones. CHD affects the vascular system supplying the heart muscle due to build-up of atheromatous plaques that cover the lining of the coronary arteries.³

At the same time, dementia is an important health problem due to increasing incidence rates and its impact on health and daily life.⁴ Major modifiable risk factors for cognitive impairment and dementia relate to or impact the vascular system including hypertension, smoking, obesity, diabetes, hypercholesterolemia, and lack of physical exercise.^{5,6} Notably, these factors are also risk factors for CHD.⁷ While CHD is a candidate risk factor for dementia or cognitive impairment, the evidence base has not been established to a similar extent, yet.⁸ In a recent systematic review of the literature on modifiable risk factors, several studies on heart disease were identified, of which the majority reported a higher risk for cognitive impairment or dementia.⁸ Also other types of heart disease have been related to cognitive decline or dementia risk, with most substantial evidence for atrial fibrillation.⁹⁻¹¹ A meta-analysis of seven prospective studies found that individuals with atrial fibrillation had a 36 percent increased risk of developing cognitive impairment or dementia.⁹ To date, no meta-analysis exists for major heart diseases such as MI and AP.

Therefore, the aim of the present study is to summarize the outcome of all available population-based studies investigating the relation between CHD, notably MI and AP, and risk for cognitive impairment or dementia in a systematic review and meta-analysis.

MATERIALS AND METHODS

Data sources and searches

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 (e.g. only studies in human, language restrictions). The complete search strategy is provided in S1 Appendix.

Study selection

All publications until 8 January 2016 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 possibly missing articles.

Data extraction and quality assessment

The selection process followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (S2 and S3 Appendices).^{12, 13} Titles and abstracts were screened by two independent assessors (KD, MFR) based on the abovementioned eligibility criteria. Next, full text articles of potentially relevant citations were scrutinized by two independent investigators (KD, MFR). A standardized data collection form was used to extract information such as study design, study cohort, demographics, predictor variable, outcome, and effect estimate. In case of discrepancy, discussion with a third reviewer (SK) took place. Corresponding authors were contacted by e-mail if full-text articles were not available or information was missing (e.g. effect estimates, sample sizes, definition of CHD) or ambiguous (with maximum three reminders in case of non-response). The Newcastle–Ottawa Scale (NOS) was used to assess study quality.¹⁴ For cross-sectional studies, an adapted version of the NOS was applied (S4 Appendix).

Data synthesis and analysis

Studies qualifying for pooling in meta-analyses were analysed with random effects models to estimate the pooled odds ratios (OR) and their 95% confidence intervals (CI). Estimates from the most fully adjusted model were used. Meta-analyses were conducted for each exposure separately, i.e. for MI, AP, and CHD. The latter included all studies that reported a risk estimate for MI, AP, or a combination of MI and AP. In case a study reported risk estimates for multiple exposures the combination estimate (first choice) or the effect estimate with the smallest standard error (i.e. largest sample size; second choice) was chosen. Studies with overlapping study populations were only included if they used other study designs (e.g. cross-sectional and prospective). Heterogeneity among studies was assessed using the I^2 statistic and the 95% CI for I^2 was calculated using the non-central χ^2 approach. Potential sources of heterogeneity (including mean age at baseline, mean follow-up duration,

percentage of women, outcome measurement, and study quality) were explored by meta-regression. The 95% prediction interval was estimated for each meta-analysis including at least three observational studies. This measure takes into account the between-study heterogeneity and provides an interval for the expected estimate of a future observational study and has been recommended to be standardly included in meta-analysis.¹⁵ Potential publication bias (i.e. small study effects) was assessed by visual inspection of funnel plots and the Egger's test. All tests were two-sided at an alpha-level of 0.05 and all analyses were performed in Stata 13.1 (StataCorp, TX).

RESULTS

The search yielded 6,132 abstracts, of which 142 (2.3%) were included for full-text review. Of these, 119 were excluded due to different reasons based on the exclusion criteria (see Figure 1). Six authors were contacted to obtain full-text articles that were not available to us, of which five responded to our request. Additionally, 10 authors were contacted for missing or ambiguous information, of whom seven responded. Two additional studies were found from cross-references,^{16, 17} of which one could be included.¹⁶ This resulted in eight cross-sectional studies, five case-control studies, 10 prospective cohort studies and one study with both cross-sectional and prospective analyses (designated as cross-sectional regarding study quality). Quality assessment of all 24 included studies was sufficient (overall mean NOS score = 6.8, SD = 1.29, range = 3-9). Separate analyses for each study design showed similar results for prospective (mean NOS score = 6.91, SD = 1.04, range = 5-8) and cross-sectional studies (mean NOS score = 7.22, SD = 0.97, range = 6-9), but the quality of case-control studies was somewhat lower (mean NOS score = 5.8, SD = 1.92, range = 3-8), mainly due to the effects of one particular study with a score of three. All 24 studies and their details and results are summarized in detail in Table 1-3 and Table A in S5 Appendix.

Figure 1. Flowchart of the literature search and selection

Prospective cohort studies

From the 11 prospective cohort studies, seven focused on MI,^{16, 18-23} four on AP,^{19, 22-24} and four on the CHD compound.^{22, 25-27} Of those focusing on MI, four studies did not find an association with dementia, Alzheimer's disease, vascular dementia, or decline to mild cognitive impairment or dementia.²⁰⁻²³ Three studies did find a significant association between MI and dementia,¹⁸ Alzheimer's disease and Alzheimer's disease/vascular dementia (but only for MI ascertained at the late-life visit),¹⁶ and possible dementia/mild cognitive impairment.¹⁹ Two out of the four AP studies did find that AP increased the risk of dementia or possible dementia/mild cognitive impairment,^{19, 24} whereas the other two studies did not find an association.^{22, 23} For the CHD compound, three studies did not find a relation with cognitive decline or decline to dementia/mild cognitive impairment,^{22, 25, 27} whereas one study found that CHD was a significant predictor of vascular dementia.²⁶

In the meta-analysis, a total of 10 studies representing 24,801 persons could be included.^{16, 18-26} CHD was associated with a 45 percent increased risk of dementia, cognitive impairment or cognitive decline (OR = 1.45, 95%CI = 1.21-1.74, $p < 0.001$; Figure 2). Heterogeneity was low ($I^2 = 25.7\%$, 95%CI = 0-64, $p = 0.207$), without suggestion of small-study effects (Egger's test, $p = 0.739$; for the funnel plot, see Figure A in S5 Appendix). No statistically significant source of heterogeneity was identified in a meta-regression analysis. Associations were slightly stronger in studies ($n = 7$) focusing on dementia (OR = 1.55, 95%CI = 1.20-2.00, $p = 0.001$; $I^2 = 40.6\%$, 95%CI = 0-74, $p = 0.121$).^{16, 18, 20, 21, 23, 24, 26} There were too few studies to conduct separate meta-analyses for the different subtypes of dementia. Similar significant results were found for MI (OR = 1.46, 95%CI = 1.16-1.84, $p = 0.001$, Figure B in S5 Appendix) and AP (OR = 1.36, 95%CI = 1.12-1.65, $p = 0.002$, Figure C in S5 Appendix) separately.

Case-control studies

Four out of five case-control studies reported on MI. Three of these found no association between MI and dementia or Alzheimer's disease,²⁸⁻³⁰ whereas one nested case-control study did find a significant association between MI and dementia risk.³¹ Two case-control studies investigated the relation between AP and risk for dementia, Alzheimer's disease or vascular dementia. Both studies showed no significant associations.^{30, 32}

Four studies representing 6,397 individuals could be included in the meta-analysis.^{28, 30-32} CHD was not significantly associated with risk of total or vascular dementia (OR = 1.14, 95%CI = 0.79-1.64, $p = 0.482$; Figure D in S5 Appendix). There were signs of moderate heterogeneity ($I^2 = 60.3\%$, 95%CI = 0-85, $p = 0.056$). There was no strong evidence for small-study effects

based on the Egger's test ($p = 0.062$) and visual inspection of the funnel plot (Figure E in S5 Appendix). No statistically significant source of heterogeneity was identified in a meta-regression analysis. Separate meta-analyses for MI and AP showed comparable non-significant results (MI: OR = 1.32, 95%CI = 0.78-2.21, $p = 0.302$, Figure F in S5 Appendix; AP: OR = 0.98, 95%CI = 0.71-1.36, $p = 0.911$, Figure G in S5 Appendix).

Cross-sectional studies

Out of nine cross-sectional studies, six studies reported on MI,^{27, 33-37} three on AP,^{34, 36, 37} and five on the CHD compound (MI+AP).^{27, 37-40} Of the six studies investigating MI, four found a significant relation with poor cognitive functioning,^{27, 33, 34, 37} and two found no association with prevalent cognitive impairment.^{35, 36} For AP, two studies found a significant association with poor cognitive functioning,^{34, 37} whereas one study found no association with mild cognitive impairment.³⁶ For the CHD compound studies, three studies found a significant association with poor cognitive functioning,^{27, 37, 40} one study found no relation with cognitive function or cognitive impairment,³⁸ and one study found a significant association with dementia risk.³⁹

In the meta-analysis, four studies representing 623,588 persons could be included.^{35, 36, 38, 39} CHD was not significantly associated with an increased risk of cognitive impairment or dementia (OR = 1.23, 95%CI = 0.76-1.97, $p = 0.398$; Figure H in S5 Appendix). In the CHD meta-analysis, substantial heterogeneity was observed ($I^2 = 81.2\%$, 95%CI = 26-91, $p = 0.001$). No statistically significant source of heterogeneity was identified in a meta-regression analysis, although inclusion of some study characteristics (e.g. mean age at baseline, outcome measurement and study quality) led to a reduction in I^2 (e.g. mean age at baseline: 81.2% to 53.1%). There was no evidence for small-study effects based on the Egger's test ($p = 0.407$) and visual inspection of the funnel plot (Figure I in S5 Appendix). Similar non-significant results were found for MI (OR = 1.11, 95%CI = 0.79-1.57, $p = 0.548$; Figure J in S5 Appendix). It was not possible to perform a meta-analysis for AP since there was only one study.³⁶

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; FU	Outcome; cognitive test, diagnostic criteria	Predictor; ascertainment of exposure	Adjustment for confounders	Most important results
Aronson et al., 1990 ¹⁸	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-ADRD, 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 ²⁵	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 ²⁶	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 ¹⁶	North Karelia Project and FINMONICA study; N = 1,287; age range: 65-79; mean FU = 21 years	AD, AD/VaD; 1) screening phase with MMSE; 2) clinical phase where participants (MMSE $\leq$ 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-ADRD)	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

Table 1. continued

Authors	Cohort; sample; age; FU	Outcome; cognitive test, diagnostic criteria	Predictor; ascertainment of exposure	Adjustment for confounders	Most important results
Verhaeghen et al., 2003 ²⁷	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 ²³	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 ²⁰	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, CAGB, APOE genotype	MI was not significantly associated with dementia (HR = 1.13 [0.59-2.03])

Table 1. continued

Authors	Cohort; sample; age; FU	Outcome; cognitive test, diagnostic criteria	Predictor; ascertainment of exposure	Adjustment for confounders	Most important results
Ikram et al., 2008 ²¹	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-ADRD, 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 [0.77-1.64]). 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 ²⁴	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, 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])

Table 1. *continued*

Authors	Cohort; sample; age; FU	Outcome; cognitive test, diagnostic criteria	Predictor; ascertainment of exposure	Adjustment for confounders	Most important results
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 ²²	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]) *

Abbreviations: 3MSE = Modified Mini-Mental State Examination; AD = Alzheimer's disease; APOE = apolipoprotein E; AP = angina pectoris; 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 Internationale pour la Recherche l'Enseignement en Neurosciences criteria; OR = odds ratio; VaD = vascular dementia.

* Number of participants and ORs were 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 ³¹	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 [1.2-7.2])
Massaia et al., 2001 ²⁹	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 ²⁸	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 ³²	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])*
Takahashi et al., 2012 ³⁰	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])

Abbreviations: 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 Recherche l'Enseignement en Neurosciences criteria; OR = odds ratio; USA = United States of America; VaD = vascular dementia.

Note: 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 ³³	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 ³⁵	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 ³⁴	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-Ma-noux et al., 2003 ³⁷	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

Table 3. *continued*

Authors	Cohort; sample; age	Outcome; cognitive test, diagnostic criteria	Predictor; ascertainment of exposure	Adjustment for confounders	Most important results
Verhaeghen et al., 2003 ³⁷	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* CHD was negatively associated with cognition
Singh-Ma-noux et al., 2008 ⁴⁰	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 fluency

Table 3. continued

Authors	Cohort; sample; age	Outcome; cognitive test, diagnostic criteria	Predictor; ascertainment of exposure	Adjustment for confounders	Most important results
Roberts et al., 2010 ³⁶	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 ³⁸	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 with any of the cognitive tests

Table 3. continued

Authors	Cohort; sample; age	Outcome; cognitive test, diagnostic criteria	Predictor; ascertainment of exposure	Adjustment for confounders	Most important results
Heath et al., 2015 ³⁹	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 anticholinesterase inhibitor	IHD**, 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])

Abbreviations: AH4-1 = Alice Heim 4-1; a-MCI = amnesic 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-amnesic mild cognitive impairment; OR = odds ratio; SES = socioeconomic status; UK = United Kingdom.

* More specific results were obtained after contact with the corresponding author.

** Definition of IHD was obtained after contact with the corresponding author.

Figure 2. Forest plot of prospective cohort studies assessing the relation between coronary heart disease and cognitive impairment or dementia

DISCUSSION

The results of the meta-analysis of prospective cohort studies indicate that individuals with CHD have, on average, a 45 percent 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 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), majorly found 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 risk of cognitive impairment or dementia is still unknown, but several candidate pathways exist. CHD and dementia share common risk factors such as obesity, type 2 diabetes, smoking, hypertension, physical inactivity, and hypercholesterolemia.^{7, 8} 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.^{7,9} Additionally, CHD and accompanying vascular insufficiency can lead to cerebrovascular changes such as reduced cerebral blood flow (which can lead to hypoperfusion),⁴¹ white matter lesions and brain infarctions,²¹ which in turn are associated with reduced cognitive functioning and risk of dementia.^{42, 43} CHD might however not itself be causally related to cognition, but brain-effects (e.g. cognitive impairment with vascular origin) might be due to underlying atherosclerosis, which increases both the risk of CHD and dementia.^{44, 45}

Policy makers and health workers must become more aware that identification of individuals at high risk for CHD or dementia is essential to intervene at an early stage by targeting 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 reducing incidence rates and disease burden.^{5, 46} Concerted actions focusing on the heart-brain connection might be key to fostering healthy aging. Future public health campaigns focusing on preventing CHD and dementia should join forces and consider placing a greater emphasis on targeting shared risk factors.

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, particularly 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 and diluted or even 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 between-study difference in effect estimates. By using a random-effects meta-analysis we have tried to account for variability within and between studies. The abovementioned 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 prospective cohort studies, but thereby 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 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.⁴⁷ While this has led to the exclusion of studies affirming the association between CHD and cognitive impairment or dementia, our focus was on MI and AP as the most prevalent conditions. Using a broader search strategy that includes all causes of IHD led to more than 12,000 search hits (now 6,132), which was considered unfeasible. Fifth, there were unfortunately too few studies to conduct separate meta-analyses for the different subtypes of dementia. Sixth, it would have been interesting to conduct stratified meta-analyses for gender, but unfortunately gender-specific risk estimates are scarce.

In conclusion, 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 (e.g. hypertension, arterial stiffness, common genetic variants) that link CHD and risk of cognitive impairment or dementia.

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SUPPLEMENTAL DATA

S1 Appendix. Complete search strategy

Medline

- S1: (dement* or Alzheimer* or cognit* or neuropsychol*).af.
- S2: (((ischemic or ischaemic or coronary) and (heart OR artery)) or myocardium or myocardial or angina).af.
- S3: 1 and 2
- S4: limit 3 to (humans and (dutch or english or french or german))

Embase

- S1: (dement* or Alzheimer* or cognit* or neuropsychol*).ti,ab.
- S2: (((ischemic or ischaemic or coronary) and (heart or artery)) or myocardium or myocardial or angina).ti,ab.
- S3: 1 and 2
- S4: limit 3 to (humans and (dutch or english or French or german))

PsycINFO

- S1: dement# OR Alzheimer OR cognit# OR neuropsychol#
- S2: (((ischaemic OR ischemic OR coronary) AND (heart OR artery)) OR myocardium OR myocardial OR angina)
- S3: S1 AND S2

CINAHL

- S1: (((ischaemic OR ischemic OR coronary) AND (heart OR artery)) OR myocardium OR myocardial OR angina)
- S2: dement# OR Alzheimer OR cognit# OR neuropsychol#
- S3: S1 and S2

Section/topic	Checklist item	Reported on page #
TITLE		
Title	1 Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT		
Structured summary	2 Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2-3
INTRODUCTION		
Rationale	3 Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4 Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS		
Protocol and registration	5 Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6 Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5
Information sources	7 Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4-6

Section/topic	Checklist item	Reported on page #
Search	8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1 Appendix
Study selection	9 State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4-6
Data collection process	10 Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11 List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12 Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5
Summary measures	13 State the principal summary measures (e.g., risk ratio, difference in means).	Page 6
Synthesis of results	14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6
Risk of bias across studies	15 Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 6
Additional analyses	16 Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 6

Section/topic	Checklist item	Reported on page #
RESULTS		
Study selection	17 Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7; Figure 1
Study characteristics	18 For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-3; S5 Table 1
Risk of bias within studies	19 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 7
Results of individual studies	20 For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1-3; S5
Synthesis of results	21 Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 7-10; Table 1-3; S5
Risk of bias across studies	22 Present results of any assessment of risk of bias across studies (see Item 15).	Page 7-10
Additional analysis	23 Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 7-10
DISCUSSION		
Summary of evidence	24 Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10-11

Section/topic	Checklist item	Reported on page #
Limitations	25 Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 11-12
Conclusions	26 Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 12-13
----- FUNDING		
Funding	27 Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not applicable

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org

S3 Appendix. MOOSE Checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	4
4	Type of exposure or intervention used	4
5	Type of study designs used	4
6	Study population	4
Reporting of search strategy should include		
7	Qualifications of searchers (e.g. librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	5
9	Effort to include all available studies, including contact with authors	5-6
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (e.g. explosion)	N/A
12	Use of hand searching (e.g. reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	5
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	5-6
16	Description of any contact with authors	5-6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5-6
18	Rationale for the selection and coding of data (e.g. sound clinical principles or convenience)	5-6
19	Documentation of how data were classified and coded (e.g. multiple raters, blinding, and interrater reliability)	5-6
20	Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	5-6

Item No	Recommendation	Reported on Page No
21	Assessment of study quality, including blinding of quality assessors, stratification, or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6
23	Description of statistical methods (e.g. complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	Figure 1-2, Table 1-3, S5
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2, S5 Figure 1,3,4,6,7,9,10
26	Table giving descriptive information for each study included	Table 1-3, S5 Table 1
27	Results of sensitivity testing (e.g. subgroup analysis)	8-10
28	Indication of statistical uncertainty of findings	7-10
Reporting of discussion should include		
29	Quantitative assessment of bias (e.g. publication bias)	7-10
30	Justification for exclusion (e.g. exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	7
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	10-12
33	Generalization of the conclusions (i.e. appropriate for the data presented and within the domain of the literature review)	10-12
34	Guidelines for future research	12-13
35	Disclosure of funding source	N/A

S4 Appendix. Newcastle-Ottawa quality assessment scale adapted for cross-sectional studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories, with the exception for 'Assessment for outcome' from the Outcome category. A maximum of two stars can be given for Comparability.

Selection (Maximum four stars)

1. Representativeness of the exposed cohort
 - a) Truly representative of the general population (random sampling) *
 - b) Somewhat representative of general population (non-random sampling) *
 - c) Selected group of users (e.g. nurses, volunteers)
 - d) No description of the sampling strategy
2. Sample size, response rate, and comparability between respondent and non respondents
 - a) Sample size is justified, response rate AND the comparability between respondents and non-respondents characteristics are described *
 - b) Sample size is justified and the response rate OR the comparability between respondents and non-respondents characteristics is described *
 - c) Sample size is justified, but no description of the response rate and the characteristics of the responders and non-responders
 - d) Sample size is not justified, and there is no description of the response rate or the characteristics of the responders and non-responders
3. Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort *
 - b) Drawn from a different source
 - c) No description of the derivation of the non-exposed cohort
4. Ascertainment of exposure
 - a) Validated measurement tool *
 - b) Non-validated measurement tool, but the tool is available or described *
 - c) Self-report
 - d) No description

Comparability (Maximum two stars)

5. Comparability of cohorts on the basis of the design or analysis
 - a) Study controls for the most important factor *
 - b) Study controls for any additional factor *
 - c) No control for any important factor

Outcome (Maximum three stars)

6. Assessment of outcome
 - a) Independent blind assessment **
 - b) Record linkage **
 - c) Self-report
 - d) No description
7. Statistical test
 - a) The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value) *
 - b) The statistical test is not appropriate, not described or incomplete

S5 Appendix. Further supporting information

- **S5 Table A.** Overview of studies assessing the relation between angina pectoris, myocardial infarction, coronary heart disease, and cognition or dementia
- **S5 Figure A.** Funnel plot of prospective cohort studies included in the coronary heart disease meta-analysis showing the effect estimates by their standard errors
- **S5 Figure B.** Forest plot of prospective cohort studies assessing the relation between myocardial infarction and cognitive impairment or dementia
- **S5 Figure C.** Forest plot of prospective cohort studies assessing the relation between angina pectoris and cognitive impairment or dementia
- **S5 Figure D.** Forest plot of case-control studies assessing the relation between coronary heart disease and cognitive impairment or dementia
- **S5 Figure E.** Funnel plot of case-control studies included in the coronary heart disease meta-analysis showing the effect estimates by their standard errors
- **S5 Figure F.** Forest plot of case-control studies assessing the relation between myocardial infarction and cognitive impairment or dementia
- **S5 Figure G.** Forest plot of case-control studies assessing the relation between angina pectoris and cognitive impairment or dementia
- **S5 Figure H.** Forest plot of cross-sectional studies assessing the relation between coronary heart disease and cognitive impairment or dementia
- **S5 Figure I.** Funnel plot of cross-sectional studies included in the coronary heart disease meta-analysis showing the effect estimates by their standard errors
- **S5 Figure J.** Forest plot of cross-sectional studies assessing the relation between myocardial infarction and cognitive impairment or dementia

S5 Table A. Overview of studies assessing the relation between angina pectoris, myocardial infarction, coronary heart disease, and cognition or dementia

Authors	Study design	Predictor	Outcome	Included in meta-analysis? (If yes, which meta-analysis? If no, reason of exclusion?)
Aronson et al., 1990	Prospective	MI	Dementia	Yes, MI and CHD meta-analysis
Kalmijn et al., 1996	Prospective	CHD	Cognitive decline	Yes, CHD meta-analysis
Ross et al., 1999	Prospective	CHD	VaD	Yes, CHD meta-analysis
Kivipelto et al., 2002	Prospective	MI	AD, AD/VaD	Yes, MI and CHD meta-analysis
Newman et al., 2005	Prospective	MI, AP	Dementia, AD with no VaD, AD with or without VaD	Yes, MI, AP and CHD meta-analysis
Hayden et al., 2006	Prospective	MI	Dementia, AD, VaD	Yes, MI and CHD meta-analysis
Ikram et al., 2008	Prospective	MI	Dementia	Yes, MI and CHD meta-analysis ^a
Chen et al., 2011	Prospective	AP	Dementia	Yes, AP and CHD meta-analysis
Haring et al., 2013	Prospective	MI, AP	Possible dementia, MCI, Possible dementia/MCI	Yes, MI, AP and CHD meta-analysis
Lipnicki et al., 2013	Prospective	MI, AP, CHD	Decline to MCI or dementia	Yes, MI, AP and CHD meta-analysis
Brayne et al., 1998	Nested case-control	MI	Dementia, AD	Yes, MI and CHD meta-analysis
Massaia et al., 2001	Case-control	MI	AD	No, only continuous outcome measures
Bursi et al., 2006	Case-control	MI	Dementia	Yes, MI and CHD meta-analysis
Hughes et al., 2010	Case-control	AP	Dementia, AD	Yes, AP and CHD meta-analysis
Takahashi et al., 2012	Case-control	MI, AP	VaD	Yes, MI, AP and CHD meta-analysis
Elwood et al., 2002	Cross-sectional	MI, AP	Cognitive function	No, only continuous outcome measures
Singh-Manoux et al., 2003	Cross-sectional	MI, AP, CHD	Cognitive function	No, only continuous outcome measures
Verhaeghen et al., 2003	Cross-sectional, prospective	MI, CHD	Cognitive function, cognitive decline	No, only continuous outcome measures
Singh-Manoux et al., 2008	Cross-sectional	CHD	Cognitive function	No, only continuous outcome measures
Roberts et al., 2010	Cross-sectional	MI, AP	MCI	Yes, MI and CHD meta-analysis
Antzén et al., 2011	Cross-sectional	CHD	Cognitive function; cognitive impairment	Yes, CHD meta-analysis ^b
Heath et al., 2015	Cross-sectional	CHD	Dementia	Yes, CHD meta-analysis

Abbreviations: AD = Alzheimer's disease; AP = angina pectoris; CHD = coronary heart disease; MCI = mild cognitive impairment; MI = myocardial infarction; VaD = vascular dementia.

^a Hazard ratios for recognized myocardial infarction were taken into account due to larger number of participants.

^b Odds ratios for women and the Tapping test were taken into account due to larger number of participants.

S5 Figure A. Funnel plot of prospective cohort studies included in the coronary heart disease meta-analysis showing the effect estimates by their standard errors

S5 Figure B. Forest plot of prospective cohort studies assessing the relation between myocardial infarction and cognitive impairment or dementia

S5 Figure C. Forest plot of prospective cohort studies assessing the relation between angina pectoris and cognitive impairment or dementia **S5 Figure D.** Forest plot of case-control studies assessing the relation between coronary heart disease and cognitive impairment or dementia

S5 Figure E. Funnel plot of case-control studies included in the coronary heart disease meta-analysis showing the effect estimates by their standard errors

S5 Figure F. Forest plot of case-control studies assessing the relation between myocardial infarction and cognitive impairment or dementia

S5 Figure G. Forest plot of case-control studies assessing the relation between angina pectoris and cognitive impairment or dementia **S5 Figure H.** Forest plot of cross-sectional studies assessing the relation between coronary heart disease and cognitive impairment or dementia

S5 Figure I. Funnel plot of cross-sectional studies included in the coronary heart disease meta-analysis showing the effect estimates by their standard errors

S5 Figure J. Forest plot of cross-sectional studies assessing the relation between myocardial infarction and cognitive impairment or dementia

3

Cognitive changes in prevalent and incident cardiovascular disease: a 12-year follow-up in the MAastricht Aging Study (MAAS)

Syenna H. J. Schievink, Martin P. J. van Boxtel,
Kay Deckers, Robert J. van Oostenbrugge,
Frans R. J. Verhey, Sebastian Köhler

ABSTRACT

Aims: Cardiovascular disease (CVD) has been suggested to accelerate cognitive decline and to be a risk factor for dementia, but still little is known about the cognitive course after a first cardiovascular event. Therefore, the present study aims to investigate the cognitive trajectories in both prevalent and incident CVD over a 12-year time period in the general population.

Methods and Results: Cognitively healthy participants (age 24-82 years, $n = 1,823$) of a prospective cohort study were serially assessed at baseline, 6, and 12 years. Verbal memory, executive function, and information processing speed were analysed in adults with prevalent, incident, and no CVD. Random effects models were used to test the association between CVD and change in cognitive function over time. At baseline, participants with prevalent CVD showed more decline in memory and information processing speed than healthy controls. Participants with incident CVD also showed more decline in these cognitive domains, but this was only significant in the follow-up period from 6 to 12 years. Associations were more pronounced in participants aged younger than 65 years at baseline and in sub-analyses with angina pectoris or myocardial infarction as the most prevalent CVD conditions.

Conclusion: Prevalent and incident CVD predict cognitive decline in middle-aged individuals. Findings for incident CVD suggest that the onset of decline is linked in time with the vascular event itself. Timely CVD management may delay the onset of decline.

INTRODUCTION

Cardiovascular disease (CVD) predisposes individuals to cerebrovascular damage and its incidence rises with age.¹ CVD may lead to cognitive and functional impairment and increases dementia risk.² Ischemic brain lesions involved in the pathology of late-onset Alzheimer's disease and vascular dementia have been found in CVD.³ However, current guidelines on CVD prevention of the European Society of Cardiology do not comment on the association between CVD and cognitive decline.⁴

While associations between prevalent CVD and cognition or dementia have been reported in cross-sectional⁵⁻⁹ and prospective studies,^{7, 10-12} non-significant associations exist, too.¹³⁻¹⁶ Inconsistencies may stem from differences in definition and severity of CVD, cognitive assessment, follow-up duration, and sample size.

Given the pathological cascade leading from CVD to brain lesions to cognition takes time to evolve, effects on cognition probably vary by CVD exposure duration, so that cognitive changes are still modest in incident cases. Next, associations between CVD and cognitive decline might be more pronounced in younger individuals, as has been shown for hypertension¹⁷ and diabetes.¹⁸ Insight into the onset and course of cognitive functions after incident CVD could show whether there is a margin in time for prevention.

Therefore, we studied the cognitive trajectories of individuals with prevalent and incident CVD over 12 years. It was hypothesized that (1) prevalent CVD shows large cognitive decline, and (2) incident CVD shows a more modest though more decline than those without CVD. Since sex and age differences exist in CVD and rate of cognitive decline, their possible effect modification was studied as well.

METHODS

Participants

The Maastricht Aging Study (MAAS) is a prospective cohort study on determinants of cognitive aging.¹⁹ In total, 10,801 people were invited from the Registration Network Family Practices (RNH), a patient register of collaborating general practitioners, representative of the Dutch population. Exclusion criteria were major cerebrovascular pathology, nervous system tumour or congenital malformation, multiple sclerosis, parkinsonism, epilepsy, dementia,

organic psychosis, schizophrenia, affective psychosis, and intellectual disability. From those remaining, a sample of 1,823 individuals was drawn using optimal stratified sampling design with strata for age, sex, and occupational achievement (low/high). Participants underwent repeated assessments of blood pressure, medical history, lifestyle, and anthropomorphic and neurocognitive measures, at six (mean 6.2, SD 0.2) and 12 years (mean 12.5, SD 0.3) after baseline. The study complies with the Declaration of Helsinki. The local ethics committee of Maastricht University Medical Centre approved the research protocol (MEC05-107). All participants gave informed consent.

Measures

Cardiovascular disease

People were classified with CVD if they had been diagnosed with one of the following conditions: peripheral artery disease, angina pectoris (AP), myocardial infarction (MI), heart insufficiency, heart valve disease, bypass surgery, or open-heart surgery. Individuals who reported one of these at baseline were classified as prevalent CVD. Individuals who reported one of these at six- or 12-year follow-up were classified as incident CVD.

Neuropsychological assessment

Psychologists or trained test assistants administered a neuropsychological battery at each wave. In the present study, the delayed recall of the visual Verbal Learning Test (VLT) was used to assess verbal memory,²⁰ the shifting score of the Concept Shifting Test (CST) to assess executive function,²¹ and the Letter Digit Substitution Test (LDST) to assess information processing speed.²²

Covariates

Potential confounders were demographic variables: age, sex, educational level (low, middle, high), and health-related conditions: present or past smoking (yes/no), alcohol abuse (yes/no), type 2 diabetes (yes/no, self-report based on physician's diagnosis and current anti-diabetic medication use), hypertension (yes/no, mean systolic blood pressure ≥ 140 mmHg and mean diastolic blood pressure ≥ 90 mmHg measured three times at five-minute intervals by an automatic recording device - Critikon Dinamap 8100; Critikon, Tampa, FL - or current use of antihypertensive medication), body-mass-index (BMI, weight in kg/height in m²), and depressive symptoms by using the total score of the 16 items of the depression subscale (range 16–80) of the revised 90-item Symptom Checklist.²³ Hypertension, diabetes, BMI, and depression were assessed at each wave.

Statistical analyses

Baseline differences between participants with and without CVD were analysed using independent samples *t*-tests and χ^2 -tests. In addition, all analyses were back-weighted to the RNH source population from which the sample was drawn, and we therefore report the design-based *F*-statistic (see Table 1). The delayed recall score of the VLT and shifting score of the CST needed square and logarithmic transformation respectively, which led to a better (approximately normal) distribution. Random effects models tested the association between CVD (prevalent and incident) and change in cognition over time. As suggested by likelihood-ratio testing, the model included a random intercept and slope with an unstructured correlation matrix. In order to allow for nonlinear effects, a CVD-by-time interaction term with time entered as dummy variable for each of the two follow-ups was included in the model. Also, two inverse probability weights were added: an attrition weight that takes into account the likelihood of being lost to follow-up, and a sampling weight to generalize estimates to the total RNH population structure. All analyses were first adjusted for age, age², sex, education, followed by fully adjusted models that included hypertension, alcohol abuse, smoking, type 2 diabetes, BMI, and depressive symptoms. Only fully adjusted models are presented. Additional analyses were stratified by sex and age (<65 and ≥65 years). All analyses were two-sided with an 0.05 alpha and performed in Stata 13.1 (StataCorp, TX).

RESULTS

Baseline differences

Of the 1,823 participants, 195 (10.7%) were classified with prevalent CVD. They were on average older, more often smokers, hypertensive, overweight, diabetic, experiencing depressive symptoms, and had a lower educational level (Table 1). At follow-up, 204 (15.2%) individuals had incident CVD. They were on average older, less educated, overweight, hypertensive, diabetic, and reported more depressive symptoms.

Prevalent CVD and cognitive decline

At baseline, the prevalent CVD group did not have significantly lower cognitive scores, but a significant group-by-time interaction suggested more decline over time in verbal memory and information processing speed than the group without CVD (Table 2). As seen in Figure 1, both groups' scores increased from baseline to first follow-up in verbal memory and information processing speed, but this was less pronounced for the CVD group, suggesting

a deviation from age-normal levels. No differences were found for executive functioning (Figure 1).

Effect modification by sex and age

Sex-stratified analyses suggest that men dictated the overall effect of CVD on verbal memory, while both sexes declined more in information processing speed if CVD was prevalent. In younger individuals, CVD predicted faster decline in memory and information processing speed, whereas in older individuals no significant decline in any domain was predicted (Table 2).

Incident CVD and cognitive decline

Regarding incident CVD, the interaction with time suggested a significant decline in verbal memory and information processing speed relative to those without CVD (Table 3, Figure 2). Time-stratified analyses showed that decline was apparent from six- to 12-years follow-up only (verbal memory: $\chi^2 = 3.90$, $df = 1$, $p = 0.048$; information processing speed: $\chi^2 = 21.81$, $df = 1$, $p < 0.001$). The interaction between incident CVD and time for executive function was not significant ($\chi^2 = 5.56$, $df = 2$, $p = 0.062$), but a similar time-lagged drop was observed in the six- to 12- years follow-up period ($\chi^2 = 5.05$, $df = 1$, $p = 0.025$).

Effect modification by sex and age

For information processing speed, incident CVD was associated with more decline in both sexes. Stratification by age showed that decline was statistically significant only in younger individuals (Table 3). Large standard errors in the older group suggest more heterogeneity in individual cognitive trajectories. Stratified effects in other cognitive domains were statistically inconclusive.

Post-hoc analysis: prevalent AP, MI, other CVD, and cognitive decline

Since AP and MI were most common in prevalent CVD, their individual effects were studied in post-hoc analysis. We analysed those with AP only ($n = 67$), those with MI (with or without AP, $n = 68$), and those with other CVD ($n = 60$) relative to the no CVD group ($n = 1,628$). AP and other CVD were significantly associated with decline in information processing speed and MI with decline in verbal memory. To increase power, we then combined the MI/AP group as suggested by directionally similar individual effects. The interaction effects were significant for verbal memory and for information processing speed, but again not for executive function (Supplementary Table 4).

Table 1. Baseline characteristics of the CVD groups^S

Characteristic	Prevalent CVD			Incident CVD				
	No, n=1628	Yes, n=195	F-statistic	df	No, n=1138	Yes, n=204	F-statistic	df
Age	50.5±17.7	69.5±9.8	394.20***	1,1822	46.8±16.2	58.8±13.6	101.99***	1,1341
Female	854 (55.4)	56 (33.7)	26.27***	1,1822	585 (54.0)	95 (51.2)	0.49	1,1341
Education								
Low	569 (37.8)	96 (51.4)	6.05**	2,3633	340 (32.0)	106 (54.7)	18.09***	2,2680
Middle	678 (39.4)	68 (32.8)			507 (42.6)	67 (30.7)		
High	380 (22.9)	30 (15.8)			291 (25.4)	31 (14.6)		
Smokers	999 (64.1)	145 (73.5)	5.14*	1,1701	694 (63.0)	127 (68.3)	1.64	1,1252
Alcohol abuse	47 (3.1)	4 (1.4)	2.24	1,1822	29 (2.4)	5 (3.0)	0.16	1,1341
Hypertension	504 (32.2)	156 (80.4)	145.68***	1,1822	287 (25.1)	99 (49.1)	42.44***	1,1341
Body mass index	26.5±4.4	27.9±3.7	21.30***	1,1819	26.2±4.3	27.7±4.3	16.25***	1,1339
Diabetes mellitus	49 (3.4)	19 (10.4)	15.83***	1,1822	17 (1.5)	14 (7.3)	21.70***	1,1341
Depressive symptoms	20.8±6.5	21.7±6.4	2.96	1,1781	20.5±6.0	21.3±6.7	2.11	1,1326
Cardiovascular diseases [#]								
Myocardial infarct	-	67 (33.0)	N/A	-	-	47 (21.1)	N/A	-
Angina pectoris	-	92 (49.3)	N/A	-	-	68 (34.2)	N/A	-
Peripheral artery disease	-	41 (21.7)	N/A	-	-	73 (37.4)	N/A	-
Heart insufficiency	-	26 (13.5)	N/A	-	-	15 (8.4)	N/A	-
Bypass surgery	-	28 (13.4)	N/A	-	-	57 (26.2)	N/A	-
Heart valve disease	-	17 (8.8)	N/A	-	-	29 (12.8)	N/A	-
Open-heart surgery	-	6 (3.2)	N/A	-	-	11 (5.4)	N/A	-

Table 1. continued

Characteristic	Prevalent CVD			Incident CVD		
	No, n=1628	Yes, n=195	F-statistic	df	No, n=1138	Yes, n=204
Neuropsychological tests						
Verbal learning test (raw)	9.7±3.1	7.5±2.9	71.78***	1,1815	10.2±2.9	9.0±2.7
Verbal learning test (transformed)	103.8±57.5	66.0±44.7	91.36***	1,1815	111.8±56.3	88.0±48.7
Concept shifting test (raw)	12.1±12.0	17.2±12.9	17.70***	1,1794	10.5±9.5	14.7±13.0
Concept shifting test (transformed)	2.2±0.9	2.6±0.8	22.63***	1,1733	2.1±0.9	2.4±0.9
Letter digit substitution test (raw)	48.5±12.2	39.2±9.6	116.78***	1,1818	50.7±11.5	44.7±10.4

Abbreviations: df = degrees of freedom; SD = standard deviation.

Note: means, SDs, percentages, F-statistic, and df are design-based estimates that are back-weighted to the sampling frame (n = 10658) from which participants were drawn. Percentages may not sum up to 100 because of rounding, or *participants could have multiple conditions.

^sData are presented as either mean±SD or n (%).

*P<0.05, **P<0.01, ***P<0.001

Table 2. Mean differences (and 95% confidence intervals) in baseline cognition and in rate of cognitive decline (slopes) from baseline between those with prevalent cardiovascular disease (CVD, $n = 195$) and those without ($n = 1,628$)

Parameter	Time					
	Baseline difference		Change baseline to 6-year FU		Change baseline to 12-year FU	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Verbal memory						
Total	1.68	-6.01 to 9.37	-10.82*	-20.09 to -1.56	-24.23**	-38.76 to -9.70
Women	0.02	-14.77 to 14.81	-4.58	-22.56 to 13.39	-15.02	-42.01 to 11.97
Men	2.53	-6.26 to 11.32	-13.70*	-24.34 to -3.07	-26.99**	-42.45 to -11.53
Aged <65 years	5.33	-7.27 to 17.93	-11.75	-26.91 to 3.41	-23.47**	-41.16 to -5.78
Aged ≥65 years	-5.43	-15.21 to 4.36	-2.71	-15.09 to 9.67	-5.05	-32.27 to 22.17
Executive function						
Total	-0.05	-0.22 to 0.13	0.08	-0.12 to 0.29	0.10	-0.19 to 0.39
Women	-0.08	-0.36 to 0.21	0.31*	0.01 to 0.61	-0.22	-0.65 to 0.21
Men	-0.02	-0.24 to 0.20	-0.04	-0.30 to 0.22	0.31	-0.04 to 0.67
Aged <65 years	-0.08	-0.37 to 0.20	0.06	-0.27 to 0.39	0.19	-0.20 to 0.58
Aged ≥65 years	-0.02	-0.24 to 0.21	0.12	-0.17 to 0.42	-0.54	-1.14 to 0.06
Information processing speed						
Total	1.35	-0.18 to 2.88	-2.81***	-4.10 to -1.52	-5.42***	-7.47 to -3.37
Women	0.97	-2.03 to 3.98	-2.81**	-4.91 to -0.72	-4.99**	-8.10 to -1.88
Men	1.27	-0.42 to 2.95	-2.84***	-4.43 to -1.25	-5.50***	-8.00 to -3.00
Aged <65 years	0.88	-1.52 to 3.29	-2.16**	-3.69 to -0.64	-3.91***	-5.54 to -2.28
Aged ≥65 years	0.94	-1.12 to 2.99	-1.33	-3.43 to 0.77	-1.24	-6.18 to 3.70

Abbreviations: FU = follow-up; CI = confidence interval.

Note: estimates from different cognitive domains are on different scales and cannot be directly compared.

Model: CVD, time, CVDxTime, sex, age¹, education, baseline smoking, baseline alcohol abuse, body mass index, diabetes, depressive symptoms.¹ X²-test (2 degrees of freedom) of interaction between CVD (yes, no) and time (baseline, 6-yr, 12-yr follow-up); omnibus test of the null hypothesis of no difference in rate of change over time between CVD groups.

*P<0.05, **P<0.01, ***P<0.001

Figure 1. Cognitive trajectories of individuals with prevalent CVD (n = 195) and those without (n = 1,628). CVD = cardiovascular disease

Figure 2. Cognitive trajectories of individuals with incident CVD (n = 204) and those without (n = 1,138). CVD = cardiovascular disease

Table 3. Mean differences (and 95% confidence intervals) in baseline cognition and in rate of cognitive decline (slopes) from baseline between those with incident cardiovascular disease (CVD, $n = 204$) and those without ($n = 1,138$)

Parameter	Time						
	Baseline difference			Change baseline to 6-yr FU		Change baseline to 12-yr FU	
	Estimate	95% CI		Estimate	95% CI	Estimate	95% CI
Verbal memory							
Total	-1.07	-8.87 to 6.74		-4.85	-13.10 to 3.40	-14.91**	-25.69 to -4.12
Women	1.67	-10.16 to 13.50		-2.78	-16.85 to 11.29	-16.68	-35.90 to 2.54
Men	-3.98	-14.14 to 6.18		-6.29	-15.83 to 3.25	-11.40*	-22.78 to -0.03
Aged <65 years	-4.24	-13.49 to 5.01		1.05	-9.38 to 11.48	-8.18	-20.68 to 4.32
Aged ≥65 years	-4.49	-18.60 to 9.63		-8.82	-21.87 to 4.22	1.01	-23.12 to 25.13
Executive function							
Total	0.07	-0.09 to 0.23		-0.00	-0.17 to 0.16	0.24*	0.02 to 0.46
Women	0.17	-0.06 to 0.41		-0.02	-0.27 to 0.23	0.09	-0.27 to 0.46
Men	-0.03	-0.24 to 0.18		0.01	-0.22 to 0.23	0.39**	0.12 to 0.66
Aged <65 years	0.04	-0.14 to 0.22		-0.04	-0.22 to 0.15	0.24	-0.00 to 0.48
Aged ≥65 years	0.22	-0.08 to 0.51		-0.06	-0.40 to 0.28	-0.16	-0.74 to 0.42
Information processing speed							
Total	0.61	-0.91 to 2.13		-1.00	-2.25 to 0.25	-3.72***	-5.43 to -2.02
Women	0.02	-2.43 to 2.46		-1.30	-3.53 to 0.94	-3.74*	-6.88 to -0.60
Men	1.08	-0.73 to 2.88		-0.79	-2.09 to 0.51	-3.79***	-5.54 to -2.03
Aged <65 years	-0.75	-2.57 to 1.08		0.25	-0.78 to 1.28	-1.65*	-2.93 to -0.37
Aged ≥65 years	1.63	-0.93 to 4.20		-1.14	-3.82 to 1.54	-1.76	-6.65 to 3.14

Abbreviations: FU = follow-up; CI = confidence interval.

Note: estimates from different cognitive domains are on different scales and cannot be directly compared.

Model: CVD, time, CVDxTime, sex, age, age², education, baseline smoking, baseline alcohol abuse, body mass index, diabetes, depressive symptoms.

χ^2 -test (2 degrees of freedom) of interaction between CVD (yes, no) and time (baseline, 6-yr, 12-yr follow-up); omnibus test of the null hypothesis of no difference in rate of change over time between CVD groups.

*P<0.05, **P<0.01, ***P<0.001

DISCUSSION

The present study investigated the effect of prevalent and incident CVD on cognitive decline over 12 years. Prevalent CVD predicted faster decline in memory and processing speed. The effect on memory was stronger in men and below age 65. For processing speed, the effect was stronger in both sexes and below 65. Incident CVD showed a faster decline in memory and processing speed over time, but this effect was more modest and only evident during the period between the six- and 12-year follow-up, i.e. after onset of CVD. Incident CVD predicted decline in processing speed only in the younger age group.

Comparison with other studies is hampered by differences in the definition and severities of CVD, choice of cognitive measures, and study design. In general, our findings are in line with previous studies,^{5, 8, 12} but not all,^{7, 16} and in line with a recent systematic review,² suggesting that CVD is associated with worse cognitive test performance and faster decline.

Other studies also found a decline in executive function.^{24, 25} Rostamian et al. used the LDST to measure executive functions, which we consider a test for information processing speed²⁵ for which the present study found an association, too. To test executive function, we used the CST shifting index, which might not have been sensitive enough for decline. Notably, this is similar to our previous findings in MAAS.^{17, 18}

The effect of incident CVD on cognition was not examined before. In the present study, cognitive decline in incident CVD showed an insidious onset after six years and declined from that moment. We reported similar findings for incident hypertension before.¹⁷ This trajectory indicates a window of opportunity for slowing of cognitive decline by timely preventive measures. Indeed, recent studies showed that an approach targeting multiple risk factors simultaneously is most promising.² For instance, the recent FINGER study²⁶ used a multifactorial approach including diet, exercise, cognitive training, and vascular risk monitoring in at-risk elderly to investigate whether cognition can be improved or maintained by targeting health and lifestyle factors relating to CVD. While the six-year preDIVA trial¹²⁷ did not result in reduced dementia risk through a nurse-led intensive vascular care program in adults aged 70-78 years, intervention effects were observed in participants without a history of CVD, which is in line with our finding of no significant decline in the pre-diagnostic phase (from baseline to six-year follow-up). Taken together, these findings imply that primary prevention and timely management of CVD can reduce dementia risk

from a lifetime perspective. This heart-brain connection makes a strong case that prevention of CVD and prevention of dementia should go hand in hand.

A dementia diagnosis requires impairment in two or more domains, next to interference with independence in activities of daily living due to these impairments. In this regard, our finding that CVD leads to decline in both memory as well as information processing speed is noteworthy. Processing speed is sensitive to damage to the brain's connectivity and white matter integrity, which is a hallmark of late-onset Alzheimer's disease, next to the aggregation of amyloid plaques and neurofibrillary tangles. Dementia and CVD share many risk factors related to vascular health, including hypertension, obesity, cholesterol, diabetes, healthy diet, and physical activity.² CVD may lead to cerebrovascular changes, reduced cognitive functioning, and dementia through vascular insufficiency caused by atherosclerosis. Other underlying pathophysiological mechanisms such as cerebral hypoperfusion and low cardiac output,²⁸ lower cerebral perfusion and affect the neurovascular unit that ascertains constancy of cerebral blood flow, leading to blood-brain barrier damage and cerebral small vessel disease.³ Indeed, previous studies found MI to be associated with presence of white matter lesions.²⁹ In addition, other risk factors for white matter lesions might exert stronger effects in people with a history of MI, including high diastolic blood pressure.³⁰ Besides this, inflammation and oxidative stress compromise repair mechanisms of damaged white matter.^{31, 32}

Above findings were more pronounced in midlife. This is in line with our previous studies,^{17,18} and supports current recommendation to start health- and lifestyle interventions aimed at reducing dementia risk in midlife or earlier.³³ Possibly, midlife CVD exert stronger effects because they impact on a relatively intact brain, which leads to sharper contrasts with unexposed norm groups. In later life, multimorbidity and wear-and-tear forces (oxidative stress, low-grade inflammation) are prevalent and may cause brain damage that dilutes the effect of any specific risk factor. Since large differences exist in severity and duration of such exposures, this causes inter- and intra-individual variability in cognitive performance as people age, as has been reported with increasing age for choice reaction time,³⁴ memory, and fluid cognitive abilities.^{35, 36} Alternatively, selective attrition could have led to an underestimation of the associations between CVD and cognitive decline because older participants were more likely to drop out of the study.³⁷ Even though the maximum-likelihood estimate and the attrition weights were used to minimize the effect of loss to follow-up, this possibility cannot be excluded.

This study provides weak evidence for sex differences in the association between CVD and cognitive decline. Sex-stratified analyses showed that associations were inconclusive in men with prevalent CVD, whereas a significant decline in memory was found in women. In contrast, decline in processing speed after prevalent CVD and decline in memory and processing speed after incident CVD was equal in both sexes. More research into this important topic is warranted.

This study has several strengths, including its large sample size, broad age range, long follow-up, serial assessment of several cognitive domains, and the ascertainment of relevant confounders. However, limitations should be mentioned. CVD and some covariates were based on self-report, which may have led to non-differential misclassification. Also, information on severity of the CVDs is lacking although this may affect the association differentially. Furthermore, some selection bias may have occurred by loss of older participants, as discussed. And due to the explorative nature of the study, we did not control for multiple comparisons and should therefore carefully interpret the results.

To conclude, this study indicates that individuals with prevalent CVD show more cognitive decline in memory and processing speed than controls. In incident CVD, decline is insidious and more modest, which might provide an opportunity for prevention of cognitive deficits.

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SUPPLEMENTAL DATA

Supplementary Table 4. Mean differences (and 95% confidence interval) in baseline cognition and in rate of cognitive decline (slopes) from baseline between those with prevalent angina pectoris only (AP, $n = 67$), prevalent myocardial infarction with or without AP (MI, $n = 68$), other cardiovascular disease (other CVD, $n = 60$), MI and AP combined (MI/AP, $n = 135$) and those without any cardiovascular disease at baseline as reference group ($n = 1,628$)

Parameter	Time		Baseline difference		Change baseline to 6-year FU		Change baseline to 12-year FU		CVDxTime ¹
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
Verbal memory									
AP	4.77	-7.29 to 16.83	-16.01	-33.32 to 1.29	-22.79	-49.63 to 4.05			5.05
MI	3.38	-8.26 to 15.01	-10.36	-23.51 to 2.80	-34.19***	-51.10 to -17.28			15.70***
Other CVD	-3.47	-15.60 to 8.66	-6.03	-20.72 to 8.67	-19.01	-42.57 to 4.56			2.81
MI/AP	3.95	-4.98 to 12.88	-12.95*	-24.23 to -1.66	-26.31**	-44.18 to -8.43			11.03**
Executive function									
AP	0.19	-0.02 to 0.40	-0.07	-0.32 to 0.18	-0.18	-0.60 to 0.24			0.80
MI	-0.21	-0.53 to 0.12	0.12	-0.26 to 0.50	0.43	-0.10 to 0.95			2.56
Other CVD	-0.16	-0.47 to -0.15	0.23	-0.14 to 0.60	0.13	-0.37 to 0.62			1.62
MI/AP	-0.00	-0.21 to 0.20	0.02	-0.21 to 0.26	0.10	-0.25 to 0.44			0.32
Information processing speed									
AP	2.97*	-0.54 to 5.41	-3.33***	-4.84 to -1.81	-5.05***	-7.30 to -2.80			25.36***
MI	0.60	-1.73 to 2.94	-2.65	-5.31 to 0.02	-4.51*	-8.86 to -0.17			5.74
Other CVD	0.25	-2.22 to 2.73	-2.43*	-4.69 to -0.17	-6.94**	-11.08 to -2.79			10.85**
MI/AP	1.92*	0.12 to 3.71	-2.99***	-4.51 to -1.47	-4.73***	-6.96 to -2.51			22.09***

Abbreviations: FU = follow-up; CI = confidence interval; CVD = cardiovascular disease; AP = angina pectoris; MI = myocardial infarction.

Note: estimates from different cognitive domains are on different scales and cannot be directly compared. Estimates for MI/AP are from separate analyses with individuals without prevalent CVD as reference group.

Model: CVD, time, CVDxTime, sex, age, age², education, baseline smoking, baseline alcohol abuse, body mass index, diabetes, depressive symptoms.

¹ X²-test (2 degrees of freedom) of interaction between CVD (yes, no) and time (baseline, 6-yr, 12-yr follow-up); omnibus test of the null hypothesis of no difference in rate of change over time between CVD groups.

*P<0.05, **P<0.01, ***P<0.001

4

Post-acute cognitive functions predict mortality risk in stroke: a 10-year follow-up of the Sydney Stroke Study (SSS)

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ABSTRACT

Objective: Cognitive impairment is a common consequence of stroke and has been associated with poor long-term outcomes. We examined whether cognitive functioning in different domains 3 to 6 months after stroke predicted mortality and dementia long-term outcomes.

Method: Data were obtained from 164 patients with stroke or transient ischemic attack participating in the Sydney Stroke Study, a hospital-based cohort study into the outcomes of stroke. Factor analysis was used to reduce tests from a neuropsychological battery to their latent cognitive domains. The latter were then used as predictors of 10-year mortality and 5-year dementia outcomes in structural equation models adjusted for age, gender and years of education.

Results: Four cognitive factors (verbal memory, executive functioning, information processing speed, and verbal fluency) were identified in factor analysis. For mortality, the highest predictive values were found for executive functioning, information processing speed, and verbal fluency in adjusted analyses. Verbal memory did not predict mortality. In addition, none of the cognitive domains predicted incident dementia 5 years after stroke in adjusted analyses.

Conclusions: Lower cognitive functioning 3 to 6 months after stroke in executive functioning, information processing speed, and verbal fluency predicts mortality up to 10 years later and might delineate a population of frail stroke patients. Difference in cognitive functions did not predict post-stroke dementia over 5 years.

INTRODUCTION

Cognitive impairment is a frequent sequela after stroke, affecting various cognitive domains.¹ Cognitive deficits can affect a patient's independence, the ability to return to work, and limit social engagement.² In both community-based and clinical studies, worse cognition in stroke patients has been related to a higher risk for dementia and increased mortality compared with healthy controls.^{3,4} While poor cognition might thus explain the excessive risk of patients compared to controls, it is less clear whether cognition can also indicate which patients are at most risk. For this, it is necessary to compare cognitive performance across multiple domains among stroke patients only. Using such an approach in the Sydney Stroke Study, we found that vascular mild cognitive impairment and vascular dementia, next to older age and lower ADL/iADL scores, were significantly associated with 10-year mortality in 167 stroke patients.⁵ However, we did not study differential associations across different cognitive domains.

Studying different cognitive domains within a stroke population might result in a better understanding of their prognostic value. If some, but not all, neuropsychological markers are predictors of a post-stroke prognosis, cognitive rehabilitation targeting these markers might have the most benefit for the patient's long-term outcome. This might allow for a more specific selection of at-risk patients, studying underlying mechanisms and designing optimal rehabilitation programs.

Therefore, the aim of the present study is to test the prognostic value of domain-specific cognitive function for predicting 10-year outcomes of mortality among a clinical sample of stroke survivors. Our secondary aim was to determine which cognitive domain contributes most to predicting five-year outcomes of dementia.

METHODS

Participants

The present sample was drawn from the Sydney Stroke Study (SSS), of which the design has been described in detail elsewhere.⁶ In brief, the SSS is a prospective clinical cohort study of cognitive, medical, psychiatric, and brain imaging changes after stroke. Community-dwelling stroke or transient ischemic attack (TIA) patients, aged between 49-87 years, were recruited from the local areas of two major teaching hospitals affiliated with the University of New

South Wales in Sydney during May 1997 and June 2000. Two neurologists independently diagnosed ischemic stroke. Individuals with dementia prior to the stroke or a dementia diagnosis at baseline assessment, a medical history at baseline of alcohol abuse, or other major neurological or psychiatric conditions that could affect cognition were excluded. The ethics committees of the University of New South Wales and the South-Eastern Sydney Illawarra Health Service approved this study. The procedures followed were in line with the institutional guidelines and in accordance with the Helsinki Declaration. All participants gave written informed consent.

Clinical assessment

Baseline assessments were performed within one week of hospital admission and included medical history, functional assessment, and the Mini-Mental State Examination (MMSE).⁷ Index assessments performed between three and six months after the index stroke consisted of a detailed neuropsychological assessment, which was repeated during follow-up waves at one, three, and five years after the index assessment.

Neuropsychological assessment

The neuropsychological test battery consisted of a comprehensive series of measures purported to tap into various cognitive domains. Of these, the following were included in the present study because these represent the main cognitive domains that are most often studied (memory, attention/information processing speed, and executive function) while assuring that we included at least two tests for a cognitive domain in the factor analyses: Logical Memory I and II, and Mental Control from the Wechsler Memory Scale-Revised;⁸ Digit Span forwards and backwards, Arithmetic, Block Design, and Similarities, and Picture Completion from the Wechsler Adult Intelligence Scale Revised;⁹ Trail Making Test Parts A and B;¹⁰ Symbol Digit Modalities Test;¹¹ Colour Form Sorting Test;¹² Controlled Oral Word Association Test;¹³ and verbal fluency (animals).¹⁴ Trained clinical psychologists performed the assessments. Participants were given breaks where appropriate to minimize the effects of fatigue on performance. Participants who were judged to be clinically depressed were not tested until their depression had been satisfactorily treated, considered to be either a Geriatric Depression Scale¹⁵ score <5 or a reduction in self-reported symptoms of depression, or as based on informant report, or further psychiatric assessment.⁶

Outcome assessment

Consensus dementia diagnoses were made at each follow-up visit by a neurologist, neuropsychiatrist, a psychogeriatrician, and a research psychologist during case conferences at which all medical, psychiatric, neuropsychological, and neuroimaging data were presented. The criteria for dementia were a definite impairment (performance of <5th percentile on at least one test) in two or more cognitive domains (memory impairment not necessary), and demonstrated evidence of functional decline due to cognitive deficits (decline in the Social and Occupational Functioning Assessment Scale;¹⁶ score of ≤ 20 from the premorbid estimate or failure on one item of activities of daily living (ADL) or two items of instrumental activities of daily living (IADL) due to cognitive deficits as judged by consensus).¹⁷ Death records were obtained from the Australian National Death Index up to 10 years after the baseline assessment. All-cause mortality was the outcome of interest.

Statistical analysis

In order to reduce the observed neuropsychological variables to their underlying (latent) domains, exploratory factor analysis with an oblique (geomin) rotation was conducted first. The number of factors to be retained was decided upon by examination of the scree plot (supplementary Figure 1) and Kaiser's criterion of eigenvalues >1.0 . After having decided on the number of factors, a confirmatory factor analyses was then conducted to test the model fit of the factor structure of the exploratory solution. Goodness of fit was assessed by using Bentler's Comparative Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA). The CFI can range from 0-1 with values $>.90$ representing acceptable fit and values $>.95$ representing good fit. The RMSEA can range from 0-1 with values $<.08$ representing acceptable fit and values $<.06$ representing good fit.

Finally, the factor solutions were used in the measurement part of a structural equation model in which outcomes (dementia and mortality) were regressed on the factors using a probit regression in the structural part of the model. For direct comparison of effect sizes of different cognitive domains (secondary aim), we report standardized β coefficients, for which negative estimates indicate a decrease in predicted probability for the outcome and positive estimates indicate an increase in predicted probability. First a crude model was tested in which the effect of each factor is reflected on the outcome variable at hand. A second model tested the effect of each factor separately while age, sex, and education were adjusted for. Separate analyses were conducted for the two outcome variables. All tests were two-sided with an alpha-level of 0.05. All analyses were performed in Mplus 7.2 (Muthen & Muthen).

RESULTS

The mean age of the patients was 71.3 years (range 49-87), 72 participants (43.9%) were female, and the mean duration of education was 10.2 years ($SD = 2.8$). The majority experienced a stroke ($n = 132$, 80.5%) and 32 participants a TIA (19.5%). One-hundred and nineteen participants (69.6%) suffered a first-ever stroke or TIA, whereas 45 (30.4%) had suffered stroke or TIA before. Clinical and neuropsychological characteristics of the participants are presented in Table 1. Mean performance scores of the participants on the neuropsychological tests that were included in the factor analysis and percentages of participants with impaired scores (z -score ≤ -1) are shown in Table 2.

Factor analyses

An exploratory factor analysis was run on the 15 neuropsychological test scores. The scree plot (supplementary Figure 1) and Kaiser's criterion suggested that three or four factors accounted for the majority of variance in the neuropsychological data. In the subsequent confirmatory factor analysis, the model fit for the three-factor solution was slightly worse ($RMSEA = .076$, $90\%CI = .057-.095$, $CFI = .897$) than for the four-factor solution, which showed acceptable fit ($RMSEA = .076$, $90\%CI = .056-.095$, $CFI = .901$). After inspection of modification indices and step-wise modifications of the four-factor model (block design and mental control were omitted, residuals for digit span forward and backward were allowed to correlate within the factor), the fit was good ($RMSEA = 0.042$, $90\%CI = 0.000-.070$, $CFI = .975$). Figure 1 lists each factor and the loading of each variable on their respective factor. Based on these loadings, the factors were labelled as follows: (1) verbal memory; (2) information processing speed; (3) executive functioning; (4) verbal fluency.

Table 1. Demographic and clinical characteristics of the patients at baseline[§]

Characteristic	All patients (n = 164)
Age	71.3 ± 9.1
Female	72 (43.9)
Years of education	10.2 ± 2.8
Mini-Mental State Examination	28.4 ± 1.9
Premorbid intelligence	106.4 ± 10.2
Aetiology	
Stroke	132 (80.5)
TIA	32 (19.5)
European Stroke Scale	87.3 ± 15.2
Vascular risk factors	
Prior stroke or TIA	45 (30.4)
Smoker (past or current)	92 (56.1)
Diabetes	22 (13.5)
Myocardial infarction	35 (21.5)
Atrial fibrillation	36 (22.0)
Hypertension	96 (70.07)
Instrumental Activities of Daily Living	8.8 ± 2.4
Activities of Daily Living	5.8 ± 0.9
Incident dementia cases 5 years after stroke	27 (16.5)
Mortality rate 10 years after stroke	56 (34.2)

Abbreviations: SD = standard deviation; TIA = transient ischemic attack.

[§]Data are presented as either mean ± SD or n (%).

Table 2. Performance of patients on neuropsychological tests included in factor analysis and percentage of patients with impaired performance

Neuropsychological test	Mean $\pm$ SD	n (%) impaired*
Logical Memory I ⁸	23.5 $\pm$ 6.7	23 (16.67)
Logical Memory II ⁸	17.7 $\pm$ 8.2	29 (21.01)
Trail Making Test A ¹⁰	58.0 $\pm$ 35.1	13 (9.85)
Trail Making Test B ¹⁰	149.2 $\pm$ 94.1	11 (8.87)
Digit Span forward ⁹	7.3 $\pm$ 2.0	22 (15.83)
Digit Span backward ⁹	6.0 $\pm$ 1.9	36 (25.90)
Arithmetic ⁹	10.6 $\pm$ 3.5	40 (29.20)
Mental Control ⁸	5.0 $\pm$ 1.1	37 (27.21)
Symbol Digit Modalities Test ¹¹	37.0 $\pm$ 11.5	42 (33.60)
Block Design ⁹	18.6 $\pm$ 9.5	45 (33.58)
Similarities ⁹	13.6 $\pm$ 0.5	66 (48.53)
Picture Completion ⁹	11.2 $\pm$ 4.3	51 (37.78)
Controlled Oral Word Association Test ¹³	29.8 $\pm$ 11.7	53 (38.69)
Colour Form Sorting Test ¹²	3.5 $\pm$ 1.0	28 (20.59)
Animal Fluency ¹⁴	15.1 $\pm$ 4.4	53 (38.69)

Abbreviations: SD = standard deviation.

Note: Z-scores were determined using means and SDs of 100 age- and sex matched controls.

* Impaired: z-score $\leq$ -1.

Table 3. Standardized regression coefficients (from probit regression) for stroke patients ($n = 164$) expressing the increase or decrease in 5-year probability of dementia or 10-year probability of death with a one unit increase in factor scores

Outcome measure	Crude analyses			Adjusted analyses*		
	β	SE	p value	β	SE	p value
Dementia						
VM	-0.333	0.150	.027	-0.163	0.136	.231
IPS	-0.293	0.126	.020	-0.207	0.138	.133
EF	-0.265	0.122	.029	-0.162	0.126	.199
VF	-0.333	0.134	.013	-0.252	0.149	.092
Death						
VM	-0.633	0.119	<.001	-0.221	0.117	.058
IPS	-0.599	0.097	<.001	-0.420	0.107	<.001
EF	-0.528	0.097	<.001	-0.332	0.105	.002
VF	-0.595	0.099	<.001	-0.414	0.117	<.001

Abbreviations: β = estimate from probit regression with dementia or death as the outcome; SE = standard error; VM = verbal memory; IPS = information processing speed; EF = executive function; VF = verbal fluency.

Note: Higher factors scores represent better performance.

* adjusted for age, gender, and education.

Figure 1. Factor loadings from the final confirmatory factor analysis that allows for correlated factors and residual correlations among neuropsychological tests

Abbreviations: LM 1 = Logical Memory 1; LM 2 = Logical Memory 2; TMT A = Trail Making Test A; TMT B = Trail Making Test B; SDMT = Symbol Digit Modalities Test; DS fw = Digit Span forward; DS bw = Digit Span backward; CFST = Colour Form Sorting Test; COWAT = Controlled Oral Word Association Test.

Associations between cognitive factors and dementia and mortality

The four cognitive factors identified were investigated as predictors of dementia and mortality. Table 3 shows the standardized regression coefficients expressing the increase or decrease in predicted probability of dementia or mortality with a one unit increase in latent factor scores. All four cognition factors predicted dementia and mortality in crude analyses. Next, multivariable adjusted analyses were carried out with age, gender, and education as covariates. iADL functioning and history of stroke or TIA were considered possible confounders but were not significantly associated with dementia or mortality.

These were therefore not included in the present analyses. For dementia, however, no significant associations were observed in the adjusted models, but the predicted probability for mortality increased with worse scores in executive functioning, information processing speed, and verbal fluency. No significant association was found for verbal memory.

DISCUSSION

The present study used structural equation modelling to investigate whether domain-specific cognitive functioning in the post-acute phase of stroke predicts dementia within five years or mortality within 10 years. For mortality, significant associations were found after adjustment for age, gender and education, which were highest for worse performance in executive functioning, information processing speed, and verbal fluency. None of the cognitive domains significantly predicted incident dementia five years after stroke.

Our findings are in line with previous post-stroke studies that found cognitive impairment¹⁸⁻²⁰ in general (regardless of the domain) and cognitive decline²¹ to be predictive of mortality. Likewise, we previously showed that mild vascular cognitive impairment in any domain and vascular dementia are predictive of mortality.⁵ Also community dwelling individuals with cognitive impairment showed increased mortality risk²² and higher risk of death of cardiovascular disease and stroke.²³ The present study adds that executive functioning, which is often impaired after stroke,^{2, 24} has the highest prognostic value for predicting mortality up to ten years after stroke. Other studies have also reported this domain to predict post-stroke mortality.^{1, 25}

Besides executive functioning, we found processing speed and verbal fluency to predict mortality. Other studies have reported different findings, including visuospatial and constructional abilities predicting mortality over 12 years in stroke patients,¹ and disorientation, aphasia, and visuospatial neglect predicting death within the first year after stroke.² Another study did not find any cognitive domain to independently predict mortality during up to five years of follow-up.²⁰ Methodological differences probably contribute to these discrepancies, including the choice of neuropsychological tests used, the a priori selection of cognitive domains to be tested, the phase after stroke (acute, post-acute, chronic) in which the neuropsychological assessment took place, and the duration of follow-up. Slowed processing speed is a prominent impairment after stroke.²⁶ Information processing speed underlies performance on other cognitive tasks²⁷ and is considered

to be a measure of global damage and connectivity changes due to the stroke; e.g. by interrupting prefrontal subcortical loops that leads to impaired prefrontal lobe functioning and information processing.²⁸ Also, age-related slowing of information processing has been suggested to be a marker for aging of the central nervous system, and might be expected to reduce adaptive capacity in a general way that increases the risk of mortality.²⁹ Verbal fluency is often considered part of executive functioning,^{2,30} and while certainly dependent on executive functioning, in the current study verbal fluency emerged as a separate domain from factor analysis. Common to the cognitive domains that predicted mortality in the present study is a heavy reliance on largely distributed cortical and subcortico-cortical networks necessary for planning, problem solving and functions in everyday life. Disconnections in these networks might lead to greater difficulties in ADLs and self-care, contributing to individual frailty and higher mortality risk.

In the present study, none of the factors predicted a five-year dementia diagnosis. Previous studies found cognition to explain the higher dementia risk among stroke patients compared with controls. For example, verbal and visual memory predicted incident dementia over a five-year follow-up when comparing stroke patients to healthy controls.²⁶ Our results add to this that the cognitive domains of the present study cannot be used as prognostic markers for individual stroke patients. This includes a lack of an association with verbal memory, whereas subjective and objective functioning in memory and praxis predicted dementia risk in self-reported stroke patients in the Cognitive Function and Ageing Study (CFAS).³¹ It must be noted that we used the VASCOG criteria (as opposed to DSM-III-R criteria in CFAS) to define major neurocognitive impairment, and memory problems are not necessary for this definition. In addition, standardized probit regression coefficients in our analyses consistently pointed to a lower predicted probability for dementia with better cognition scores. Relatively large standard errors suggest that substantial inter-individual variability diluted stronger effects, and larger sample sizes might be needed to establish such an association. Ongoing international efforts to harmonize or pool individual stroke cohorts such as VASCOG-STROKOG (<https://cheba.unsw.edu.au/group.strokog>) and METACOHORTS³² might provide new opportunities for such endeavours. In addition, we found cognition to predict mortality, and lack of associations with dementia could thus be related to competing risks: individuals who died before follow-up might also be at higher risk for dementia but did not develop dementia because death happened first and thereby ‘prevented’ dementia.³³ Unfortunately, the current design does not allow us to directly model the impact of this competing risk.

Strengths of the current study include the detailed neuropsychological assessment, the long follow-up period, and use of factor analysis to identify cognitive domains and using these as predictors in a structural equation model. The use of factor analysis is more objective than grouping neuropsychological tests based on their face validity since most tests rely on multiple cognitive functions and some domains include a heterogeneous set of functions. In addition, the latent factor can be considered a purer representation of the underlying cognitive dimension because it only uses the common variance of the neuropsychological tests, while unique (residual) variance is treated as random measurement error. To decide on the number and composition of factors, we did not only take correlations, and modification and fit indices into account, but also conceptual plausibility. However, some limitations deserve further attention. Although verbal fluency emerged as a separate factor, only two neuropsychological tests loaded onto it with relatively low loadings, so the factor was just-identified. On the other hand, the verbal nature of the COWAT and animal fluency tests make them conceptually different to the other included tests, so we decided to retain the verbal factor. While the sample size was comparable to previous studies of stroke cohorts, it did not allow for sub-analyses such as sex or age differences or testing of interaction effects. Related to this, it would have been interesting to test for effect mediation by white matter pathology or neurodegenerative markers such as hippocampal volume, but MRI data were available for a subsample only, and power was considered too low for use in the present study. Also, other studies found domain-specific impairments to predict disturbances in IADLs²⁵ and dependence.²⁰ Moreover, the degree of IADL functioning and a history of stroke or TIA may confound associations with cognitive functioning. It is noteworthy that none of these variables predicted dementia or mortality in our sample (data not shown), and therefore we did not include these variables in our model. Unfortunately, we could not study associations with decline in iADL due to a substantial amount of missing data.

Taken together, the present study shows that lower cognitive functioning relating to executive functions, verbal fluency and processing speed during the post-acute phase of stroke is a prognostic marker of mortality up to 10 years later. Future studies with a larger sample should look at potential causal pathways and whether competing risks account for the lack of an association with dementia.

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SUPPLEMENTAL DATA

Supplementary Figure 1. Scree plot of Eigenvalues for different numbers of extracted factors from exploratory factor analysis

5

The Cognition and Affect after Stroke – a Prospective Evaluation of Risks (CASPER) study: rationale and design

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ABSTRACT

Background: Cognitive impairment and neuropsychiatric syndromes, like depression and apathy, are frequent residual consequences of stroke. These have a large impact on quality of life and long-term prognosis. Several factors are involved in the development of these residual syndromes, although their exact role and their interrelationships remain still rather unclear. The Cognition and Affect after Stroke: a Prospective Evaluation of Risks (CASPER) study has been primarily designed to examine whether stroke-specific (e.g. lesion location, volume, type, severity), cerebrovascular and neurodegenerative (e.g. white matter changes, atrophy, microbleeds, perivascular spaces), inflammatory, endothelial, and (epi) genetic markers are associated with cognitive impairment, post-stroke depression, and post-stroke apathy, and whether they predict their course over 12 months. The secondary aims are to investigate how the above-mentioned markers interact with each other, and to determine if patients with apathy and depression after stroke differ in pathogenesis, course, and outcome (e.g. functional outcome, neurocognitive performance, quality of life).

Methods/design: CASPER is a 1-year prospective clinical cohort follow-up study in 250 stroke patients recruited at the neurological in- and outpatient services at Maastricht University Medical Center (MUMC+, Maastricht, the Netherlands), and Zuyderland Medical Center (Sittard and Heerlen, the Netherlands). At baseline (3 months post-stroke), a neuropsychological assessment, neuropsychiatric interview, blood sample, and brain magnetic resonance imaging (MRI) scan are conducted. Assessment of neuropsychiatric and neurocognitive status are repeated 6 and 12 months later.

Discussion: The CASPER study investigates stroke-specific, vascular, neurodegenerative, inflammatory, and genetic markers of the development of vascular cognitive impairment, depression, and apathy after stroke. This creates the possibility to study not only the contribution of these individual markers but also their joint contribution, which differentiates this study from earlier stroke cohorts who lacked long-term follow-up data, a large sample size, an extensive MRI protocol, and markers from the blood. The knowledge we derive from this study might help in identifying markers that are associated with, or can predict the onset, maintenance, and progression of vascular cognitive impairment, depression, and apathy after stroke, and could provide new insights into possibilities for treatment and rehabilitation that result in better functional outcome after stroke.

BACKGROUND

Stroke is one of the leading causes of disability in the Western world. According to the Global Burden of Disease Study in 2010 the stroke incidence worldwide was around 17 million persons per year, with 33 million people being still alive after stroke, with about 70 percent of all stroke patients staying with residual symptoms.¹ Stroke is the second most frequent cause of death, after coronary heart disease.² As a result of the aging population, this number will probably increase steadily in the next decades.³ At the same time, case fatality rates are declining due to better acute treatment. Therefore, more and more individuals will need to learn how to deal with the residual disabilities and handicaps.¹ Frequent impairments after stroke are cognitive impairments and neuropsychiatric syndromes, including depression and apathy^{4, 5} which have an impact on long-term prognosis (higher mortality and more disability), and quality of life (QoL) of stroke survivors.^{6, 7}

Vascular cognitive impairment

Vascular cognitive impairment (VCI) describes the full spectrum from mild to severe cognitive impairment in people with cerebrovascular disease, including vascular mild cognitive impairment and vascular (or post-stroke) dementia (VaD).⁸ Risk factors of VCI after stroke include event-related factors such as infarct severity, lesion volume, age, low education, history of diabetes or atrial fibrillation, and number of recurrent strokes.⁹ The risk for post-stroke dementia is known to be highest within the first year, with an estimated incidence rate of 20-30 percent, which is nine-times the general population's risk.⁹

It has been suggested that both vascular and neurodegenerative pathologies contribute to post-stroke VCI.¹⁰ Cognitive impairments can be the result of strategic infarcts, but (pre-existing) white matter hyperintensities (WMH) and atrophy of the medial temporal lobes can contribute as well, and they probably interact with each other, though the nature of these interactions is not well understood.¹¹ In addition, a higher risk for VCI has been reported in carriers of the Apolipoprotein E (ApoE) $\epsilon 4$ allele, which is the major genetic risk factor for Alzheimer's disease (AD) dementia.¹² Indeed, evidence accumulates that AD and VaD should not be regarded as mutually exclusive diagnoses, but rather as a continuum with pure AD and VaD at its extremes, and most people showing mixtures of both type of pathologies.¹³ While the dominating view is that vascular changes work as a catalyst of primary neurodegenerative changes in AD, it is largely unknown whether the opposite is true for VCI, i.e. whether AD-related changes work as a catalyst for post-stroke dementia.

Next to neurodegeneration, neuro- and vascular inflammation might contribute to VCI by partly mediating the pathophysiology underlying VCI as part of a final common pathway.¹⁴ Following stroke, increased auto-immune activity is a common response, and it has been shown that up-regulated inflammation markers like C-reactive protein (CRP), as a consequence of a prolonged auto-immune response, relate to poor prognosis. This includes a higher risk of additional future strokes and mortality, but also more severe VCI.¹⁵ ¹⁶ Other enzymes, molecules, and ligands (myeloperoxidase, soluble intercellular adhesion molecule, soluble vascular cell adhesion molecule-1, soluble E selectin, soluble P selectin, and CD40 ligand) are involved in vascular inflammation as part of an inflammatory response to stroke, and have also been found to be increased in AD.¹⁷⁻²⁰ Also, up-regulation of pro-inflammatory cytokines (interleukin-6 and tumor necrosis factor alpha) and proteins (high sensitivity CRP) are risk factors for both dementia^{21, 22} and cardiovascular disease.²³ It is unknown whether similar inflammation mechanisms are involved in cognitive deterioration in VCI, and therefore, research is needed to investigate whether inflammation contributes to VCI independently or in joint action with other (e.g. neurodegenerative) factors.

Finally, genetic factors are also suggested to play a role in the pathogenesis of VCI, but in contrast to AD, evidence is still scarce. A genome-wide association study in VaD identified a novel genetic locus near the androgen receptor, and this finding was replicated in two independent validation datasets.²⁴ Polymorphisms and mutations on the genes coding for angiotensin-converting enzyme and methylenetetrahydrofolate reductase are risk factors for cardiovascular disease and might be related to the development of VaD, although this relationship is still controversial.²⁵ For AD, several genetic risk loci are already identified next to ApoE, including clusterin (CLU), phosphatidylinositol binding clathrin assembly protein (PICALM), and encoding complement component [3b/4b] receptor 1 (CR1),²⁶ but their effects are generally small (see <http://www.alzgene.org>). Whether they contribute to post-stroke dementia is not known.

Post-stroke depression

Depression is a common neuropsychiatric syndrome following stroke. According to a recent systematic review by Hackett et al.,²⁷ around one-third of the stroke survivors experiences depression in the first three months post-stroke, and studies with long-term follow-up have shown that it is often a chronic disorder, with a remitting-relapsing pattern.²⁸ Patients with post-stroke depression (PSD) have worse functional recovery,²⁹ a higher risk for cognitive impairment,⁷ and higher mortality risk.^{30, 31}

Early studies implied that PSD is mainly associated with anterior lesions in the left hemisphere, however, a major systematic review and meta-analysis found no support for this ‘lesion location hypothesis’.³² Vataja et al.³³ suggested that lesions in fronto-subcortical regions in general are involved in developing PSD, often accompanied by impairments in executive functioning, leading to what has been called the ‘depression-executive dysfunction syndrome’. Other factors that have been associated with the development of PSD are cognitive impairment, stroke severity, physical disability, and pre-stroke depression and anxiety.⁷ Diminished QoL and also low social support can both contribute independently to the severity of depression.³⁴ A study by van Mierlo et al.³⁵ investigated the association between a broad range of psychological factors and PSD with a multivariable logistic regression analysis. They showed that more passive coping and more helplessness, less acceptance, and less perceived benefits were all significantly and independently associated with symptoms of post-stroke depression. Furthermore, fatigue after stroke has been associated with PSD, although not all patients with fatigue develop symptoms of depression and vice versa.²⁸

Neuroinflammation might also play a role in the underlying mechanisms of PSD. Levels of CRP, soluble E selectin, CD40 ligand, interleukin-6, tumor necrosis factor alpha, and high sensitivity CRP are deregulated in patients diagnosed with major depressive disorder.^{14, 18, 22, 23, 36-38} In addition, high plasma levels of neopterin are found in people with depression, and might predict the development of PSD.³⁹ Markers of endothelial function might be important as well, since increased expression of soluble intercellular adhesion molecule and soluble vascular cell adhesion molecule-1 are associated with depression.⁴⁰⁻⁴³ Although several inflammation markers have been related to symptoms of depression, studies examining these associations in PSD specifically are relatively scarce. Some studies found an elevation in interleukin-6 and tumor necrosis factor alpha in PSD.⁴⁴ Recently, a study by Tang et al.³⁹ showed an association between elevated serum levels of neopterin in the acute phase after stroke and PSD at six-month follow-up. High plasma levels of homocysteine are known to increase the risk for cerebrovascular disease, but have also been associated with depressive disorders. Increased levels of homocysteine result in cerebrovascular disease and a deficiency in monoamine neurotransmitters, which might lead to a depressed mood.⁴⁵ Homocysteine, folate, and vitamin B12 are all involved in methylation reactions that are necessary for monoamine neurotransmitter production, but also the production of phospholipids and nucleotides. A deficiency in folate and vitamin B12 has also been associated with depressive disorders.⁴⁶

Post-stroke apathy

Apathy has been defined as a disorder of diminished motivation, characterized by lowered initiative, restricted engagement in social interactions and activities, diminished cognitive activities, and lack of emotional response.⁴⁷ It was traditionally seen as a symptom of other syndromes (e.g. depression or dementia), but mounting evidence suggests that it might be an independent syndrome with a different etiology.⁴⁸⁻⁵⁰ Post-stroke apathy (PSA) is as frequent as PSD, with a mean prevalence rate of 34.6 percent at four months post-stroke.⁵ However, PSA gained relatively less attention in research in comparison with PSD, and most research focuses on the difference between the two.

While PSD is suggested to be associated with left anterior lesions,^{51, 52} PSA has been associated with right hemispheric subcortical lesions, particularly in the basal ganglia and in the anterior cingulate circuit which is involved in motivational processes.⁵³⁻⁵⁵ Other factors associated with PSA are older age, lower education, and severity of VCI.^{4, 5, 51, 56} Furthermore, both PSD and PSA have been associated with poor functional recovery and low QoL.^{5, 29} Overall, lack of longitudinal studies, differences between time of measurement after stroke (acute/chronic phase), and lack of studies with a sufficient sample size make it difficult to interpret study results.

In conclusion, several factors play a role in the development of VCI, PSD, and PSA. However, most studies investigated the underlying mechanisms in isolation and did not take into account how several factors interact with each other. The Cognition and Affect after Stroke, a Prospective Evaluation of Risks (CASPER) study incorporates a broad range of psychosocial, blood and neuroimaging markers to be able to study their role alone and in combination with each other to predict individual differences in the onset and course of the cognitive and neuropsychiatric consequences of stroke.

Study aims

The primary aim of CASPER is to identify stroke-related, cerebrovascular, neurodegenerative, (epi)genetic, endothelial, and inflammation markers that are associated with VCI, PSD, and PSA in patients with ischemic or hemorrhagic stroke. The secondary aims are to investigate how the above-mentioned markers interact with each other, and to determine if patients with apathy and depression after stroke differ in pathogenesis, course, and outcome (e.g. functional outcome, neurocognitive performance, quality of life).

The main research questions are:

1. Are stroke-specific, additional vascular, neurodegenerative, inflammatory or genetic markers a) associated with VCI at three months after stroke and b) predictive for its course over 12 months?
2. Are stroke-specific, additional vascular, neurodegenerative, inflammatory or genetic markers a) associated with PSD and PSA at three months after stroke and b) predictive for their course over 12 months?
3. Do the above-mentioned markers interact on the VCI, PSD, and PSA outcome?
4. Which psychosocial factors are associated with the development of VCI, PSD, and PSA?
5. Do PSA and PSD differ in their pathogenesis, cognitive profile, course, and outcome?

METHODS**Study design**

CASPER is a prospective clinical cohort study into cognitive impairments and neuropsychiatric syndromes after stroke with a follow-up of one year. Baseline measurements take place in the post-acute phase after stroke (i.e. 10-12 weeks post-stroke) to assess presence and severity of VCI, PSD, and PSA. Serial assessments take place at six and 12 months after baseline. The total duration of the study will be approximately 3.5 years, from June 2013 (first in) until November 2016 (last out).

Patients

In total, 250 consecutive patients with either ischemic or hemorrhagic stroke are included. Patients who are admitted to the Stroke Unit of the Maastricht University Medical Center+ (MUMC+), Maastricht, the Netherlands, the Stroke Unit of Zuyderland Medical Center in Sittard-Geleen and Heerlen, the Netherlands, or those who visit the Transient Ischemic Attack clinic of MUMC+ for a non-fatal ischemic or intracerebral hemorrhagic stroke, and fulfill the in- and exclusion criteria are asked to participate. Stroke is defined as a clinical stroke syndrome (sudden neurological dysfunction lasting >24 hours, with no apparent cause other than that of vascular origin). The stroke can be a first-ever event or a recurrent supra- or infratentorial stroke in a patient who recovered from a previous event without obvious residual symptoms. Ischemic strokes might be cortical or lacunar, and could be included with or without evidence of ischemia on clinical brain scan. Hemorrhagic strokes are non-traumatic deep, lobar, cerebellar, or brainstem hemorrhages as evidenced by a

clinical brain scan. Eligibility criteria are chosen to make sure that the sample will represent the current clinical situation (Table 1). Participation of an informant who knows the patient well enough to answer questions about his/her functioning over the last approximately five years is desirable but not required.

Table 1. In- and exclusion criteria

Inclusion criteria	Exclusion criteria
- Ischemic or hemorrhagic stroke	- Subarachnoidal hemorrhage, traumatic hemorrhage, primary intraventricular hemorrhage and transient ischemic attack
- MMSE score ≥ 15 (to ensure valid testing)	- Age <40 years (to exclude atypical strokes)
- Written informed consent	- Severe aphasia (as it interferes with performance on and understanding of the instructions of the neuropsychological tests)
- Sufficient knowledge of the Dutch language	- Evidence for pre-stroke dementia (based on clinical diagnosis or IQ-CODE) in the 5 years prior to the stroke
	- Other existing psychiatric and neurological diagnoses that are known to affect cognition (Parkinson's disease, bipolar disorder, epilepsy, schizophrenia, or substance abuse) ¹

Abbreviations: IQ-CODE = Informant-Questionnaire on Cognitive Decline in the Elderly; MMSE = Mini-Mental State Examination.

¹ Lifetime history of depression is not considered as a reason for exclusion as it might be a risk factor for post-stroke depression.

Assessments

The baseline measurement (T0) is scheduled three months post-stroke to avoid confounding effects by the acute event, including acute inflammatory responses. At T0, patients undergo a venepuncture, brain magnetic resonance imaging (MRI) scan, neuropsychological assessment, and neuropsychiatric interview. They fill in several questionnaires to assess the presence and severity of PSD and PSA, and to evaluate other factors such as functional ability, fatigue, personality, and QoL. A semi-structured interview with an informant is performed to provide additional information about functional outcome of the patient and presence of neuropsychiatric syndromes. Six (T1) and 12 months (T2) after T0, the neuropsychological assessment and questionnaires are repeated. The venepuncture, MRI scan, neuropsychological assessment, and neuropsychiatric interview all take place in the academic hospital in Maastricht and are performed by specially trained nurses (venepuncture), radiology assistants (MRI scan) and trained research (neuro)psychologists (neuropsychological assessment and neuropsychiatric interview). If a patient is not able to

visit the hospital due to reduced mobility, the patients are visited at their current place of residence.

Patients who suffer from a recurrent stroke during the 12-month follow-up period will be followed-up normally, if the health status of the patient allows this, and if the patient does not suffer from severe aphasia after the recurrent stroke. Information about the type, location, and severity of the lesion of the recurrent stroke is collected, which also allows us to study the potential impact of recurrent strokes on our outcome measures. Recurrent strokes are taken into account in our analyses with longitudinal data to avoid confounding effects.

Clinical data

In a standardized case record form, data on demographics (e.g. age, gender, educational level, ethnicity, marital status), medical history (e.g. personal and family history of cardiovascular, neurological, or psychiatric disorders), medication use, physical examination (e.g. weight, height, blood pressure, cholesterol), and lifestyle (smoking behaviour, alcohol consumption, drug use, physical activity) are collected.

Neuropsychological assessment and cognitive endpoints

The neuropsychological assessment consists of a standardized battery of cognitive tests measuring specific cognitive domains: global cognition, episodic memory, working memory, information processing speed, executive functioning, visuoconstruction, neglect, premorbid IQ, and language (dysphasia). An overview of all test instruments and their cognitive domains is presented in Table 2. The neuropsychological tests are administered according to a standardized test protocol by trained research (neuro)psychologists.

VCI is defined as a score ≤ 1.5 standard deviations below the general population mean in one or more cognitive domains, based on available norm scores for age, gender, and level of education for the Dutch general population. In addition, there should not be any interference in daily activities and no diagnosis of dementia according to DSM-5 criteria.⁵⁷ Impairments have to represent a significant decline from premorbid levels of functioning. The diagnosis and type of dementia is made by an experienced neuropsychiatrist or neuropsychologist based on DSM-5 criteria.⁵⁷ A consensus meeting is arranged when there is a discrepancy in diagnosis, and if no consensus can be reached, the patient will be considered not demented. The diagnosis of AD is made according to the standardized clinical criteria for AD based on the National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.⁵⁸ The diagnosis of

VaD is made according to the criteria proposed by the National Institute of Neurological Disorders and Strokes – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN).⁵⁹

The Informant Questionnaire on Cognitive Decline in the Elderly (IQ-CODE; short form) is used to detect possible dementia prior to the index stroke, and is rated retrospectively (past five years prior to the index stroke),⁶⁰ in combination with information from medical records. A cut-off score ≥ 3.60 is used to indicate possible dementia prior to the stroke, as has been used in a previous study with stroke patients.⁶¹

Table 2. Neuropsychological measures and neuropsychiatric questionnaires

	Instrument	T0^a	T1^a	T2^a
Global cognition	MMSE ⁶²	X	X	X
Episodic Memory	15-Word Verbal Learning Test ⁶³	X	X	X
Working memory	Digit-span of the WAIS-III ⁶⁴	X	X	X
Information processing speed	Digit Symbol Substitution Test (DSST) Trail Making Test (TMT; part A and B) ^{64, 65}	X	X	X
Executive functioning	TMT (interference), BADS Zoo Map & Key Search, Verbal Fluency (60 seconds; animals and professions) ⁶⁵⁻⁶⁷	X	X	X
Visuoconstruction	Clock drawing ⁶⁷	X	X	X
Neglect	Star cancellation ⁶⁸	X		
Premorbid IQ	NLV ⁶⁹	X		
Language / aphasia	Boston Naming Test ⁷⁰	X		
Depression	MINI, MADRS, HADS, NPI ⁷¹⁻⁷⁴	X	X	X
Apathy	AES, NPI ^{74, 75}	X	X	X
Premorbid dementia	IQ CODE ⁶⁰	X		
Functional ability	Barthel Index, Lawton ^{76, 77}	X	X	X
Quality of life	SS-QoL ⁷⁸	X	X	X
Fatigue	FSS ⁷⁹	X	X	X
Personality	NEO-FFI ⁸⁰	X		

Abbreviations: MMSE = Mini-Mental State Examination; WAIS = Wechsler Adult Intelligence Scale; BADS = Behavioral Assessment of the Dysexecutive Syndrome; NLV = Nederlandse leestest voor volwassenen (Dutch version of the National Adult Reading Test); MINI, Mini International Neuropsychiatric Interview; MADRS = Montgomery-Åsberg Depression Rating Scale; HADS = Hospital Anxiety and Depression Scale; NPI = Neuropsychiatric Inventory; AES = Apathy Evaluation Scale; IQ-CODE = Informant-Questionnaire on Cognitive Decline in the Elderly; SS-QoL = Stroke-Specific Quality of Life; FSS = Fatigue Severity Scale; NEO-FFI = NEO-Five Factor Inventory.

^aT0: baseline measurement, T1: 6-month follow-up, T2: 12-month follow-up.

Neuropsychiatric assessment

Depression

The symptoms of a major depressive disorder according to DSM-IV and DSM-5 are assessed with the Mini International Neuropsychiatric Interview (MINI).⁷¹ The MINI is a semi-structured interview administered to the patient and consists of three different parts, which aim to determine whether the patient can be diagnosed with a current major depressive disorder, a depressive episode lifetime, or a current dysthymic disorder. The clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS) is used to assess the severity of symptoms of depression.⁷² This rating scale consists of 10 items to evaluate the severity of depressive symptoms and is filled out by the clinician.⁷² In addition, the Hospital Anxiety and Depression Scale (HADS), a 14-item self-report scale, is used to identify clinically significant levels of anxiety and depression.⁷³ According to a study by Kang et al.,⁸¹ the HADS and MADRS are especially valid as screening instrument for PSD (in both the acute and chronic phase), since these scales focus less on the presence of somatic symptoms, resulting in less misclassification.

Apathy

The Apathy Evaluation Scale (AES) is an 18-item scale used to evaluate the presence and severity of apathy.⁷⁵ Three different versions of the AES are available, a clinician-rated (administered to the patient), informant-rated, and a patient-rated version. The AES has been rated as the most favourable instrument for assessing apathy, with the clinician-rated version being most valid of the three.⁸² Both the informant-rated and clinician-rated version (administered to the patient) of the AES are used in the CASPER study.

Generic

The Neuropsychiatric Inventory (NPI) is administered as a semi-structured interview to the informant of the patient.⁷⁴ The NPI is originally developed to evaluate neuropsychiatric symptoms in dementia, but is also frequently used in the stroke population.²⁸ It evaluates the presence and severity of 12 different neuropsychiatric symptoms (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, sleep, and appetite).⁸³ The validity and reliability of the NPI, including the Dutch version, has been well established.^{84, 85}

Additional Interviews

Fatigue after stroke is assessed with the Fatigue Severity Scale (FSS).⁷⁹ This nine-item self-rating scale can be answered on a seven-point scale, with higher scores representing more fatigue. The Barthel Index⁷⁷ is used to evaluate impairments in activities of daily living (ADL), and the Lawton Scale⁷⁶ is used to assess impairment in instrumental ADL. Furthermore, the Stroke-Specific Quality of Life Scale (SS-QoL) is used to evaluate health-related QoL, which is defined as the physical, psychological, and social aspects of life that can be influenced by a change in health status.⁷⁸ The NEO Five Factor Inventory (NEO-FFI) is used to assess the big-five dimensions of personality, which are extraversion, neuroticism, openness to new experiences, agreeableness, and conscientiousness.⁸⁰

Neuroimaging

A standardized brain MRI protocol is used as described in Table 3. The MRI scans are all performed on the same 3.0 Tesla head-only scanner equipped with an 8-channel head coil (Philips Achieva, Philips Medical Systems, Best, The Netherlands), using the same standardized scanning protocol for every patient. This protocol has been optimized for stroke and WMH segmentation, as well as segmentation of the hippocampus.⁸⁶ One scanning session takes approximately 30 minutes. After acquisition of the MR images, an anonymisation procedure is performed, to make sure that all imaging data are pseudonymised.

Table 3. Brain MRI protocol

Sequence name/ Acquisition method	Field of View (mm)	Matrix	Slices	Inter-slice gap (mm)	Thick- ness (mm)	Voxel (mm)	TR /TE/TI (ms)
Coronal 3D T1-weighted (TFE)	240x240	240x240	160	0	1	1x1x1	8.2/3.8
2D Axial T2-weighted (FSE)	230x185	328x225	48	0	3	0.7x0.8x3	3000/80
3D fluid-attenu- ation inversion recovery	250x250	228x226	283	0	1.1	0.6x1.1x1.1	8000/332/2400
T2* diffusion weighted imaging Gradient echo EPI	240x240	128x128	28	0	5	1.85x1.85x5	10000/72/2400
SWI	220x180	220x180	260	0	0.5	1x1x0.5	16/22

Abbreviations: TR = repetition time; TE = echo time; TI = inversion time; TFE = turbo field echo; FSE = fast spin echo; EPI = echo planar imaging; SWI = susceptibility weighted imaging.

MRI markers

Several stroke characteristics are visually scored by an experienced vascular neurologist and consist of: presence and type of symptomatic stroke lesion (ischemic/haemorrhagic), location of the lesion, number, type, and location of old infarcts and old haemorrhages, number and location of microbleeds, and degree of perivascular spaces in the basal ganglia and centrum semiovale. The Fazekas visual rating scale is used to score deep and periventricular WMH.⁸⁷ In addition, a semi-automatic brain tissue segmentation program, based on the program used in the Rotterdam Scan Study,⁸⁸ is used to measure WMH volumes and to calculate the volume of global brain atrophy, corrected for total intracranial volume. The accuracy of this semi-automated method appeared to be within the range of the inter-observer variability of fully manual segmentations but is less time-consuming while still requiring some manual correcting. The medial temporal lobe atrophy (MTA) visual rating scale⁸⁹ is used to indicate the level of atrophy in the medial temporal lobes (ranging from zero to four), separately for the left and the right hemisphere. Furthermore, hippocampal volume is measured based on atlas registration with high accuracy using the robust and validated method of learning embeddings for atlas propagation (LEAP).^{90, 91}

Blood markers

At baseline, fasting blood samples are taken. All patients take their morning medication after the venepuncture. In total, 35.5 mL of blood are taken and directly analysed or stored. We measure several inflammation markers. In addition, standard lab procedures to assess levels of glucose, cholesterol (total, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol), and triglycerides will be performed directly after the venepuncture.⁹²⁻⁹⁴ Biomaterial (including deoxyribonucleic acid and ribonucleic acid) is stored anonymously for 15 years after the end of the study. Table 4 lists the blood markers investigated in CASPER.

Ethics, consent, and permissions

The study protocol has been approved by the Medical Ethics Committee of MUMC+. The research is performed according to the principles of the Declaration of Helsinki 59th WMA General Assembly, Seoul (October 2008), and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). All eligible patients are informed about the aim of the study and both the patient and informant receive an information letter. All patients receive enough time to consider participation and if they agree to participate, an appointment is scheduled to sign informed consent. There are no risks for the patients participating in this study. All assessments in the study consist of routine operations and all patient data are pseudonymised. Contraindications for MRI are checked for every

patient, and patients with contraindications are excluded for MRI. If a patient decides to withdraw from the study, this has no consequences or risks for the patients. Patients who refuse follow-up assessment are contacted to determine the reason for refusal.

Table 4. Blood sampling procedure

Tubes	Blood markers	Procedure
EDTA tube (4x 6.0 mL)	Myeloperoxidase, neopterin, soluble intercellular adhesion molecule, soluble vascular cell adhesion molecule-1, soluble E selectin, soluble P selectin, CD40 ligand, interleukin-6, tumor necrosis factor alpha, Homocysteine	Transported on ice to the Biobank Maastricht UMC+ where the blood is pre-processed before storing. EDTA plasma is centrifuged and stored at -80°C until analysis.
Natriumfluoride/ EDTA tube (1x 4.0 mL) Coagulation tube (1x 5.0 mL)	Glucose, total cholesterol high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglyceride, folate, vitamine B12, high sensitivity C-reactive protein	Direct analyses of these markers are performed at the laboratory on the day of sample collection after centrifuging.
Buffyc coats from the 4 EDTA tubes for DNA extraction	Apolipoprotein E, clusterin, phosphatidylinositol binding clathrin assembly protein, encoding complement [3b/4b] receptor 1, angiotensin-converting enzyme, methylenetetrahydrofolate reductase	Buffyc coats are taken from 4 EDTA tubes and separately stored at the Biobank until analysis.
Epigenetics 1 PAX- gene tube (2.5 mL)	RNA	Blood is collected in PAXgene tubes to ensure long-term stability of ribonucleic acid and the tubes are stored at the Biobank. RNA extraction and subsequent analysis of expression of inflammatory and stroke-related genes at the mRNA level will be done.

Abbreviations: mL = milliliter; EDTA = ethylenediaminetetraacetic acid; DNA = deoxyribonucleic acid; RNA = ribonucleic acid; mRNA = messenger ribonucleic acid.

Power calculation and sample size

Based on results of the CODAS study,⁹⁵ a previous study with stroke patients of our research group, it is expected that 50 percent of the stroke patients will have VCI and 10 percent will have VaD after one year. Furthermore, it is expected that 35 percent of the patients will have minor or major depression after one year post-stroke.⁹⁶ A power calculation was performed with the freeware program G*Power version 3.1 (<http://www.gpower.hhu.de>) assuming categorical independent variables to which 50 percent are exposed and 50 percent are not exposed (median-split), since no reliable estimates are available for our main predictors from literature (MRI, inflammation and genetics). Based on a one-year follow-up, a two-sided alpha level of .05, and an expected drop-out rate of 20 percent based on the CODAS study

(about 10 percent due to death), a sample size of 250 resulted in a power of 86 percent to detect a relative risk of 2.00, or 80 percent to detect a relative risk of 1.89 for PSD, and a 96 percent power to detect a relative risk of 2.00, or 80 percent power to detect a relative risk of 1.70 for VCI.

Statistical analyses

Categorical data will be presented on group level expressed in absolute numbers and percentages, whereas continuous data will be presented by their mean, confidence interval, and standard deviation. In case of non-normality, continuous data will be presented as medians with their corresponding inter-quartile range. Differences between groups will be analysed using *t*-tests for continuous variables or appropriate non-parametric counterparts, and χ^2 -tests for categorical variables. Pearson's correlation coefficient will be used to assess the association between two continuous variables. Random effects models will be used to measure cognitive decline from baseline to follow-up, which has the advantage over repeated measures ANOVA that it is not restricted to study completers. The effect of baseline predictors on PSD, PSA, and VCI will be estimated with Poisson and Cox regression, taking into account differences in individual follow-up time. Furthermore, multivariate finite mixture modelling will be used to test the existence of separate PSD and PSA subtypes, using lesion location, WMH, inflammation markers, genetic risk factors, functional impairment, and cognitive functioning as subtype indicators. Age, gender, and education will be included as covariates in the multivariate models. Based on theory and statistical evaluation to see whether a variable might be a probable confounder it will be decided which additional covariates will be added on each analysis.

DISCUSSION

The CASPER study is a prospective clinical cohort study examining predictors of onset and course of VCI, PSD, and PSA using a deep phenotyping approach. It is an observational study with minimal risks for the participating patients. The longitudinal design creates the possibility to study independent predictors of VCI, PSD, and PSA. The CASPER study provides the possibility to study the course of these conditions and potential bidirectional relationships between them. A relatively large sample size and a MRI protocol that uses state-of-the-art volumetry of WMH and hippocampal atrophy make it more likely to find subtle differences in the brain's macrostructure. Therefore, the CASPER study has an additional value to earlier stroke cohort studies (e.g. Sydney Stroke Study, The Fogarty-

Mexico Stroke Cohort, CODAS).^{10, 95, 97} Furthermore, CASPER includes extensive blood-based biomarker data which results in a rich phenotyping approach generating both blood-based biomarker data and clinical brain MRI data, creating the possibility to study cerebrovascular, neurodegenerative, inflammatory, and genetic markers, and their inter-relationships. This is valuable since this gives a better account of how these changes occur in patients, namely in combination. Hence, the combination of these markers may predict individual differences in the development of VCI, PSD, and PSA better than each marker in isolation. Taken together, these methodological strengths promise to yield novel insights into the underlying mechanisms of the burdensome consequences of stroke.

However, some limitations of the study protocol have to be acknowledged here. Although the extensive in- and exclusion criteria were formulated with caution, they can possibly result in a less representative group of patients compared to the general stroke population. For instance, patients who are aphasic or who have pre-existing cognitive disturbances are excluded. No data are collected in the acute phase after stroke, which could yield additional information on the association between VCI, PSD, PSA and the earlier mentioned investigated markers, but a post-acute baseline time point is chosen to avoid confounding effects in the acute phase (e.g. generic acute inflammatory response, sickness behaviour). The MRI scan and venepuncture are only performed on T0, since it is not feasible due to logistical and financial reasons to repeat them at T1 and T2. However, if these data could also have been collected more information on the causes of VCI, PSD, and PSA could have been gathered, e.g. by linking longitudinal changes on MRI to changes in outcomes. Furthermore, patients with severe stroke are less probable to participate in the study, as the assessment is quite extensive. This can result in a cohort of patients with relatively mild stroke, which may influence the frequency of VCI, PSD, and PSA. Both ischemic and haemorrhagic strokes are included to increase the inclusion rate, however, due to the different aetiologies of these strokes, it is likely that this limits the generalizability of the results. Therefore, we have to correct for stroke type in our analyses to take this into account. It is also likely that patients with depression or apathy after stroke are less motivated to participate in the study, resulting in an underestimation of the PSD and PSA prevalence in the study sample. In addition, the current follow-up period of one year allows testing predictions in the post-acute to early chronic phase, but is too short to study long-term consequences. Finally, CASPER allows for in-depth phenotyping and also covers a broad spectrum of factors impacting on the consequences of stroke, but it is not powered to test for more subtle associations or to use complex genetic models or testing of rare variants. Therefore, the study is also designed

as to allow harmonization with other stroke cohorts in larger meta-studies as part of the STROKOG consortium (<https://cheba.unsw.edu.au/group/strokog>).

In conclusion, the CASPER study allows studying the role of several markers, consisting of cerebrovascular, neurodegenerative, and inflammatory markers, and their inter-relationships, in the development of VCI, PSD, and PSA. Furthermore, the longitudinal design and sample size provide the possibility to study the course of PSA, PSD, and VCI and explore individual differences in their development. Better understanding of the role of all of these markers will make it possible to provide new or adapt existing treatment techniques, both on a biological and psychological level, which can result in better QoL and functional outcome of stroke patients.

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6

The association of white matter hyperintensity volume, hippocampal volume, and global atrophy with post-stroke cognitive functioning

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ABSTRACT

Background: Cognitive decline after stroke is frequent and may depend on ageing-related brain pathology, other than stroke lesion volume. The present study addresses the question whether volumetric imaging markers of cerebral small vessel disease and neurodegeneration are associated with cognition following stroke cross-sectionally and whether these markers can predict cognitive performance at follow-up.

Methods: In a prospective cohort study, 168 stroke patients underwent baseline 3 Tesla magnetic resonance imaging and neuropsychological assessment at baseline and 1-year follow-up. White matter hyperintensity volume was semi-automatically determined on T2-weighted fluid-attenuated inversion recovery (FLAIR) images, and hippocampal and global atrophy volumes were quantified on T1-weighted images. Stroke lesion volumes were manually delineated on FLAIR/T1-weighted images and classified as small, medium, or large. Cognitive composite scores were calculated for memory, information processing speed, and executive function.

Results: Multiple linear regression models tested the association between imaging markers and cognition. Large stroke volumes, larger volumes of white matter hyperintensity, and more severe global atrophy were all negatively associated with baseline performance of information processing speed and executive functions. No association was found with memory performance. None of the baseline volumetric measurements predicted change in cognition after 1 year.

Conclusions: In addition to stroke lesion volume, volumes of white matter hyperintensity and global atrophy are associated with cognitive performance following stroke in the post-acute phase, but do not predict change in cognition after 1 year. Future studies with longer follow-up times are needed to assess whether vascular and neurodegenerative factors can predict long-term post-stroke cognitive decline.

INTRODUCTION

Many stroke patients suffer from persistent cognitive impairment,¹ which is a major determinant of a poor long-term outcome.^{2, 3} However, it remains unclear to what extent cognitive decline is caused by the stroke event itself or additional ageing-related brain damage accumulated before the stroke. Besides the stroke lesion, white matter hyperintensities (WMH),⁴ medial temporal lobe atrophy,⁵ and global cerebral atrophy have all been suggested to contribute to post-stroke cognitive decline.⁶ This suggests that brain pathology underlying post-stroke cognitive impairment may be of vascular, degenerative, or mixed origin. As such, stroke or pre-existing vascular lesions may precipitate⁷ or exacerbate degenerative pathology.^{8, 9} Although many studies have assessed cognitive impairment as a function of either vascular lesions or degenerative measures,¹⁰⁻¹³ only few studies have assessed these concurrent processes on cognitive functioning after stroke simultaneously.^{6, 14}

In the present study, we therefore examined the individual as well as relative contribution of stroke lesion volumes, WMH, the hippocampus volumes, and global brain atrophy (GA) to post-stroke cognitive functioning in the post-acute phase after stroke and change in cognition one year thereafter.

METHODS

Participants

Participants were enrolled in the Cognition and Affect after Stroke: a Prospective Evaluation of Risks (CASPER) study, a prospective cohort study examining predictors of post-stroke cognitive impairment, dementia, depression, and apathy in stroke survivors. Details on its design have been described elsewhere.¹⁵ In short, 250 patients with an ischemic or haemorrhagic stroke were recruited from the Stroke Unit of the Maastricht University Medical Center (MUMC+) and Zuyderland Medical Center, the Netherlands, between June 2013 and November 2015. Baseline measurements took place approximately three months after stroke to avoid interference with acute care and rehabilitation. Exclusion criteria were <40 years of age, pre-stroke dementia, pre-existing cognitive impairment (as assessed by a score ≥ 3.60 on the Informant Questionnaire on Cognitive Decline in the Elderly),¹⁶ mental retardation, a Mini-Mental State Examination score <15,¹⁷ neurological or psychiatric diseases other than depression known to affect cognition, insufficient knowledge of the Dutch language, too severe aphasia to understand the study procedure, blindness, history

of stroke <3 years or residual symptoms from previous stroke, and post-surgery stroke or post-anoxic encephalopathy. The study complies with the Declaration of Helsinki,¹⁸ the local ethics committee of MUMC+ approved the research protocol, and all participants gave informed consent.

For the present sample stroke patients were included for whom magnetic resonance imaging (MRI) scans according to CASPER protocol at baseline and neuropsychological results at baseline (three months post-stroke; mean 2.9 months, standard deviation [SD] 0.46), and 12 months after baseline (mean 15.1 months post-stroke, SD 0.69) were available.

Measures

Cognitive assessment

Well-trained research psychologists administered an extensive neuropsychological test battery at baseline and follow-up. Three cognitive domains were considered as outcomes: memory, measured with the Dutch adaptation of the Rey Verbal Learning Test (immediate and delayed recall);¹⁹ information processing speed, measured with the Trail Making Test part A²⁰ and the Digit Symbol Substitution Test;²¹ and executive function, assessed with the Trail Making Test part B²⁰ and verbal fluency tests (animal and profession categories).¹⁹ Z-scores were calculated for each test, adjusted for age, sex, and highest level of education based on available norms.²¹⁻²³ Composite scores were derived for each cognitive domain by averaging the z-scores of the tests within each domain.

Magnetic Resonance Imaging

All structural brain MRI scans were acquired using the same 3.0 Tesla (3T) scanner (Philips, Achieva, Philips Medical Systems, Best, the Netherlands), according to a standardized protocol with the following sequences: 3D T1-weighted, axial T2-weighted, 3D fluid-attenuation inversion recovery (FLAIR), diffusion-weighted and susceptibility-weighted sequences (details have been described elsewhere).¹⁵

Imaging markers

Cortical gray and white matter were segmented on T1-weighted scans using FreeSurfer software.²⁴ Ischemic strokes were classified as infratentorial, lacunar or cortical based on the clinical syndrome and radiological findings on either computed tomography or MRI made on the day of presentation. The radiological classification was used if there was a discrepancy between clinical syndrome and radiological imaging. The clinical classification was used if there was no recent stroke lesion visible on brain imaging that could correspond with the

symptoms presented. An experienced neurologist (JS) indicated the symptomatic ischemic or haemorrhagic stroke lesion and old and/or silent infarct lesions. These were segmented manually (ED) on FLAIR scans and separately masked. Stroke lesion volume was normalized to total intracranial volume (ICV), which was derived from FreeSurfer.

WMH volume was semi-automatically segmented²⁵ on FLAIR scans, guided by the results from the gray and white matter segmentation on the T1-weighted scan. These volumes were manually corrected by two trained researchers (ED and DH) under supervision of an experienced neurologist (JS), in order to differentiate between normal appearing white matter and WMH, and to exclude stroke lesion tissue. The inter-rater agreement score, expressed by intraclass correlation coefficient in a two-way random effects model was high (0.98, 95% confidence interval 0.88–1.00). WMH volume was normalized to ICV.

GA was calculated as one minus whole brain volume, which was measured by using the ratio of brain parenchymal volume to total ICV.

Automated hippocampal volumetry was performed using the ‘Learning Embeddings for Atlas Propagation’ (LEAP) method²⁶ and was visually inspected to identify failed segmentations. Hippocampal volume (HCV) was normalized for head size by dividing the native space volume by the affine scaling factor, which was derived from LEAP as well.²⁷ Left and right HCV were summed in the analyses.

Statistical analysis

Linear regression models tested the association of each cognitive outcome variable as dependent variable with each volumetric marker at baseline as independent variable. WMH volume was skewed and therefore logarithmically transformed to yield a better distribution. Stroke lesion volume could not be transformed and was therefore categorized into tertiles representing none/small, medium, and large lesion volumes. First, a crude model was tested in which the baseline cognitive domain outcome was regressed on the volumetric marker. Since several analyses showed residual confounding by age and education, we decided to adjust all models for demographic variables (age, sex, education). Then, the effect of the volumetric marker was adjusted for age, sex, and education. Finally, all volumetric markers were combined in a single model to study their independent effects and adjusted for age, sex, and education to study their concurrent effects. For this, standardized β regression coefficients were requested in order to compare their relative contributions to the prediction model. Next, crude and adjusted lagged regression analyses studied change in cognition

by regressing the 12-months follow-up cognition outcome on the volumetric markers and baseline values in cognition. Separate analyses were conducted for each cognitive domain. All tests were two-sided with an alpha of 0.05. All analyses were performed in Stata 13.1 (StataCorp, TX, USA).

RESULTS

Baseline characteristics

From the 250 participants of the CASPER cohort, brain 3T MRI at baseline was available for 189 participants. One participant was excluded from analyses because neuropsychological test results were considered unreliable, resulting in a total of 188 patients. Volumetric data were unavailable for 20 participants due to different scanning protocols ($n = 17$) or technical problems during image processing ($n = 3$). Table 1 presents the baseline characteristics of the remaining 168 participants. Participants excluded from the present study ($n = 62$) were significantly older, more often female, and had a lower education level compared to the included participants. Baseline characteristics of the final 168 participants are presented in Table 1. In 122 participants, a symptomatic stroke lesion was identified on MRI. The remaining 46 (27%) participants did not have a visible lesion on the MRI, and they were included in the 'none/small lesions' group.

Predictors of cognitive functioning at baseline

Results for the baseline associations between cognition and MRI measures are shown in Table 2. Stroke lesion volume, WMH, and GA significantly predicted mean information processing speed and executive function scores in the model adjusted for stroke lesion volume and demographics. In the adjusted model with all MRI measures, standardized β coefficients showed the strongest associations for GA (information processing speed $\beta = -.45$, $p < 0.001$; executive function $\beta = -.27$, $p = 0.005$), followed by WMH (information processing speed $\beta = -.16$, $p = 0.043$; executive function: $\beta = -.21$, $p = 0.016$) and large stroke lesion volumes (information processing speed $\beta = -.14$, $p = 0.068$; executive function $\beta = -0.28$, $p = 0.002$). None of the MRI markers predicted mean memory scores at baseline.

Predictors of change in cognitive functioning from baseline to 12-month follow-up

Results for the associations between volumetric markers and 12-months change in cognition are shown in Table 3. In separate analyses, larger baseline stroke lesion volume, WMH, and

GA were associated with worse cognition at 12-months follow-up in information processing speed and executive functions. However, none of the volumetric variables significantly predicted inter-individual differences in change from baseline to follow-up.

Table 1. Baseline characteristics of participants included in analyses[§]

Variable	Total sample (n = 168)
Age in years	65.1 ± 11.1
Female	48 (28.6)
Education	
Low	57 (34.1)
Middle	63 (37.7)
High	47 (28.1)
Time since stroke (months)	2.9 ± 0.5
Ischemic stroke	158 (94.1)
Left-sided stroke lesion	75 (44.6)
Stroke type	
Cortical / non-lacunar	62 (60.2)
Lacunar	39 (37.9)
Infratentorial	2 (1.9)
Stroke lesion volume (% ICV)	
Small	0.002 ± 0.01
Medium	0.82 ± 0.56
Large	1.16 ± 1.12
WMH volume (% ICV)	0.65 ± 0.97
GA (% ICV)	0.33 ± 0.04
HCV (mm ³)	5562.33 ± 636.8
Memory ^a (n = 166)	0.04 ± 1.2
IPS ^b (n = 167)	-0.54 ± 0.9
EF ^c (n = 166)	-0.38 ± 0.8

Abbreviations: EF = executive function; GA = global brain atrophy; HCV = hippocampal volume; IPS = information processing speed; WMH = white matter hyperintensities.

[§] Data are presented as either mean ± SD or n (%).

^a Composed of: immediate and delayed recall of a 15-word learning test.¹⁹

^b Composed of: trail making test, part A,²⁰ digit symbol substitution test.²¹

^c Composed of: trail making test, part B,²⁰ verbal fluency of animal and profession categories.¹⁹

Table 2. Adjusted models for the associations between brain volumetric markers and cognition at baseline

Outcome	Predictor	Model 1 ^a		Model 2 ^b		Model 3 ^c	
		B (95% CI)	P-value	B (95% CI)	P-value	B (95% CI)	P-value
Memory	Stroke lesion volume						
	small	(reference group)					
	medium	0.03 (-0.43, 0.49)	0.885				
	large	-0.33 (-0.79, 0.13)	0.164				
	WMH	-0.11 (-0.24, 0.02)	0.089	-0.13 (-0.26, 0.00)	0.056		
	HCV	0.11 (-0.22, 0.43)	0.514	0.07 (-0.25, 0.40)	0.660		
	GA	0.17 (-0.41, 0.74)	0.569	0.22 (-0.36, 0.80)	0.454		
IPS	Stroke lesion volume						
	small	(reference group)					
	medium	-0.23 (-0.55, 0.09)	0.156			-0.19 (-0.49, 0.10)	0.194
	large	-0.33 (-0.65, -0.01)	0.047			-0.27 (-0.57, 0.02)	0.068
	WMH	-0.12 (-0.21, -0.33)	0.007	-0.13 (-0.22, -0.04)	0.006	-0.09 (-0.17, -0.00)	0.043
	HCV	0.17 (-0.06, 0.39)	0.140	0.14 (-0.09, 0.36)	0.239		
	GA	-1.08 (-1.44, -0.71)	<0.001	-1.06 (-1.42, -0.69)	<0.001	-0.99 (-1.36, -0.62)	<0.001
EF	Stroke lesion volume						
	small	(reference group)					
	medium	-0.21 (-0.49, 0.08)	0.149			-0.16 (-.43, 0.11)	0.240
	large	-0.46 (-0.75, -0.18)	0.002			-0.45 (-0.72, -0.17)	0.002
	WMH	-0.11 (-0.19, -0.02)	0.011	-0.12 (-0.20, -0.04)	0.005	-0.10 (-0.18, -0.02)	0.016
	HCV	-0.01 (-0.22, 0.19)	0.894	-0.07 (-0.27, 0.14)	0.522		
	GA	-0.61 (-0.96, -0.26)	0.001	-0.56 (-0.91, -0.22)	0.002	-0.49 (-0.84, -0.15)	0.005

Abbreviations: EF = executive function; GA = global brain atrophy; HCV = hippocampal volume; IPS = information processing speed; WMH = white matter hyperintensities. *Note:* Stroke lesion volume is added as covariate in model 2 and 3, therefore no coefficient is shown for this predictor separately. Scores of HCV and GA were divided by 1000 and multiplied with 10 (resp.) to ease interpretation of coefficients.

^a Model 1: each predictor corrected for age at baseline, sex, and highest level of education.

^b Model 2: model 1 + correction for stroke lesion volume.

^c Model 3: combined model of significant predictors corrected for demographics and stroke lesion volume.

Table 3. Adjusted models for the associations between brain volumetric markers and change in cognition from baseline to 12-month follow-up

Outcome	Predictor	Model 1 ^a		Model 2 ^b		Model 3 ^c	
		B (95% CI)	P-value	B (95% CI)	P-value	B (95% CI)	P-value
Memory	Stroke lesion volume						
	small	(reference group)					
	medium	0.31 (-0.21, 0.84)	0.237				
	large	-0.23 (-0.75, 0.28)	0.377				
	WMH	-0.02 (-0.17, 0.12)	0.773	0.07 (-0.03, 0.17)	0.169	0.06 (-0.04, 0.16)	0.220
	HCV	0.18 (-0.19, 0.56)	0.341	0.01 (-0.24, 0.26)	0.942	0.02 (-0.23, 0.28)	0.859
IPS	GA	-0.09 (-0.78, 0.60)	0.799	-0.22 (-0.68, 0.23)	0.337	-0.23 (-0.69, 0.23)	0.333
	Stroke lesion volume						
	small	(reference group)					
	medium	-0.22 (-0.59, 0.15)	0.248				
	large	-0.34 (-0.71, 0.02)	0.067				
	WMH	-0.16 (-0.26, -0.06)	0.002	-0.06 (-0.13, 0.01)	0.103	-0.06 (-0.13, 0.01)	0.090
EF	HCV	0.05 (-0.21, 0.31)	0.717	-0.08 (-0.25, 0.09)	0.349	-0.08 (-0.26, 0.09)	0.339
	GA	-1.06 (-1.51, -0.61)	<0.001	-0.21 (-0.55, 0.14)	0.236	-0.20 (-0.55, 0.14)	0.247
	Stroke lesion volume						
	small	(reference group)					
	medium	-0.17 (-0.49, 0.16)	0.314				
	large	-0.28 (-0.60, 0.04)	0.086				
	WMH	-0.09 (-0.18, -0.00)	0.046	0.00 (-0.05, 0.06)	0.939	0.01 (-0.05, 0.07)	0.746
	HCV	0.06 (-0.17, 0.29)	0.579	0.06 (-0.08, 0.20)	0.411	0.08 (-0.06, 0.22)	0.252
	GA	-0.70 (-1.11, -0.29)	0.001	-0.21 (-0.48, 0.05)	0.114	-0.22 (-0.48, 0.04)	0.101

Abbreviations: EF = executive function; GA = global brain atrophy; HCV = hippocampal volume; IPS = information processing speed; WMH = white matter hyperintensities. **Note:** Stroke lesion volume is added as covariate in model 2 and 3, therefore no coefficient is shown for this predictor separately. Scores of HCV and GA were divided by 1000 and multiplied with 10 (resp.) to ease interpretation of coefficients.

^a Model 1: each predictor corrected for age at baseline, sex, and highest level of education.

^b Model 2: model 1 + correction for neuropsychological baseline performance.

^c Model 3: model 2 + correction for stroke lesion volume.

DISCUSSION

The present study examined the association between stroke lesion related, vascular, and neurodegenerative volumetric MRI markers assessed at baseline and cognitive change during a 12-month follow-up. Patients with larger volumes of WMH and GA measured three months post-stroke had worse information processing speed and executive function performance both at baseline and at follow-up, and more decline in these domains at follow-up. Larger stroke lesion volume was significantly related to worse executive functions only. In contrast, memory performance was not associated with any of the MRI markers. Also, none of the markers were associated with change in cognitive performance from baseline to 12-months follow-up.

Our findings demonstrate that both WMH volume and GA are predictors of cognitive functioning, over and above stroke lesion volume. With regard to WMH, our findings are in line with previous studies in stroke patients that found WMH to be a longitudinal⁴ predictor for executive function^{4,11} and information processing speed.¹¹ Likewise, studies in patients with cerebral small vessel disease,²⁸ subcortical ischemic vascular disease,²⁹ and in the general population^{30,31} found WMH to be associated with cognitive decline. This indicates the importance of this MRI marker as a contributor to age-related cognitive decline. Our results with regard to GA are also in line with other studies that associated measures of atrophy with cognitive impairment after stroke.³² In addition, similar associations have been found in patients with cerebrovascular disease,³³ subcortical cerebrovascular brain injury,³⁴ and the general population.³⁵ Few studies have investigated both volumetric measures concurrently after stroke. In a recent study, cortical gray matter volume was the only significant predictor of cognitive impairment, independent of WMH and stroke volume.³⁶

We did not find associations with hippocampal volume, a key marker of neurodegeneration that is strongly associated with Alzheimer's disease.^{34,37} Some studies found medial temporal lobe atrophy (MTA) to be predictive for cognitive measures. A study including stroke patients⁴ found both WMH and MTA to be related to cognition. However, participants in this study were on average eight years older than our cohort, more often suffered from haemorrhagic strokes and TIAs, and 'degenerative' damage was visually rated as opposed to our hippocampal volumetric measure. Another study⁵ also found a visually-rated MTA and GA score to be predictive of cognition in stroke patients. Yet, participants in that study were again older (>75 years). In addition, a global measure of cognitive ability was used rather than a comprehensive neuropsychological assessment. The strong association between age

and Alzheimer's disease could explain the differences between the present study and the previous ones. Our relatively young study sample most likely contained fewer individuals with (preclinical) Alzheimer's disease than the other studies. The resulting lack of variance in HCV in our study compared with the others might have masked associations with cognitive performance in our study, and memory performance in particular. This might be due to the relatively young age of our cohort as memory deficits might be more frequent in older patients due to higher prevalence of concomitant neurodegenerative pathology. In addition, we used the IQ-CODE to exclude individuals with pre-existing cognitive impairment or dementia, which may have influenced the results regarding amnesic cognitive impairments. Our results suggest that a generalized pattern of cerebral small vessel disease and post-stroke vascular damage rather than primary degenerative damage is causing cognitive dysfunction after stroke in a cohort of relatively young stroke patients.

Several mechanisms may underlie the association of WMH and GA with processing speed and executive function. White matter damage might lead to a disconnection of frontal-subcortical circuits, thereby compromising the integrity of the frontal lobe, leading to executive dysfunctions.³⁸ Ischemic damage to axons in the subcortical white matter may lead to deafferentation of cortical-subcortical connections and subsequent cortical neurodegeneration.³⁹ Additional cerebral small vessel disease may cause demyelination, loss of axons, oligodendrocytes and other glial cells in the subcortical gray matter leading to decrements in information processing.⁴⁰

Strengths of our study include the volumetric quantification of several brain measures in a sizeable proportion of participants, which allowed for direct comparisons of strengths of associations. Additional strengths are the longitudinal design, the comprehensive neuropsychological assessment of different cognitive domains, and the exclusion of patients with pre-stroke dementia.

Potential limitations are the relatively short follow-up period of one-year, which might have resulted in too subtle changes in cognition to detect. Indeed, coefficients from the lagged regression appear to be directionally congruent with the hypothesis that more brain damage leads to faster decline, but standard errors were large leading to wide confidence intervals. Next, use of a single MRI scan did not allow for correlating change in cognition with change in structural brain markers. Longitudinal studies with multiple and longer follow-up times in stroke survivors with volumetric measures of WMH, (local) brain atrophy, and stroke

lesion and elaborate neuropsychological testing to assess a range of cognitive domains are needed.

In conclusion, this study shows that higher vascular pathology burden is associated with worse cognitive performance at baseline and 12-months follow-up post-stroke, with WMH and GA being independently associated with processing speed and executive function over and above stroke lesion volume.

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7

General discussion

GENERAL DISCUSSION

Heart disease and stroke are major leading causes of death and disability in the elderly. Besides physical and emotional changes, cognitive impairment is a common consequence experienced by survivors of such events, causing additional significant distress in both patients and their families. Indeed, heart disease and stroke are both considered important risk factors for dementia¹ by causing cerebrovascular damage. In 2015, the global prevalence of dementia was 46.8 million people,² with 16 percent attributable to cerebrovascular disease.³ This figure is expected to rise to over 130 million in 2050. Therefore, identifying and treating risk conditions for major neurocognitive disorders should be a public health priority. Several studies have shown a link between cardiovascular risk factors and disease and late-life brain functioning, which has led to the notion of a ‘heart-brain connection’.⁴ In this thesis, we further investigated this heart-brain connection by studying whether cardiovascular disease (CVD) is a robust risk factor for dementia by means of meta-analysis (chapter two). We also examined the timing between onset of CVD and onset of cognitive decline (chapter three). In addition, we studied the prognostic value of domain-specific cognitive functioning after stroke with regard to long-term outcomes of dementia and mortality (chapter four). In order to investigate volumetric imaging markers as predictors of cognitive functioning after stroke (chapter six), the Cognition and Affect after Stroke: a Prospective Evaluation of Risks (CASPER), a one-year prospective clinical stroke cohort follow-up study (chapter five) was set up.

In this final chapter, the main findings of the individual studies that are described in this thesis are presented and discussed in relation to our current understanding of factors that influence vascular cognitive impairment (VCI). In addition, methodological considerations, implications for clinical practice, and directions for future research are given.

MAIN FINDINGS

Heart disease and cognition

Heart diseases have been related to cognitive decline and dementia,⁵ with most robust evidence for atrial fibrillation⁶ and heart failure.⁷ Results from studies on other forms of heart disease, such as coronary heart disease, have shown less consistent results. A systematic review and Delphi consensus study by our group⁸ previously identified coronary heart disease as a *potential* modifiable risk factor, but the evidence was yet to be established

and required further research. Our meta-analysis (chapter two) provided evidence that coronary heart disease is, on average, associated with a 45 percent increased odds of developing cognitive impairment or dementia. When focusing on the most common subtypes of coronary heart disease, i.e. myocardial infarction and angina pectoris only, similar significant results were found in prospective studies. There were no differences between studies that did or did not correct for cardiovascular risk factors, implying that the association between coronary heart disease and dementia cannot solely be explained by these shared cardiovascular risk factors. These findings have important implications, because progressive loss of cognitive function and cardiac dysfunction are common health problems in an aging society,⁴ which can be expected to rise in prevalence as a result of the aging of the world's population.⁹ The notion that they are interrelated and that CVD might be a causal risk factor or a non-causal risk marker asks for studies that focus on shared (modifiable) risk and lifestyle factors for primordial prevention of dementia.

In addition, no population-based prospective studies on cognitive decline after a first cardiovascular event have been reported before. In chapter three, we compared the cognitive trajectories of individuals with prevalent, incident, and no CVD in the Maastricht Aging Study (MAAS) and found that both prevalent and incident CVD groups showed a faster cognitive decline in the domains of memory and information processing speed than the group without CVD. Interestingly, for the incident CVD group, this effect was only evident in the last follow-up period (from six to 12 years after baseline), i.e. the time following the event. This coupling of both the CVD event and onset of decline in cognitive function in time is indicative, though not proof, of a causal relationship and strongly supports the 'heart-brain connection'. Our MAAS results further suggest that there might be a window of opportunity for slowing of cognitive decline by applying early preventive measures in people with CVD risk factors. Such prevention or intervention strategies may reduce dementia risk from a lifetime perspective. Indeed, findings from the large Prevention of Dementia by Intensive Vascular Care (preDIVA) trial in 3,526 individuals aged 70-78 years showed that a nurse-led intensive cardiovascular risk management did not lower dementia risk at the total population level, but was effective in those with previously untreated hypertension and in people without evident CVD at baseline if they adhered to the intervention.¹⁰ Since cognition and heart disease share causal mechanisms,¹¹ prevention of CVD and prevention of dementia should go hand in hand, in line with the slogan "What is good for the heart, is good for the brain". The importance of improving cardiovascular health for the prevention of dementia has been stressed recently in a paper by the Lancet Commission on Dementia prevention, intervention, and care.¹²

Domain-specific cognitive functions after stroke

Cognitive impairment in various neuropsychological domains is a frequent and well-described sequel after stroke and has also been associated with poor long-term outcomes such as dementia and mortality.^{13, 14} Previous studies have often compared stroke patients with healthy control participants to find that cognition is a *predictive* marker for the higher dementia risk in stroke survivors compared with controls. As such, it is less well understood whether post-stroke cognitive performance is also a *prognostic* marker of differential mortality and dementia risk within stroke patients themselves, i.e. whether it predicts who is at-risk of a poor prognosis, and whether this differs across cognitive domains. In chapter four, we examined the prognostic value of cognitive performance within a group of stroke survivors and found that cognitive functioning in rather specific domains is associated with mortality up to ten years after the stroke. Significant associations were observed for executive functioning, information processing speed, and verbal fluency. These domains rely heavily on largely distributed networks necessary for planning, problem solving and daily functions. Disconnections might lead to greater difficulties in these and self-care, contributing to individual frailty and higher mortality risk. In contrast, none of these cognitive domains significantly predicted incident dementia after stroke. These results suggest a competing risk: individuals who died before follow-up might also be at higher risk for dementia but did not develop dementia due to the occurrence of death.

Imaging markers

Cognitive deficits after stroke have typically been linked to the stroke event and its localization. However, individuals who have had a stroke often show other signs of vascular or neurodegenerative brain damage such as white matter hyperintensities (WMH) and brain atrophy on magnetic resonance imaging (MRI), too. It remains unclear whether these markers are predictors of post-stroke cognition, and what their effect is upon the stroke lesion itself. The Cognition and Affect after Stroke: a Prospective Evaluation of Risks (CASPER) described in chapter five was, among other study aims, designed to address this question. In chapter six, we used data from the CASPER study to show that imaging markers of WMH volume and global brain atrophy were significant predictors of cognitive function and cognitive change 15 months after stroke. These results were independent of stroke lesion volume, age, sex, and education. Results imply that brain pathology existing pre-stroke plays an important role in predicting long-term post-stroke cognitive functioning.

Taken together, results presented in this thesis suggest that both cardio- and cerebrovascular events have a negative effect on cognition, worsen the impact of pre-existing pathology on

cognition, and impact on long-term prognosis, thereby providing further support for the importance of the heart-brain connection.

OTHER FACTORS INFLUENCING DEVELOPMENT OF VCI

Other cerebral pathology

Pathological factors related to dementia may impact on cognition after a vascular event. Alzheimer's disease (AD) pathology, more specifically beta-amyloid depositions, is common in the elderly population and increases with age.¹⁵ AD is the most common cause of dementia, followed by vascular dementia (VaD). Although AD has long been seen as a distinct (neurodegenerative) disease entity, recognition of a close interrelation between vascular and Alzheimer like pathology has grown.¹⁶ Vascular pathology often co-occurs with neurodegenerative pathology as observed in post-mortem research, and these pathologies also contribute to VCI. The mechanisms of how these factors interact or to what extent these contribute to VCI are not well understood. Comorbid neurodegenerative pathology in stroke patients may impact on cognitive decline by leading to preclinical brain damage. Indeed, our findings in chapter six suggest that global atrophy, white matter lesions and stroke lesion volume are all important yet independent predictors of cognitive functioning after stroke. It should be noted, however, that brain atrophy may not only be due to AD but can also be due to pre-stroke cerebral small vessel disease as well as atrophic changes in remote brain regions caused by the ischemic infarct.^{17, 18} This 'secondary neurodegeneration' is mediated by loss or degeneration of the fiber tracts connecting the area in which vascular injury took place with distant gray matter, resulting in focal or widespread loss of white matter and cortical thinning.

Risk factors of CVD and stroke

Also, shared risk factors of CVD and stroke such as hypertension, diabetes, or smoking are known to affect vascular brain health and lead to dementia.¹⁹ These risk factors can affect the cerebrovascular system and, with increasing exposure time, cause accumulating brain damage.²⁰ Previous studies have shown that several of these risk factors present during midlife have a strong impact on late-life cognitive performance, possibly because of their chronic, long-term presence.²¹ This is in line with our findings in MAAS, showing that a faster cognitive decline in the younger age group (<65 years) with CVD. In contrast, older individuals did not decline significantly. Similarly, the association between hypertension (another vascular risk factor for dementia) and poor cognitive functioning attenuates with

increasing age.²² Possibly, the impact of risk factor exposure is stronger on a relatively intact or healthier brain in contrast to the older brain in which damage accumulates over life due to, for instance, multimorbidity and the wear-and-tear that comes with aging, which in turn dilutes the effect of a specific risk factor. Interestingly, we also found that those with incident CVD showed evidence of significant, albeit subtle, cognitive decline after the onset of CVD but not before. In MAAS, a similar coupling effect between the onset of hypertension and onset of cognitive decline,²³ as well as onset of diabetes and cognitive decline,²⁴ has been shown. Taken together, this suggests that individuals who are exposed to risk factors for longer intervals have a higher risk of future cognitive decline that is mild in the beginning but might accelerate as exposure duration increases. The abovementioned findings support current recommendation to start health and lifestyle interventions aimed at reducing dementia risk in midlife or even earlier.^{12,25}

Individual differences in onset of cognitive decline

The extent to which each of abovementioned factors affects an individual's cognitive functioning is, besides the vascular event itself, also dependent on individual differences in brain and cognitive reserve and/or pre-existing subclinical brain damage. The concept of cognitive reserve can be defined as the brain's ability to optimize or maximize performance by using different brain networks or applying alternative strategies.²⁶ It reflects the capacity to provide a buffer against the effects of brain pathology so that a higher amount of reserve requires a greater burden of pathology before cognitive decline or dementia become apparent.²⁷ Especially after an acute vascular event, these individual differences become apparent. The amount of reserve in later life is to a good degree determined by the engagement in mental activity during the life course (most notably childhood education, work-related cognitive demand and leisure-time activities), and, as suggested in a recent epidemiological study, also dependent on other factors that comprise an individual's lifestyle, such as a healthy diet, more physical activity, moderate alcohol intake, engagement in social activities, and refraining from smoking.²⁷ Both biological factors ('brain reserve', i.e. brain volume, synapse density, or vascular resilience) and environmental factors ('cognitive reserve', i.e. educational level or ease of coping strategies) thus influence the relation between brain pathology and clinical symptoms. Stated otherwise: whether a certain amount of (vascular) pathology in the brain produces cognitive symptoms is dependent on the premorbid brain condition. Interestingly, previous work has shown that many cognitively normal older individuals show evidence of AD pathology, but that highly educated people indeed have more amyloid deposition compared with lower educated people with the same level of cognitive functioning.¹⁵ Probably, it takes a higher pathology load in the former to

bring cognition to the same level as in the latter group because of a higher brain reserve. Additionally, the relationship between abovementioned factors and an individual's reserves is probably bidirectional, in that people with more brain reserve might seek more cognitive challenging activities and lead a more brain-healthy life.

Cognitive decline, hypoperfusion, and cerebral microinfarcts

We found longitudinal associations between CVD or stroke and cognitive decline or cognitive functioning, but underlying pathophysiological mechanisms were not explored. Under normal physiological conditions, autoregulation enables a constant blood pressure in the brain despite large variation in peripheral blood pressure and cardiac output.⁴ However, this autoregulation cannot always protect the brain from hypoperfusion when cardiac output is chronically reduced or atherosclerosis is present. This suggests a close link between cardiac function and large vessel atherosclerosis on the one hand and brain perfusion and cognitive functioning on the other.⁴ Hypoperfusion caused by heart disease and acute hypoperfusion caused by stroke, may be underlying the associations found. Our brain is largely dependent on a proper blood supply, delivering the nutrients and energy needed to execute cognitive functions. The increase in cerebral blood flow that follows neural activity delivers energy substrates and removes toxic byproducts of brain activity, including amyloid beta.²⁸ When cardiac output is reduced and/or atherosclerosis is prominent, hypoperfusion may become inevitable and result in an inadequate blood supply. Lasting interruption of cerebral blood flow can lead to brain atrophy, cerebral ischemia and, subsequently, to cognitive dysfunction.²⁹ Cerebral hypoperfusion has been identified in brain regions associated with cognitive function both in patients with AD and vascular dementia.^{30, 31} Presumably, variation in the amount of chronic hypoperfusion as well as acute hypoperfusion related to the vascular event (e.g. stroke or myocardial infarction) will likely influence the cognitive outcome in patients. Hypoperfusion may thus result in pre-event (subclinical) brain damage that reduces an individual's brain reserve and cause major post-event brain damage by impacting on a vulnerable brain, i.e. exert a double impact. Such relationships between (cardio-)vascular factors, the hemodynamic status of the heart and brain, and cognitive impairment are currently investigated by the Heart-Brain Study.³²

Cerebral microinfarcts may be another cause of cognitive decline. These lesions are smaller than visible lacunar infarcts and detectable by microscopic examination of brain sections. Given their high numbers and widespread distribution, these microinfarcts may disrupt cognitive networks. Therefore, they may account for some of the cognitive decline seen in association with lesions that are visible on MRI such as lacunar infarcts and WMHs.³³

METHODOLOGICAL CONSIDERATIONS

Strengths

The main strength of our studies is the rich clinico-radiological and neuropsychological phenotyping of the patients groups, in which careful assessment of multiple domains of cognitive function (chapters three, four, six) have been carried out as opposed to one global measure that only taps into some aspects of a few cognitive domains. Obviously, the use of a single global cognition test has its benefits in terms of time and cost-efficiency, and is less difficult to analyse. However, it provides limited information and might blur associations that exist with specific domains only. Studying the prognostic value of domain-specific cognitive functions post-stroke (chapter four) is per definition impossible with such a measure. Another strength of our studies is their prospective nature, which allowed us to study directionality of effects and temporal relationships (chapters three, four, and six). Other strengths are the long follow-up periods (up to 12 years), which enabled us to study long-term outcomes, and the inclusion of several relevant covariates. Furthermore, the systematic review and meta-analyses gave us insight into the predictive value of coronary heart disease as an evidence-based risk factor for cognitive impairment or dementia (chapter two). Lastly, the usage of volumetric as opposed to more subjective visual measures of white matter lesions, hippocampal, and global atrophy made it possible to obtain more precise estimates of the relation between brain changes and cognitive function (chapter six).

Limitations

Our studies also had several limitations. With regard to our meta-analysis, substantial heterogeneity was observed, which can be related to several methodological differences across studies such as participant selection, diagnostic criteria used for the outcome variable, or assessment of the predictor variable. However, meta-regression analyses did not identify a significant source of heterogeneity. Another limitation may be that in both the meta-analyses and the MAAS study (chapters two and three), predictors and covariates were based on self- or proxy report, which could have led to underestimation as this makes the variable prone to recall bias and non-differential measurement error. In addition, we did not have information on the severity of the vascular disease, though this may affect the cognitive trajectory independently from the presence of CVD alone. Another limitation might be that findings might not generalize to the whole target population. For instance, participants of the MAAS study were self-selected, and loss to follow-up might have caused additional selection bias.³⁴ This may lead to inaccurate estimates of the true population effect, usually in the form of underestimation. While some loss-to follow-up is inevitable in

population-based and clinical epidemiological studies, we tried to minimize the effect on our results by the use of probability weights to correct for attrition and selection bias. In CASPER and SSS, the stroke cohorts were primarily individuals who experienced minor to moderate strokes, with severe aphasia being excluded a priori.

CLINICAL IMPLICATIONS

Our findings have important clinical implication. First, they show that, besides the well-known effect of cerebrovascular disease, also cardiovascular diseases play an important role in the development of VCI. Therefore, clinicians, notably medical specialists such as neurologists and cardiologists but also general practitioners should be aware of the possibility of VCI to develop over time in patients who have experienced a cardiovascular event, which is even more important in the long-term given its gradual, insidious onset after a first cardiovascular event. Minor cognitive changes that are not easily detectable by standard tests may exist. Patients might already experience these changes vaguely, but might be reluctant to discuss such symptoms with their healthcare professional, as they may not link concerns about cognition to heart problems. Indeed, previous studies have shown that there is low awareness in the general population that CVD and its risk factors are also risk factors for dementia.³⁵ Obviously, much could be gained here in terms of awareness by discussing the possible cognitive consequences of a vascular event with patients. Raising awareness about the heart-brain connection may therefore lead to earlier detection of cognitive deficits and timely selected or indicated preventative measures. Moreover, subjective cognitive complaints voiced by the patient can be indicative of objective cognitive impairment or brain pathology,³⁶ therefore these complaints should be taken serious. Indeed, heart-brain clinics with multidisciplinary staff of neurologists, psychologists, neuroradiologists, and cardiovascular specialists could identify, detect, and prevent progression of vascular risk factors that predispose to cognitive impairment and development of dementia.³⁷ Such a clinic could offer multidagnostic testing which in turn could permit better risk stratification, medical decision-making, and tailored intervention of at-risk patients that goes beyond the services of the traditional, often mono-therapeutic approach.

When cognitive problems are discussed, it is important that cognition is assessed by a comprehensive neuropsychological assessment that includes measures for information processing speed, executive function, and memory. Global cognitive screening measures,

such as the Mini-Mental State Examination, are not appropriate in this context as they usually do not, or insufficiently, assess processing speed and executive function. Even if such a measure is used for screening goals, it is still questionable whether the clinician will find the subtle cognitive decline a patient may already experience in activities of daily living due the ceiling effect in these tests, especially in higher educated patients. Standardized protocols of neuropsychological tests for VCI, both in a hospital and a research setting, are warranted to increase reliability and comparability of test results in different settings and across studies.

Besides the proper assessment of possible cognitive problems, it is important that individuals and their families who are confronted with deteriorating cognitive function have easy access to appropriate care so that their well-being and quality of life are maintained. For instance, psycho-education for individuals who suffered a stroke or cardiovascular event might be important, because cognitive changes are often not as salient as physical limitations, at least in the acute to post-acute phase, causing them to be unrecognized or misunderstood. A better understanding of the cognitive consequences and improving problem-solving and communication skills for both patient and family can help in coping with such consequences in everyday life.

Also, vascular risk factors are primarily treated to reduce the risk of cardio- or cerebrovascular events, but might have collateral effects. Indeed, studies reporting on a decline in dementia incidence and prevalence in developed countries suggest that better cardiovascular risk control and treatment might have affected, at least partly, the development of cognitive deficits and dementia.^{38, 39} Moreover, the preDIVA trial mentioned before showed that participants with untreated hypertension at baseline and for individuals without a CVD history.¹⁰ This shows that good management of hypertension reduces not only the risk at a vascular event but perhaps also the dementia risk in the long run. Although the preDIVA trial reported no significant treatment effect for the total sample on incident dementia by intensive vascular risk management in primary care over seven years, this might be due to the already high standards of cardiovascular risk management in the Netherlands. In addition, our findings show that interventions should start in midlife or earlier. Obviously, it would be even better to prevent than to cure. Lifestyle interventions, or more awareness and education for people who are not at risk yet, may have a much higher impact on reducing the prevalence of VCI and dementia.¹²

DIRECTIONS FOR FUTURE RESEARCH

Several directions for future research can be identified. First, existing data should be used to its fullest potential. Already gathered data can answer (new) research questions in a very efficient and effective way when being pooled together as this is more cost-effective and more participants can be included in analyses. Initiatives that organize such approach should be priority for governments and funders. An example is the Stroke and Cognition (STROKOG) consortium, in which our CASPER clinical stroke cohort study is included.⁴⁰ This is a recently established consortium of prospective post-stroke/TIA studies from around the world, currently including 25 studies with up to 12,092 patients from 16 countries and 25 institutions worldwide. By harmonizing all these data and conducting individual participant data meta-analyses, the aim of STROKOG is to obtain a better understanding of the longitudinal trajectory of cognitive impairment after stroke and to investigate differences in the prevalence of these cognitive sequela as well as risk and protective factors between different countries and ethnic groups. Executing individual participant data meta-analyses enables us to study patient-level characteristics, adjust for the same confounding factors across studies, address new research questions (with already existing data), and reduce publication bias.^{41,42} With this approach, data that is lacking in one cohort can be complemented. For instance, it would be of interest to combine neuropsychological with imaging data on neuronal damage or with data levels of amyloid pathology (e.g. in cerebrospinal fluid or positron emission tomography) and data for presence of the apolipoprotein E genotype. By this, we might get a better insight into how these specific AD pathology biomarkers play a role in developing cognitive impairment or dementia in the presence of with and without cardio- or cerebrovascular events. METACOHORTS is another consortium with its focus on vascular contributions to dementia. This group included over 90 studies, with 600,000 subjects worldwide, with relevant data to vascular effects on neurodegeneration including cognitive consequences of stroke.⁴³ Such multinational cohorts would also be able to study geographic and ethnic variation in the association between risk factors and VCI/dementia. Since the brain's reserve can be considered as the sum of a lifetime input of education, physical activity, diet, and other lifestyle habits,⁴⁴ prospective population cohorts, ideally birth cohorts in which such markers are available should be studied as well. Such endeavours can shed more light on mechanisms that underlie cognitive reserve and individual resilience and their role in the development of VCI during the life-course, but are highly ambitious.

Second, since dementia has been attributed to modifiable factors such as midlife hypertension, midlife obesity, physical inactivity, smoking, depression, and low education, opportunities in terms of prevention exist.⁸ However, well-designed randomized controlled trials are needed to confirm them and investigate whether the prevention of both cardiovascular as well as cerebrovascular diseases can also lead to the prevention of VCI and dementia. Given that cognitive impairment and dementia are multifactorial disorders, a multifactorial and multidisciplinary approach is needed when setting up such trials. Modifiable risk factors related to lifestyle habits, for instance a balanced diet and regular physical activity, are of particular interest. These will have a beneficial effect on other (also modifiable) risk factors such as hypertension or obesity. Especially in countries where good medical care is available to most people, such lifestyle changes could come a long way in adding beneficial effects on dementia risk.

Alongside prevention, the individuals who suffered from a vascular event and are now confronted with the cognitive consequences should be studied as well. Also in this population, lifestyle changes and optimal vascular management may decrease recurrence rates that in turn are associated with increased dementia and mortality risk. In incident CVD, decline might be subtle (MAAS) and could be slowed down or even halted by timely treatment and strict adherence (preDIVA). Adopting and sustaining healthy lifestyle habits could perhaps change the cognitive trajectories of these individuals. Most individuals complete post-stroke rehabilitation within the first six months after stroke, but benefits, e.g. from exercise, are believed to persist beyond this period.⁴⁵ Physical activity leads to vasodilation, increased cerebral blood flow, a stronger immune system, and increased levels of neurotrophic factors,⁴⁶ resulting in an increase of the brain's plastic capability and resilience,^{47, 48} especially after stroke. Therapists do provide home exercises to continue physical activity after being discharged from rehabilitation, but it can be difficult to adhere to these.⁴⁵ Yoga has been shown to be effective for improving balance and functioning in older adults.⁴⁹ Evidence, although limited, suggests that the combination of postures, breathing, and meditation are most beneficial when carried out simultaneously and are considered to have different effects than simple exercises⁴⁹ due to the active mind-body component.⁵⁰ In addition, balance impairment is associated with post-stroke falls which in turn is associated with depression due to a decreased perceived health status and quality of life, fractures, and mortality after stroke.^{51, 52} Balance, fear of falling,⁵³ improved strength, motion range, and walking⁵⁴ may be improved by a modified yoga intervention for individuals who experienced a vascular event. Consequently, this could be an example of a physical activity that can be easily implemented in everyday life and that may be effective

in preventing recurrence or occurrence of vascular events and by this, preventing cognitive decline or impairment in the long term.

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Addendum

Summary

Nederlandse samenvatting (Dutch summary)

Knowledge valorization

Dankwoord (Acknowledgements)

Curriculum Vitae

List of publications

Thesis defences from MHeNS

SUMMARY

With our aging society, the global prevalence of dementia is rising dramatically. Also the numbers of individuals with cardiovascular disease (CVD) and survivors of cardiovascular events, including stroke, is increasing. Sixteen percent of dementia cases is attributable to cerebrovascular disease. Former studies have shown a link between cardiovascular risk factors and disease and late-life brain functioning, which has led to the notion of a 'heart-brain connection'. In the present thesis, we aimed to obtain a better understanding of this connection with regard to cognitive functioning.

Heart disease has been related to cognitive decline and dementia. Most substantial evidence comes from studies on atrial fibrillation and heart failure. However, no meta-analyses exist for major heart diseases such as myocardial infarction and angina pectoris. In **chapter two** we examined the relation between coronary heart disease and risk for cognitive impairment or dementia in a systematic review and meta-analysis of all available population-based studies. With this study we provide evidence that coronary heart disease is, on average, associated with a 45 percent increased risk of developing cognitive impairment or dementia. Similar results were found in separate meta-analyses of the most common subtypes of coronary heart disease, i.e. myocardial infarction and angina pectoris.

No population-based prospective studies on cognitive decline after a first cardiovascular event have been reported before. In **chapter three**, we looked into the temporal relationship between prevalent and incident CVD and cognitive functioning in the Maastricht Aging Study (MAAS). Both prevalent and incident CVD groups showed a faster cognitive decline in memory and information processing speed than the group without CVD. For those with incident CVD, decline was evident only after CVD onset, i.e. six to 12 years after the baseline measurement. This strongly supports the 'heart-brain connection' and suggests a possible window of opportunity for slowing cognitive decline. Also, this suggests that prevention of CVD can lead to reductions in dementia risk.

Cognitive impairment is a frequent and well-described sequel after stroke. Previous studies often compare individuals who have had a stroke to healthy individuals to find a predictive value of cognitive functions. In **chapter four**, we examined the prognostic value of cognitive performance within a group of stroke survivors of the Sydney Stroke Study. We aimed to understand whether cognitive functioning could predict who of these patients is at-risk of a poor prognosis in terms of mortality or dementia, and whether this prognostic value

differs across different cognitive domains. We found executive functioning, information processing speed, and verbal fluency, but not memory to be associated with mortality risk. None of the domains were associated with dementia.

Cognitive deficits after stroke have been linked to the stroke event and its localization, yet other types of brain damage are often seen on magnetic resonance imaging of individuals who have had a stroke as well. It remains unclear whether these markers are predictors of post-stroke cognition, and what their effect is in addition to the effect of the stroke itself. To answer this and related questions, the Cognition and Affect after Stroke: a Prospective Evaluation of Risks (CASPER) study was designed. **Chapter five** describes the rationale and design of CASPER. It is a prospective follow-up clinical stroke cohort follow-up study investigating predictors and biomarkers of vascular cognitive impairment, depression and apathy after stroke. We included 250 patients who experienced an ischemic or hemorrhagic stroke. The baseline measurement took place three months post-stroke and consisted of a venipuncture, recording of socio-demographic information, a neuropsychological assessment and neuropsychiatric interview, a semi-structured interview with an informant, and a structural 3-Tesla magnetic resonance imaging (MRI) of the brain. The neuropsychological assessment, neuropsychiatric interview and interview with the informant was repeated at six-month and 12-month follow-up. A three-year follow-up has been added later and is still ongoing.

In **chapter six** we then examined both the individual as well as the relative contribution of stroke lesion volumes, white matter hyperintensities (WMH), hippocampal volumes, and global brain atrophy (GA) to post-stroke cognitive functioning and cognitive change at 12-month follow-up. Individuals with larger volumes of WMH and GA had slower information processing speed and worse executive function performance both at baseline and follow-up, and more decline in these domains at follow-up. These findings show that both WMH and GA are predictors of cognitive functioning post-stroke, over and above stroke lesion volume.

Overall, the studies in this thesis gave more insight into the course and timing of both cognitive changes in prevalent and incident cardiovascular disease as well as the possible predictive and prognostic value of cognitive and imaging markers of cognitive impairment after stroke. In addition, these studies show the importance of a greater awareness of the heart-brain connection in the general population and amongst professionals, which

may lower and prevent the risk at and development of vascular cognitive impairment or dementia.

NEDERLANDSE SAMENVATTING

Vergrijzing van onze bevolking leidt tot een drastische stijging in het aantal mensen met dementie. Ook het aantal mensen met cardiovasculaire ziekten neemt toe. In 16 procent van de dementiegevallen is een cerebrovasculaire ziekte de oorzaak. Eerdere studies hebben een verband laten zien tussen cardiovasculaire risicofactoren, en cardiovasculaire ziekte enerzijds, en anderzijds het functioneren van het brein en cognitieve achteruitgang op latere leeftijd. Dit heeft geleid tot het zogenaamde 'hart-brein connectie' concept. In de artikelen in dit proefschrift pogen we om tot een beter begrip te komen van dit concept in relatie tot cognitief functioneren.

Hartziekte werd eerder al in verband gebracht met cognitieve achteruitgang en dementie. Het meest robuuste bewijs hiervoor komt uit studies naar atriumfibrilleren en hartfalen. Er bestaat echter nog geen meta-analyse van myocard infarcten en angina pectoris. In **hoofdstuk twee** hebben we de relatie tussen coronaire hartziekten en het risico op een cognitieve stoornis of dementie onderzocht door middel van een literatuuronderzoek en een meta-analyse van alle beschikbare bevolkingsonderzoeken. Met deze studie toonden we aan dat coronaire hartziekten, over het algemeen, geassocieerd zijn met een 45 procent grotere kans op het ontwikkelen van een cognitieve stoornis of dementie. Soortgelijke resultaten vonden we voor, op zichzelf staande, meta-analyses van de meest voorkomende coronaire hartziekten; myocard infarct en angina pectoris.

In **hoofdstuk drie** beschrijven we de eerste populatiestudie naar cognitieve achteruitgang na een eerste (incidente) cardiovasculaire gebeurtenis. We bekeken de temporele relatie tussen prevalentie en incidentie cardiovasculaire ziekte en cognitief functioneren in de MAastricht Aging Study (MAAS). Zowel patiënten met prevalentie als patiënten met incidentie cardiovasculaire ziekte lieten een snellere cognitieve achteruitgang zien op het gebied van het geheugen en de verwerkingsnelheid van informatie dan de groep zonder cardiovasculaire ziekte. Voor de patiënten met incidentie CVD werd dit pas na CVD onset duidelijk, dat wil zeggen zes tot 12 jaar na baseline. Dit ondersteunt zowel het 'hart-brein connectie' concept maar suggereert ook dat er een tijdsperiode is na het doormaken van een cardiovasculaire gebeurtenis waarin het afremmen van cognitieve achteruitgang mogelijk is. Tevens lijkt dit te suggereren dat preventie van cardiovasculaire ziekten kan leiden tot een afname in het risico op dementie.

Cognitieve achteruitgang is een vaak beschreven gevolg van een beroerte. Eerdere studies vergeleken mensen die een beroerte doormaakten met gezonde mensen om de voorspellende waarde van cognitieve functies te onderzoeken. In **hoofdstuk vier** onderzochten wij de prognostische waarde van cognitief functioneren uitsluitend binnen een groep mensen die een beroerte overleefden. Deze mensen waren deelnemers aan de Sydney Stroke Study. We gingen na of het cognitief functioneren van deze mensen voorspellend was voor hun risico op een slechte prognose in de zin van overlijden of het ontwikkelen van dementie. We vonden dat executief functioneren, de verwerkingssnelheid van informatie en verbale vlotheid geassocieerd waren met overlijden. Geen enkel cognitief domein kon geassocieerd worden met dementie.

Cognitieve beperkingen na beroerte worden vaker gerelateerd aan de beroerte zelf en de locatie in de hersenen waar deze beroerte schade heeft veroorzaakt. Toch worden er ook vaak andere soorten van hersenschade op beeldvorming bij mensen die een beroerte doormaakten, gezien. Het is onduidelijk welke van deze verschillende markers een voorspeller zou kunnen zijn van cognitief functioneren na beroerte en wat het individuele effect van een dergelijke marker is naast het effect van de beroerte zelf. Om deze en gerelateerde vragen te kunnen beantwoorden, zetten we de zogenaamde Cognitie en Affect na beroerte (Stroke): een Prospectieve Evaluatie van Risicofactoren (CASPER) studie op. **Hoofdstuk vijf** beschrijft de rationale en het ontwerp van deze studie. CASPER is een prospectieve follow-up studie van een beroertecohort die het mogelijk maakt voorspellers en biomarkers van vasculaire cognitieve stoornis, depressie en apathie na beroerte te bestuderen. We includeerden 250 patiënten die een ischemische of hemorragische beroerte doormaakten. De baseline meting vond drie maanden na beroerte plaats en bestond uit een bloedafname, het vastleggen van sociaal demografische informatie, een neuropsychologisch onderzoek en een neuropsychiatrisch interview, een semi-structureerd interview met een naaste en een 3-Tesla brein MRI. Het neuropsychologisch onderzoek, het neuropsychiatrisch interview en het interview met een naaste werd herhaald tijdens de zes-maanden en 12-maanden follow-up metingen. Een drie-jarige follow-up is later toegevoegd aan deze studie en vindt momenteel plaats.

In **hoofdstuk zes** hebben we op basis van de uit het CASPER onderzoek verkregen data zowel de individuele als de relatieve bijdrage van volumes van de laesie van de beroerte, witte stof hyperintensiteiten (WMH) en globale atrofie (GA) van het brein op het cognitief functioneren op baseline (drie maanden na beroerte) en veranderingen in cognitie 15 maanden na beroerte (12 maanden na de baseline meting) onderzocht. Hier vonden we

dat mensen met een groter volume aan WMH en GA slechter presteerden op taken die de verwerkingssnelheid van informatie en executief functioneren meten. Deze bevindingen laten zien dat zowel WMH als GA, onafhankelijk van het volume van de laesie van de beroerte, voorspellers zijn van cognitief functioneren na beroerte.

In het algemeen hebben de studies in dit proefschrift een beter inzicht gegeven in het beloop en tijdsbestek van zowel cognitieve veranderingen in bestaande en nieuwe gevallen van cardiovasculaire ziekten als van mogelijke voorspellers in cognitie en beeldvorming van cognitieve achteruitgang na beroerte. Tevens laten zij het belang zien van een groter bewustzijn van de hart-brein connectie onder professionals en de algemene populatie waardoor het risico op en ontwikkeling van dementie van cerebro- en cardiovasculaire oorsprong mogelijk verlaagd en voorkomen kan worden.

KNOWLEDGE VALORISATION

The general aim of this thesis was to gain more insight into predictors of cognitive functioning or cognitive impairment in individuals with manifest cardiovascular disease (CVD) and stroke. Thereby gaining a better understanding of the concept of the 'heart-brain connection' with regard to cognitive functioning. This valorisation paragraph describes the societal relevance, the possible economic implications, and the potential implementation opportunities of the results described in this thesis.

Mr. X is a 58-year-old married man who has been living with hypertension for eleven years now. His hypertension has been under control by medication use. Last year he experienced a minor heart attack. This experience shocked him and made him change his lifestyle for a while. He stopped smoking, tried to eat healthy, and went for a walk everyday. As time passed by, the fear of dying diminished and the desire to smoke became stronger. Today, Mr. X is smoking again, is eating fatty foods more often because they just taste good, and going out for a walk has become a burden. Recently, he noticed that he is no longer interested in reading the newspaper because he is unable to maintain his attention. Also at work he has difficulty concentrating. His wife is worried about him and wonders what is causing these changes. Also, she wishes he would live his life more healthy but does not want to withhold him from the things he enjoys in life.

This case describes a man who is experiencing cognitive problems after a minor heart attack and longstanding hypertension. His wife worries and wonders whether a change of lifestyle can help. Should Mrs. X tell the cardiologist or wait until she sees their general practitioner?

Societal relevance

Stroke and heart disease are major leading causes of death and disability in the elderly all over the world. Coronary heart disease is number one on the list of diseases with the highest disease burden (expressed in 'disability adjusted life years' which is the sum of lost life years and years of living with loss in quality of life), followed by stroke. In the Netherlands, around 1.4 million individuals are suffering from CVD, including stroke. Consequences of a cardiovascular event vary and can be of, not only physical, but also psychological, emotional, and/or cognitive origin. Many individuals are confronted with these cognitive difficulties. Frequently, these worsen over time and lead to significant cognitive impairment, or even develop into dementia in the long run. These cognitive consequences have a great influence on basic and instrumental activities of daily living, and on occupational, leisurely, and social aspects of people's daily lives.

In 2015, costs directly associated with cardiovascular care were 11.6 billion euro, which was 13.6 percent of the total Dutch healthcare costs (85.1 billion euro). Costs exist of expenses made by hospital visits, medication usage, and medical interventions. Costs of dementia care were 6.6 billion euros in 2015, which was 7.7 percent of the total Dutch healthcare costs. The number of individuals living with CVD or dementia is increasing with our aging society, thereby posing an enormous emotional burden on individuals and their families and an economic burden on our healthcare systems.

Therefore, there is a growing need to understand how CVD, including stroke is linked to cognitive impairment and dementia. In the general population there is little awareness of this ‘heart-brain connection’, its risk factors, and the risk for cognitive impairment and dementia. Therefore, it is also important to inform the public about this link. More awareness among patients and health care professionals may lead to earlier detection of cognitive deficits and (neuro)psychological symptoms. Indeed, our findings suggest that efforts at preventing CVD can have a significant public health implication by possible prevention of cognitive impairment and dementia.

Target audience

Findings presented in this thesis are relevant for individuals living with CVD and survivors of cardiovascular events, for health care professionals, and for researchers.

The most important target group is the one of the individuals living with CVD. They have to become more aware of how CVD affects cognition and how a healthy lifestyle influences their chances of developing dementia in the long run. They can possibly prevent cognitive impairment and dementia by adopting a healthy lifestyle. More “What’s good for your heart is good for your brain” public awareness campaigns are needed and individuals with CVD should be encouraged to share cognitive complaints or worries with their cardiologist or general practitioner. These individuals will benefit from early detection, identification, and psycho-education by becoming more aware of the effect of lifestyle on brain health. Policy makers are another important target audience as they are the ones influencing public campaigns on cognition in CVD.

Obviously, the health care professionals, including neurologists, cardiologists, geriatricians, rehabilitation physicians, general practitioners, psychiatrists, (neuro)psychologists, and practice nurses play a very important role in this and are therefore another important target audience of the results of this thesis. These professionals are involved in the treatment

and after-care of the individuals who suffer from CVD or survived a cardiovascular event. It is important for the health care professional to be aware of the connection between life style, CVD, and cognitive impairment. Those who are aware of cognitive symptoms and/or complaints are more likely to ask their patient about these possible changes and identify patients at risk of cognitive decline, and may better recognize the cognitive symptoms and complaints. They then can give psycho-education, which plays an important role in care provided. Moreover, systematic CVD screening in offices outside the cardiologist's and a checklist for cognitive and emotional consequences (e.g. CLCE-24) in offices outside the (neuro)psychologist's could possibly be tackling this.

Findings in this thesis underline the importance of a more integrated multi-disciplinary approach and handling. Promising in this regard is the development of heart-brain clinics and specialized stroke after-care clinics, which have specific expertise regarding these symptoms. These clinics provide multidisciplinary evaluations to individuals who have had neuro(psycho)logical symptoms that may be attributable to a cardiovascular or cardiac aetiology. Such clinics can specifically look into those cognitive symptoms that are not easily recognized or not mentioned by the patient during anamnesis.

In addition, clinical researchers can use our findings for their own research. By showing the association between coronary heart disease and an increased risk of cognitive impairment or dementia, more mechanistic studies can focus on the underlying biological pathways and shared risks that link CHD and risk of cognitive impairment and dementia. By showing the temporal relationship between prevalent and incident CVD and cognitive functioning, we highlighted the important effect of CVD exposure duration. Other researchers can take this a step further by looking at the influence of medication usage during this exposure time period or by looking into the different CVDs separately. We showed that there is a window in time for prevention. Other researchers can use this information when selecting a target group of patients to study the effectiveness of a preventative measure, e.g. physical exercise or healthy diet. The results also underscore the importance of evaluating several cognitive domains as opposed to less precise measures such as clinical diagnoses or a global cognitive screening test. Future studies can then aid the development of more specific cognitive treatment programs. Our results regarding the relationship between stroke event-related and additional ageing-related brain damage and cognition might also be of interest to other traumatic brain injury patient populations.

Innovation and Products

We expand the existing knowledge of the heart-brain connection by showing the associations between myocardial infarction and angina pectoris and cognition and the temporal relationship of cognitive functioning with incident CVD. We were the first to look at incident CVD whereas former studies mostly look at prevalent CVD.

The main product of our findings regarding CVD and cognition is a deepening of our knowledge on the heart-brain connection. The new insights can be used in the clinical context of prevention and intervention. The findings underline the importance of a more intensive management of CVD risk factors because universal as well as selected prevention and control of already present risk factors can also prevent cognitive impairment and dementia. In addition, the importance of screening for cognitive changes and timely identification of people who are prone to develop cognitive impairment is underlined.

Another product resulting from this thesis is the large amount of data that was collected for the CASPER study including volumetric and visual imaging measures, elaborate neuropsychological and neuropsychiatric assessment, and other biomarker data (inflammatory markers and epigenetics) from 250 individuals who suffered a stroke. These data can and will be used for future studies and are part of the STROKOG consortium (<http://cheba.unsw.edu.au/group/strokog>), which has built a database with more than 12,000 stroke patients from across the world. Harmonization of these data will give way to more research, with currently ongoing projects focusing on a better understanding of the longitudinal trajectory of cognitive impairment after stroke, differences in prevalence of cognitive consequences, and risk and protective factors between different countries and ethnic groups. Also, participants of the CASPER study are approached for participation in the three-year follow-up, for which currently data is being collected.

Implementation

Findings of neuropsychological assessment and use of imaging markers resulting from this thesis are immediately applicable for clinicians and can be translated into clinical practice through incorporation in clinical guidelines. Raised awareness of, and psycho-education, on the connection between cardiovascular events, cognitive impairment, and possibly dementia may improve early recognition of symptoms. Cognitive functioning should be included in the checklist of all health care professionals who are treating these individuals. Vice versa, information on vascular risk factors should be gathered by the neuropsychologists, psychiatrist, or other psychological health care professionals at the

general practitioner's office. This could benefit identification of individuals who are at risk for cognitive impairment and could make earlier intervention or treatment possible.

Dissemination

New insights in this thesis have been disseminated in the academic community through publications in leading international scientific journals and presentations at international conferences. Individuals who participated in our studies were updated about the results and progress of the study through newsletters.

How could Mr. X have benefited from the results of this thesis?

Mr. X and his wife meet with the cardiologist for a yearly control visit. The cardiologist is aware of the influence CVD can have on cognition. When asking how Mr. X is feeling since his last visit, he asks specifically whether he has noticed any changes in his thinking processes, whether he noticed anything different in his concentration and attention, how things are going at work and whether there are changes in his leisure and social activities. Mr. X tells the cardiologist that he does not see the relevance of these questions. The cardiologist explains to the married couple how heart and brain are connected, and how research has shown the link between heart disease and cognitive changes. Mr. X realizes that the subtle changes in concentration and attention he noticed might be important to mention. The cardiologist explains how a healthy lifestyle influences CVD and that this is not just good for the heart, but also for the brain. It may even prevent cognitive impairment and dementia. Mr. X is quite concerned and realizes there is actually something he can do to reduce the chances of this happening to him. Mrs. X is relieved and feels empowered to consequently change their lifestyles by cooking healthy food, encouraging her husband to get more physical exercise, and supporting him to quite smoking again.

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Willemijn, in je boekje las ik dat we elkaar al 10 jaar kennen. Nu alweer 12. Bah, de tijd gaat te snel. Wat hou ik van je rustige stem, wat kan ik met je lachen en wat vond ik het fijn dat we samen herinneringen konden delen.

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Whitney, de 'Amerikaanse' freeze-style. "Wehheee!", ik hoor het je nog zeggen en ik weet zeker dat je 't me nog een paar keer in mijn oor gaat schreeuwen als ik twijfel of onzeker ben. Ik heb je gemist toen je in Amerika was. Je begreep het zonder dat we er woorden aan gaven en dat voelde ik. Dankjewel.

Isabelle, mijn 'Allerhande' zwemmaatje, alles kan, niks is te gek, je bent er altijd voor in om een oplossing te bedenken voor welk probleem dan ook. Wat moeten veel mensen dat in jou waarderen. We kunnen alles delen, wat is dat mooi. Die tabel is een supergoed idee, hopelijk heb jij 'm gemaakt!

Lotte, daar zat je opeens naast me met je 'Amerikaanse' accent. Voordat we goed en wel realiseerden wat het leven ons gebracht had, waren we met elkaar verbonden. Beetje te toevallig leek het. En nog steeds. Ik ben zo dankbaar dat ik je heb leren kennen, voor de babyshower die jij organiseerde waardoor ik misschien wel twee uur lang hilde van geluk, voor de rondjes die we samen liepen, voor je arm om me heen, voor onze overeenkomsten en onze verschillen, voor de altijd gemeente knuffel, onze dromen, je verrassingen. Ik hoop dat we net zolang als dat het nu voelt dat we elkaar kennen, er voor elkaar kunnen zijn. Voor altijd dus.

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Roos, jouw kaart hangt nog steeds in onze kast en steunt me iedere dag weer. De glazen vullen zich lang niet zo vaak als voorheen. Ik mis onze kookavondjes/nachtjes.

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dat ik jou mijn vriendin mag noemen. Ik hoop dat we nog vele jaren van elkaar mogen genieten. Bedankt voor alles.

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op jullie is. Daar is veel tijd, energie, flexibiliteit en liefde van jullie kant in gaan zitten. Dank jullie wel daarvoor. Phakeme, je staat altijd voor me klaar, niks is je te gek, ik hoef je maar te bellen of appen en je bent er. Sorry dat ik af en toe tussendoor ook nog eens zeur. Lieve ouders en broer, weet dat ik er ook altijd voor jullie zal zijn.

Mijn liefste mama en papa. Jullie zijn er niet meer. Halverwege mijn promotietraject, begon de ellende. Tevergeefs hebben we alles geprobeerd om een ziekte die om zich heen slaat, af te remmen, te stoppen, te laten verdwijnen, niet waar te laten zijn; toch moest jij, mam, gaan. Daarna probeerden we papa te steunen, zijn eenzaamheid weg te nemen; maar ook jij, pap, ging. Geen kind meer zijn en jullie iedere dag moeten missen terwijl jullie je kleindochter die steeds groter wordt, niet hebben mogen leren kennen, dat zijn de moeilijkste dingen die ik de afgelopen jaren heb moeten leren doorstaan. Meerdere keren heb ik dit werk willen opgeven. Ik vond het verschrikkelijk moeilijk om iedere keer opnieuw de draad weer op te pakken en mezelf bij elkaar te rapen. Toch ligt hier nu een boekje. Ik sluit hiermee deze moeilijke periode af. Geen dag gaat voorbij zonder jullie in mijn gedachten. Waren jullie nog maar hier. Niet eens om op de eerste rij te zitten bij de verdediging zometeen, maar om samen bij ons thuis aan de keukentafel koffie te drinken en te zien hoe jullie met jullie kleindochter spelen. Kon ik jullie drietjes maar tegen elkaar horen praten. Dat is mijn grootste verdriet nu. Ik hoop dat jullie tevreden zijn als jullie terug en naar beneden kijken. Ik hou ontzettend veel van jullie.

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CURRICULUM VITAE

Syenna Schievink was born on 8 June 1983 in Geleen, the Netherlands. After secondary school she obtained her Bachelor in International Communications, specializing in Japanese language and culture at Hogeschool Zuyd in Maastricht, the Netherlands in 2004. During this study Syenna went to Kyoto University of Foreign Studies (KUFS) in Japan for six months in 2003. After her graduation from Hogeschool Zuyd, she studied at KUFS for another six months and obtained her Level 2 certificate of the Japanese Language Proficiency Test organized by the Japan Foundation. After returning to the Netherlands she started working as an interpreter, translator, and medical assistant at a Japanese diagnostic center for Japanese companies in the Benelux.

In 2009, Syenna obtained her BSc in Biological Psychology at Maastricht University. As part of this bachelor program she entered an exchange program at the University of Victoria, Canada. Here, she volunteered in animal research at prof. dr. Brian Christie's lab that was investigating the effect of exercise on hippocampal neurogenesis and behavioural functioning in fetal alcohol syndrome. In 2009, she started the two-year research master program in Neuropsychology at Maastricht University. Syenna chose to perform both a research as well as a clinical internship during the last year of this program. She spent eight months at the department of Neurosurgery of Maastricht University under supervision of prof. dr. Yasin Temel and dr. Sonny Tan. Here, she worked on research investigating mechanisms underlying depression after deep brain stimulation in Parkinson's disease. This internship resulted in an authorship on a scientific publication. A six-month clinical internship followed at the department of Medical Psychology of the Maastricht University Medical Center (MUMC+), where she acquired her psychodiagnostics registration (BAPD).

After graduation in 2012, Syenna started working on a PhD project at the department of Psychiatry & Neuropsychology of Maastricht University, in collaboration with the department of Neurology of MUMC+, under supervision of prof. dr. Frans Verhey, prof. dr. Robert van Oostenbrugge, and dr. Sebastian Köhler. During her PhD project she set up the Cognition and Affect after Stroke: a Prospective Evaluation of Risks (CASPER) Study, performed several teaching activities, and presented her work at national meetings and international conferences. Syenna currently works as a general practice-based mental health care professional at ZIO in Maastricht.

Syenna Schievink werd op 8 juni 1983 geboren te Geleen. Na de middelbare school heeft ze in 2004 aan de Hogeschool Zuyd in Maastricht haar bachelor in Internationale Communicatie behaald met als specialisatie de Japanse taal en cultuur. Tijdens deze opleiding heeft ze in 2003 een half jaar aan de Kyoto University of Foreign Studies (KUFS) gestudeerd. Na het behalen van haar diploma studeerde ze nog zes maanden aan KUFS en haalde ze haar Level 2 certificaat van de Japanese Language Proficiency Test georganiseerd door de Japan Foundation. Na terugkomst in Nederland is ze gaan werken als tolk, vertaler en medisch assistent bij een Japans diagnostisch centrum voor Japanse bedrijven in de Benelux.

In 2009 ontving ze haar BSc in Biologische Psychologie aan de Universiteit Maastricht. Tijdens deze opleiding studeerde ze een half jaar aan de University of Victoria, Canada. Hier werkte ze als vrijwilliger in het lab van prof. dr. Brian Christie mee aan dieronderzoek naar het effect van beweging op hippocampale neurogenese in het foetaal alcoholyndroom. In 2009 startte ze aan de tweejarige onderzoeksmaster Neuropsychologie aan de Universiteit Maastricht. Syenna koos ervoor om zowel een onderzoeks- als klinische stage te lopen in het laatste jaar van deze master. Ze liep acht maanden stage bij de afdeling Neurochirurgie van de Universiteit Maastricht onder begeleiding van prof. dr. Yasin Temel en dr. Sonny Tan. Hier werkte ze mee aan onderzoek naar mechanismes onderliggend aan depressie na diepe hersenstimulatie in de ziekte van Parkinson. Deze stage resulteerde in een auteurschap op een wetenschappelijke publicatie. Hierna heeft Syenna zes maanden klinische stage gelopen bij de afdeling Medische Psychologie van het Maastricht Universitair Medisch Centrum (MUMC+) waar ze haar Basisaantekening Psychodiagnostiek (BAPD) behaalde.

Na het behalen van haar MSc diploma in 2012 is Syenna onder leiding van prof. dr. Frans Verhey, prof. dr. Robert van Oostenbrugge en dr. Sebastian Köhler begonnen aan haar werk als promovendus op de afdeling Psychiatrie en Neuropsychologie van de Universiteit Maastricht in samenwerking met de afdeling Neurologie van het MUMC+. Tijdens haar promotieproject heeft Syenna de Cognitie en Affect na Stroke (beroerte): een Prospectieve Evaluatie van Risicofactoren (CASPER) studie opgezet, voerde ze verschillende onderwijsactiviteiten uit en presenteerde ze haar werk op nationale bijeenkomsten en internationale congressen. Syenna werkt momenteel als praktijkondersteuner geestelijke gezondheidszorg bij ZIO in Maastricht.

LIST OF PUBLICATIONS

International journals

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National journal

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Submitted

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Thesis defences from MHeNs - School for Mental Health and Neuroscience

2013

Rob Havermans: **Bipolar disorder in daily life; Mood and cortisol responses to naturally occurring events.** Supervisor: Prof.dr. M. de Vries; Co-Supervisor: Dr. N. Nicolson.

Véronique Moers-Hornikx: **Deep brain stimulation and the cerebellum.** Supervisors: Prof.dr. J. Vles / Prof.dr. Y. Temel; Co-Supervisor: Dr. G. Hoogland.

Nicole Veldhorst-Janssen: **Intranasal delivery of rapid acting drugs.** Supervisors: Prof.dr. M. Marcus / Prof.dr. C. Neef; Co-Supervisor: Dr. P.H. van der Kuy.

Stéphanie Knippenberg: **Vitamin D and Multiple Sclerosis: immunological and clinical outcome.** Supervisor: Prof.dr. J. Cohen-Tervaert; Co-Supervisors: Dr. J. Damoiseaux / Dr. Y. Bols.

Erik D. Gommer: **Dynamic Cerebral Autoregulation: from methodology towards clinical application.** Supervisors: Prof.dr. W.H. Mess / Prof.dr. R.B. Panerai, UK; Co-Supervisor: Dr.ir. J.P.H. Reulen.

Olga A.H. Reneerkens: **Can PDE inhibition improve cognition ? Translational insights.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. J. Prickaerts.

Lyzel S. Elias-Sonnenschein: **Clinical and biomarker correlates of genetic risk factors for Alzheimer's disease.** Supervisor: Prof.dr. F.R.J. Verhey; Co-Supervisor: Dr. P.J. Visser.

Diego F. Mastroeni: **Epigenetic Dysregulation and the Pathophysiology of of Alzheimer's Disease.** Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. P.D. Coleman, Sun City, Arizona; Co-Supervisors: Dr. B.P.F. Rutten / Dr. D.L.A. van den Hove.

Leonidas Chouliaras: **Epigenetic Regulation in Aging and Alzheimer's disease: A translational perspective.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. B.P.F. Rutten / Dr. D.L.A. van den Hove.

Liesbeth Knaepen: **Perinatal events and altered pain sensitivity in later life.** Supervisors: Prof.dr. E.A.J. Joosten / Prof.dr. D. Tibboel, EUR; Co-Supervisor: Dr. J. Patijn.

Marisela Martinez-Claros: **Hippocampal plasticity and corticosterone: From dendrites to behaviour.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. J.L. Pawluski / Dr. J. Prickaerts.

Marcus D. Lancé: **A circle of improvement in bleeding management: from laboratory to clinic and back.** Supervisors: Prof.dr. M.A.E. Marcu / Prof.dr. J.W.M. Heemskerk; Co-Supervisor: Dr. Y.M.C. Henskens.

Hilde Braakman: **Imaging the brain; neuronal correlates of cognitive impairment in children with frontal lobe epilepsy.** Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr. J.S.H. Vles; Co-Supervisors: Dr.ir. W.H. Backes / Dr. P.A.M. Hofman.

Willem H. van Zwam: **Aneurysmal subarachnoid hemorrhage: imaging strategies and cost-effectiveness aspects in diagnostic work-up and post-therapeutic follow-up.** Supervisors: Prof.dr. J.T. Wilminck / Prof.dr. J.E. Wildberger; Co-Supervisor: Dr. P.A.M. Hofman.

- Klara De Cort: **The Pathogenesis of Panic Disorder**. Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. E.J.L. Griez; Co-Supervisors: Dr. K.R.J. Schruers / Dr. I. Van Diest, Leuven.
- Kim van Wijck: **Mind the Gap; experimental studies on splanchnic hyperfusion and gastrointestinal integrity loss in man**. Supervisors: Prof.dr. W.A. Buurman / Prof.dr. C.H.C. Dejong; Co-Supervisor: Dr. K. Lenaerts.
- Yvette Roke: **Antipsychotic-induced hyperprolactinemia in children and adolescents with mainly autism spectrum disorders. Prevalence, symptoms, clinical consequences and genetic risk factors**. Supervisors: Prof.dr. P.N. van Harten / Prof.dr. J.K. Buitelaar (RUN); Co-Supervisor: Dr. A. Boot (UMCG).
- Fleur Goezinne: **Retinal detachment surgery: pre and postoperative prognostic factors**. Supervisors: Prof.dr. F. Hendrikse / Prof.dr. C.A.B. Webers; Co-Supervisor: Dr. E.C. La Heij (Amsterdam).
- Ralph L.J.G. Maassen: **The Merits of Videolaryngoscopy during Glottic Visualisation for Endotracheal Intubation**. Supervisors: Prof.dr. M. Marcus / Prof.dr. A. van Zundert (University of Queensland).
- Maria J. de Sousa Guerreiro: **The role of sensory modality in age-related distraction**. Supervisor: Prof. dr. C.M. van Heugten; Co-Supervisor: Dr. P.W.M. van Gerven.
- Ine Rayen: **Effects of developmental fluoxetine exposure on neurobehavioral outcomes**. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. J.L. Pawlusi / Dr. T.D. Charlier (Ohio University, USA).
- Nynke M.G. Bodde: **Psychogenic non-epileptic seizures; a separate disorder or part of a continuum?** Supervisors: Prof.dr. R. van Oostenbrugge / Prof.dr. K. Vonck (UZ Gent); Co-Supervisors: Dr. R. Lazeron / Dr. A. de Louw (Epilepsiecentrum Kempenhaeghe, Heeze).
- Alejandro M. Gomez: **Novel strategies for making myasthenia less gravis: targeting plasma cells and the neuromuscular junction**. Supervisor: Prof.dr. M.H. De Baets; Co-Supervisors: Dr. M. Losen / Dr. P. Martinez-Martinez.
- Mohammad S. Rahnama'i: **Prostaglandins and Phosphodiesterases in the Urinary Bladder Wall**. Supervisors: Prof.dr. Ph. Van Kerrebroeck / Prof.dr. S. de Wachter (Universiteit Antwerpen); Co-Supervisor: Dr. G. van Koevinge.
- Mariken B. de Koning: **Studying biomarkers in populations at genetic and clinical high risk for psychosis**. Supervisors: Prof.dr. T. Amelsvoort / Prof.dr. J. Booij (AMC).
- Fabien Boule: **Epigenetic regulation of BDNF/TrkB signaling in the pathophysiology and treatment of mood disorders**. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. L. Lanfumey (Universiteit Parijs); Co-Supervisors: Dr. D. van den Hove / Dr. G. Kenis.

2014

- Iris Nowak-Maes: **Tinnitus; assessment of quality of life & cost-effectiveness**. Supervisors: Prof.dr. M. Peters / Prof.dr. B. Kremer; Co-Supervisors: Dr. M. Joore / Dr. L. Anteunis.
- Marjolein Huijts: **Cognitive function in patients with cerebral small vessel disease**. Supervisor: Prof. dr. R.J. van Oostenbrugge; Co-Supervisors: Dr. A.A. Duits / Dr. J. Staals.

Markus Gantert: **Fetal inflammatory injury as origin of long term disease: Lessons from animal models.** Supervisors: Prof.dr. B. Kramer / Prof.dr. L. Zimmermann; Co-Supervisor: Dr. A. Gavilanes.

Elke Kuypers: **Fetal development after antenatal exposures: Chorioamnionitis and maternal glucocorticoids.** Supervisors: Prof.dr. B.W. Kramer / Prof.dr. H.W. Steinbusch / Prof.dr. Suhas G. Kallapur (University of Cincinnati, Ohio, USA).

Pieter Kubben: **Ultra low-field strength intraoperative MRI for Glioblastoma Surgery.** Supervisor: Prof.dr. J.J. van Overbeek; Co-Supervisor: Dr. H. van Santbrink.

Laura Baijens: **Surface electrical stimulation of the neck for oropharyngeal dysphagia in Parkinson's disease: therapeutic aspects and reliability of measurement.** Supervisor: Prof. dr. B. Kremer; Co-Supervisor: Dr. R. Speyer, Townsville.

Janneke Hoeijmakers: **Small fiber neuropathy and sodium channels; a paradigm shift.** Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-Supervisors: Dr. C.G. Faber / Dr. I.S.J. Merkies.

Stephanie Vos: **The Role of biomarkers in preclinical and prodromal Alzheimer's disease.** Supervisor: Prof.dr. F.R. Verhey; Co-Supervisor: Dr. P.J. Visser.

Muriël Doors: **The Value of Optical Coherence Tomography in Anterior Segment Surgery.** Supervisors: Prof.dr. R.M. Nuijts / Prof.dr. C.A. Webers; Co-Supervisor: Dr. T.T.J.M. Berendschot.

Anneke Maas: **Sleep problems in individuals with genetic disorders associated with intellectual disability.** Supervisors: Prof.dr. I. Curfs / Prof.dr. R. Didden.

Sebastiaan van Gorp: **Translational research on spinal cord injury and cell-based therapies; a focus on pain and sensorimotor disturbances.** Supervisors: Prof.dr. B. Joosten / Prof.dr. M. van Kleef; Co-Supervisors: Dr. J. Patijn / Dr. R. Deumens, KU Leuven.

Andrea Sannia: **High risk newborns and brain biochemical monitoring.** Supervisor: Prof.dr. J.S.H. Vles; Co-Supervisors: Dr. D. Gazzolo, Alessandria, Italy / Dr. A.W.D. Gavilanes.

Julie A.D.A. Dela Cruz: **Dopamine mechanisms in learning and memory: Evidence from rodent studies.** Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. R.J. Bodnar, New York; Co-Supervisor: Dr. B.P.F. Rutten.

René Besseling: **Brain wiring and neuronal dynamics; advances in MR imaging of focal epilepsy.** Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr.ir. W.H. Backes; Co-Supervisor: dr. J.F.A. Jansen.

Maria Quint-Fens: **Long-term care after stroke; development and evaluation of a long-term intervention in primary care.** Supervisors: Prof.dr. J.F.M. Metsemakers / Prof.dr. C.M. van Heugten / Prof.dr. M. Limburg, Almere; Co-Supervisor: dr. G.H.M.I. Beusmans.

Veronique Moulart: **Life after survival of a cardiac arrest; the heart of the matter.** Supervisors: Prof. dr. J.A. Verbunt / Prof.dr. C.M. van Heugten / Prof.dr. D.T. Wade, Oxford, UK.

Feikje Smeets: **The hallucinatory-delusional state: a crucial connection in the psychosis symptom network.** Supervisor: Prof.dr. J. van Os; Co-Supervisor: Dr. T. Lataster.

Lies Clerx: **Alzheimer's disease through the MR-eye; novel diagnostic markers and the road to clinical implementation".** Supervisor: Prof.dr. F. Verhey; Co-Supervisors: Dr. P.J. Visser / P. Aalten.

- Sonny Tan: **The subthalamic nucleus in Parkinson's disease.** Supervisors: Prof.dr. Y. Temel / Prof.dr. H.W.M. Steinbusch / Prof.dr. T. Sharp, Oxford, UK / Prof.dr. V. Visser-Vandewalle, Köln.
- Koen van Boxem: **The use of pulsed radiofrequency in the management of chronic lumbosacral radicular pain.** Supervisors: Prof.dr. M. van Kleef / Prof.dr. E.A.J. Joosten; Co-Supervisor: Assoc. Prof.dr. J. van Zundert.
- Jérôme Waterval: **Hyperostosis cranialis interna.** Supervisors: Prof.dr. J.J. Manni / Prof.dr. R.J. Stokroos.
- Sylvie Kolfschoten-van der Kruijs: **Psychogenic non-epileptic seizures; the identification of neurophysiological correlates.** Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr. K.E.J. Vonck, Universiteit Gent; Co-Supervisors: Dr. J.F.A. Jansen / Dr. R.H.C. Lazeron, Kempenhaeghe.
- Wouter Pluijms: **Spinal cord stimulation and pain relief in painful diabetic: polyneuropathy, a translational approach.** Supervisors: Prof.dr. M. van Kleef / Prof.dr. E.A. Joosten; Co-supervisor: Dr. C.G. Faber.
- Ron Handels: **Health technology assessment of diagnostic strategies for Alzheimer's disease.** Supervisors: Prof.dr. F.R.J. Verhey / Prof.dr. J.L. Severens (EUR); Co-Supervisor: Dr. M.A. Joore / Dr. C.A.G. Wolfs.
- Evelyn Peelen: **Regulatory T cells in the pathogenesis of Multiple Sclerosis: potential targets for vitamin D therapy.** Supervisors: Prof.dr. R.M.M. Hupperts / Prof.dr. J.W. Cohen Tervaert; Co-Supervisor: Dr. J.G.M.C. Damoiseaux / Dr. M.M.G.L. Thewissen, Diepenbeek.
- Reint Jellema: **Cell-based therapy for hypoxic-ischemic injury in the preterm brain.** Supervisors: Prof.dr. B.W.W. Kramer / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. W.T.V. Germeraad / Dr. P. Andriessen, Veldhoven.
- Maria Wertli: **Prognosis of Chronic Clinical Pain Conditions: The Example of Complex Regional Pain Syndrome 1 and Low Back Pain.** Supervisors: Prof.dr. M. van Kleef; Co-Supervisor: Dr. F. Brunner, Zürich / Dr. R. Perez, VUmc.
- Dagmar Zeef: **An experimental model of Huntington's disease: Validation & Stimulation.** Supervisors: Prof.dr. Y. Temel / Prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. A. Jahanshahi.
- Jeroen Decoster: **Breaking Down Schizophrenia into phenes, genes and environment.** Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. M. De Hert, KU Leuven; Co-Supervisor: Dr. R. van Winkel.
- Eaja Anindya Sekhar Mukherjee: **Fetal Alcohol Spectrum Disorders: exploring prevention and management.** Supervisor: Prof.dr. L.M.G. Curfs; Co-Supervisor: Prof. S. Hollins, St. George's University of London, UK.
- Catherine van Zelst: **Inside out; On stereotype awareness, childhood trauma and stigma in psychosis.** Supervisors: Prof.dr. Ph. Delespaul / Prof.dr. J. van Os.
- Ibrahim Tolga Binbay: **Extended Psychosis Phenotype in the Wider Social Environment.** Supervisor: Prof.dr. J. van Os; Co-Supervisor: Dr. M. Drukker.
- Frank Van Dael: **OCD matters in psychosis.** Supervisors: Prof.dr. J. van Os / Prof.dr. I. Myin-Germeys.
- Pamela Kleikers: **NOXious oxidative stress: from head toe too and back.** Supervisors: Prof.dr. H.H.H.W. Schmidt / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. B. Janssen.

José Luis Gerardo Nava: **In vitro assay systems in the development of therapeutic interventions strategies for neuroprotection and repair.** Supervisors: Prof.dr.med. J. Weis / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. G.A. Brook, RWTH Aachen.

Eva Bollen: **Cyclic nucleotide signaling and plasticity.** Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. R. D'Hooge, KU Leuven; Co-Supervisor: Dr. J. Prickaerts.

2015

Jessica A. Hartmann: **A good laugh and a long sleep; Insights from prospective and ambulatory assessments about the importance of positive affect and sleep in mental health.** Supervisor: Prof.dr. J. van Os; Co-Supervisors: C.J.P. Simons / Dr. M. Wichers.

Bart Ament: **Frailty in old age; conceptualization and care innovations.** Supervisors: Prof.dr. G.I.J.M. Kempen / Prof.dr. F.R.J. Verhey; Co-Supervisor: Dr. M.E. de Vugt.

Mayke Janssens: **Exploring course and outcome across the psychosis-continuum.** Supervisor: Prof.dr. I. Myin-Germeyns; Co-Supervisor: Dr. T. Lataster.

Dennis M.J. Hernau: **Dopayours is not dopamine: genetic, environmental and pathological variations in dopaminergic stress processing.** Supervisor: Prof.dr. I. Myin Germeyns; Co-Supervisors: Prof.dr. F.M. Mottaghy / Dr. D. Collip.

Ingrid M.H. Brands: **The adaptation process after acquired brain injury Pieces of the puzzle.** Supervisors: Prof.dr. C.M. van Heugten / Prof.dr. D.T. Wade, Oxford UK; Co-Supervisors: Dr. S.Z. Stapert / Dr. S. Köhler.

Francesco Riso: **Urinary and salivary S100B monitoring in high risk infants.** Supervisor: Prof.dr. J.S.H. Vles; Co-Supervisors: Dr. D. Gazzolo, Genoa, Italy / Dr. A.W.D. Gavilanes.

Alessandro Borghesi: **Stem and Progenitor Cells in Preterm Infants: Role in the Pathogenesis and Potential for Therapy.** Supervisor: Prof.dr. L. Zimmermann; Prof.dr. B. Kramer; Co-Supervisors: Dr. D. Gazzolo, Genoa, Italy / Dr. A.W.D. Gavilanes.

Claudia Menne-Lothmann: **Affect dynamics; A focus on genes, stress, and an opportunity for change.** Supervisor: Prof.dr. J. van Os; Co-Supervisors: Dr. M. Wichers / Dr. N. Jacobs.

Martine van Nierop: **Surviving childhood new perspectives on the link between childhood trauma and psychosis.** Supervisors: Prof.dr. I. Myin-Germeyns / Prof.dr. J. van Os; Co-Supervisor: Dr. R. van Winkel.

Sylvia Klinkenberg: **VNS in children; more than just seizure reduction.** Supervisors: Prof.dr. J. Vles / Prof.dr. A. Aldenkamp; Co-Supervisor: Dr. H. Majoie.

Anouk Linssen: **Considerations in designing an adult hearing screening programme.** Supervisor: Prof.dr. B. Kremer; Co-Supervisors: Dr. L. Anteunis / Dr. M. Joore.

Janny Hof: **Hearing loss in young children; challenges in assessment and intervention.** Supervisors: Prof.dr. B. Kremer / Prof.dr. R. Stokroos / Prof.dr. P. van Dijk, RUG; Co-Supervisor: Dr. L. Antheunis.

Kimberly Cox-Limpens: **Mechanisms of endogenous brain protection; Clues from the transcriptome.** Supervisors: Prof.dr. J. Vles / Prof.dr. L. Zimmermann; Co-Supervisor: Dr. A. Gavilanes.

Els Vanhoutte: **Peripheral Neuropathy outcome measures; Standardisation (PeriNomS) study part**

2: Getting consensus. Supervisors: Prof.dr. C. Faber / Prof.dr. P. van Doorn;

Co-Supervisor: Dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Mayienne Bakkers: **Small fibers, big troubles; diagnosis and implications of small fiber neuropathy.**

Supervisors: Prof.dr. C. Faber / Prof.dr. M. de Baets; Co-Supervisor: Dr. I. Merkies, Spaarne

ziekenhuis Hoofddorp.

Ingrid Kramer: **Zooming into the micro-level of experience: An approach for understanding and treating psychopathology.** Supervisor: Prof.dr. J. van Os;

Co-Supervisors: Dr. M. Wichers, UMC Groningen / Dr. C. Simons.

Esther Bouman: **Risks and Benefits of Regional Anesthesia in the Perioperative Setting.** Supervisors:

Prof.dr. M. van Kleef / Prof.dr. M. Marcus, HMC, Qatar / Prof.dr. E. Joosten; Co-Supervisor: Dr. H.

Gramke.

Mark Janssen: **Selective stimulation of the subthalamic nucleus in Parkinson's disease; dream or near future.** Supervisors: Prof.dr. Y. Temel / Prof.dr. V. Visser-Vandewalle, Keulen / Prof.dr. A.

Benazzouz, Bordeaux, France.

Reina de Kinderen: **Health Technology Assessment in Epilepsy; economic evaluations and**

preference studies. Supervisors: Prof.dr. S. Evers / Prof.dr. A. Aldenkamp; Co-Supervisor: Dr. H.

Majoie / Dr. D. Postulart, GGZ O-Brabant.

Saskia Ebus: **Interictal epileptiform activity as a marker for clinical outcome.** Supervisors: Prof.dr. A.

Aldenkamp / Prof.dr. J. Arends, TUE / Prof.dr. P. Boon, Universiteit Gent, België.

Inge Knuts: **Experimental and clinical studies into determinants of panic severity.** Supervisor: Prof.

dr. I. Myin-Germeys; Co-Supervisor: Dr. K. Schruers.

Nienke Tielemans: **Proactive coping post stroke: The Restored4Stroke Self-Management study.**

Supervisors: Prof.dr. C. van Heugten / Prof.dr. J. Visser-Meily, UMC Utrecht; Co-Supervisor: Dr. V.

Schepers, UMC Utrecht.

Tom van Zundert: **Improvements Towards Safer Extraglottic Airway Devices.** Supervisors: Prof.dr.

A.E.M. Marcus / Prof.dr. W. Buhre / Prof.dr. J.R. Brimacombe, Queensland, Australia / Prof.dr. C.A.

Hagberg.

Tijmen van Assen: **Anterior Cutaneous Nerve Entrapment Syndrome Epidemiology and surgical management.** Supervisors: Prof.dr. G.L. Beets / Prof.dr. M. van Kleef / Dr. R.M.H. Roumen / Dr.

M.R.M. Scheltinga, MMC Veldhoven.

Rohit Shetty: **Understanding the Clinical, Immunological and Genetic Molecular Mechanisms of Keratoconus.** Supervisors: Prof.dr. R.M.M.A. Nuijts / Prof.dr. C.A.B. Webers.

Christine van der Leeuw: **Blood, bones and brains; peripheral biological endophenotypes and**

their structural cerebral correlates in psychotic disorder. Supervisor: Prof.dr. J. van Os; Co-

supervisor: Dr. M. Marcelis.

Sanne Peeters: **The Idle Mind Never Rests; functional brain connectivity across the psychosis continuum.** Supervisor: Prof.dr. J. van Os; Co-supervisor: dr. M. Marcelis.

Nick van Goethem: **$\alpha 7$ nicotinic acetylcholine receptors and memory processes: mechanistic and behavioral studies.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. J. Prickaerts.

- Nicole Leibold: **A Breath of fear; a translational approach into the mechanisms of panic.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. K.R.J. Schruers / Dr. D.L.A. van den Hove.
- Renske Hamel: **The course of mild cognitive impairment and the role of comorbidity.** Supervisor: Prof.dr. F.R.J. Verhey; Co-supervisors: Dr. I.H.G.B. Ramakers / Dr. P.J. Visser.
- Lucia Speth: **Effects of botulinum toxin A injections and bimanual task-oriented therapy on hand functions and bimanual activities in unilateral Cerebral Palsy.** Supervisors: Prof.dr. J. Vles; Prof.dr. R. Smeets; Co-supervisor: Dr. Y. Janssen-Potten, Adelante Hoensbroek.
- Yuan Tian: **The effects of Lutein on the inflammatory pathways in age-related macular degeneration (AMD).** Supervisors: Prof.dr. C. Webers; Prof.dr. A. Kijlstra, WUR; Co-supervisor: Dr. M. Spreeuwenberg; Dr. H. Tange.
- Peggy Spauwen: **Cognition and Type 2 diabetes; the interplay of risk factors.** Supervisors: Prof.dr. F. Verhey; Prof.dr. C. Stehouwer; Co-supervisor: Dr. M. van Boxtel
- Marc Hilhorst: **Crescentic glomerulonephritis in ANCA associated vasculitis.** Supervisors: Prof.dr. J. Cohen-Tervaert; Co-supervisor: Dr. P. van Paassen
- Martin Gevonden: **The odd one out: exploring the nature of the association between minority status and psychosis.** Supervisors: Prof.dr. J-P. Selten; Prof.dr. J. Booij, Uva; Prof.dr. I. Myin-Germeys
- Bart Bialosterski: **Structural and functional aspects of sensory-motor Interaction in the urinary bladder.** Supervisors: Prof.dr. Ph. Van Kerrebroeck; Prof.dr. S. De Wachter, UvAntwerpen; Co-supervisors: Dr. G. van Koeveeringe; Dr. M. Rahnama'i.
- Alexandra König: **The use of information and communication technologies (ICT) for the assessment of patients with Alzheimer's Disease and related disorders.** Supervisors: prof.dr. F. Verhey; prof.dr. Ph. Robert, Nice, Fr; Co-supervisors: dr. P. Aalten; dr. R. David, Nice, Fr.
- Micheline Chenault: **Assessing Readiness for Hearing Rehabilitation.** Supervisors: prof.dr. M.P.F. Berger; prof.dr. B. Kremer; Co-supervisor: dr. L.J.C. Anteunis.
- Anand Vinekar: **Retinopathy of Prematurity. Recent advances in tele-medicine screening, risk factors and spectral domain optical coherence tomography imaging.** Supervisor: prof.dr. C.A.B. Webers; Co-supervisor: dr. N.J. Bauer
- Fleur van Dooren: **Diabetes and Depression: exploring the Interface between Pathophysiological and Psychological factors.** Supervisors: prof.dr. F.R.J. Verhey; prof.dr. J.K.L. Denollet, UvT; prof. dr. F. Pouwer, UvT; Co-supervisor: dr. M.T. Schram.
- Gabriëlla Pons van Dijk: **Taekwondo and physical fitness components in middle-aged healthy volunteers; the Sekwondo study.** Supervisors: prof.dr. J. Lodder; prof.dr. H. Kingma; Co-supervisor: dr. A.F. Lenssen.
- Yara Pujol López: **Development and psychoneuroimmunological mechanisms in depression.** Supervisor: prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. G. Kenis; Dr. D. van den Hove; Dr. Aye Mu Myint, München.
- Romina Gentier: **UBB⁴¹; an important switch in the onset of Alzheimer's disease.** Supervisors: Prof. H. Steinbusch; Prof. D. Hopkins; Co-supervisor: Dr. F. van Leeuwen.

Sanne Smeets: **Insights into insight: studies on awareness of deficits after acquired brain injury.**

Supervisor: Prof. C. van Heugten; Prof. R. Ponds; Co-supervisor: Dr. I. Winkens

Kim Beerhorst: **Bone disease in chronic epilepsy: fit for a fracture.** Supervisor: Prof. A. Aldenkamp;

Prof. R. van Oostenbrugge; Co-supervisor: Dr. P. Verschuure.

Alex Zwanenburg: **Cerebral and cardiac signal monitoring in fetal sheep with hypoxic-ischemic encephalopathy.** Supervisor: Prof. T. Delhaas; Prof. B. Kramer; Co-supervisors: Dr. T. Wolfs; Dr. P.

Andriessen, MMC.

Ismail Sinan Guloksuz: **Biological mechanisms of environmental stressors in psychiatry.** Supervisor:

Prof. J. van Os; Co-supervisors: Dr. B. Rutten; Dr. M. Drukker.

Seyed Ehsan Pishva MD: **Environmental Epigenetics in mental health and illness.** Supervisor: Prof.dr.

J. van Os; Co-supervisors: Dr. B.P.F. Rutten; Dr. G. Kenis.

Ankie Hamaekers: **Rescue ventilation using expiratory ventilation assistance; innovating while clutching at straws.** Supervisors: Prof.dr. W.F. Buhre; Prof.dr. M. van Kleef.

Rens Evers. **22q11.2 deletion syndrome: intelligence, psychopathology and neurochemistry at adult age.** Supervisors: Prof.dr. L.M.G. Curfs; Prof.dr. T. v. Amelsvoort.

Sarah-Anna Hescham. **Novel insights towards memory restoration.** Supervisor: Prof.dr.

Y. Temel; Co-supervisor: Dr. A. Blokland; Dr. A. Jahanshahi.

João P. da Costa Alvares Viegas Nunes. **Insulin receptor sensitization improves affective pathology in various mouse models.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. K-P. Lesch;

Dr. T. Strekalova; Dr.B.H. Cline, Oxford.

Yanny Ying-Yee Cheng. **Clinical Outcomes After Innovative Lamellar Corneal Transplantation Surgery.** Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisor:

Dr. J.S.A.G. Schouten.

2016

Oliver Gerlach. **Parkinson's disease, deterioration during hospitalization.** Supervisor: Prof.dr. R. van Oostenbrugge; Co-supervisor: Dr. W. Weber.

Remo Arts. **Intracochlear electrical stimulation to suppress tinnitus.** Supervisor: Prof.dr. R.J. Stokroos; Co-supervisor: Dr. E.L.J. Georg.

Mitchel van Eeden. **The €- Restore4stroke study: Economic evaluation of stroke care in the Netherlands.** Supervisors: Prof.dr.mr. S.M.A.A. Evers; Prof.dr. C.M. v. Heugten; Co-supervisor: dr. G.A.P. van Mastrigt.

Pim Klarenbeek. **Blood pressure and cerebral small vessel disease.** Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-supervisor: Dr. J. Staals.

Ramona Hohnen. **Peripheral pharmacological targets to modify bladder contractility.** Supervisor: Prof.dr. Ph.E.V. van Kerrebroeck; Co-supervisors: Dr. G.A. van Koeveeringe; Dr. M.A. Sahnema'i; Dr. C. Meriaux.

Ersoy Kocabicak. **Deep brain stimulation of the subthalamic nucleus: Clinical and scientific aspects.** Supervisors: Prof.dr. Y. Temel; Prof.dr. K. van Overbeeke; Co-supervisor: Dr. A. Jahanshahi.

- Sven Akkerman. **Temporal aspects of cyclic messenger signaling in object recognition memory; a pharmacological approach.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: dr. J. Prickaerts; dr. A. Blokland.
- Anja Moonen. **Emotion and Cognition in Parkinson's disease; etiology and neurobiological mechanisms.** Supervisor: Prof.dr. F.R.J. Verhey; Co-supervisor: dr. A.F.G. Leentjens.
- Anna Schüth. **Three-dimensional bladder tissue morphology.** Supervisors: Prof.dr. G.A. van Koeveeringe; Prof.dr. M. v. Zandvoort, Aachen; Prof.dr. Ph. V. Kerrebroeck.
- Elisabeth van der Ven. **Ethnic minority position as risk indicator for autism- Spectrum and psychotic disorders.** Supervisors: Prof.dr. J.P. Selten; Prof.dr. J. van Os.
- Zuzana Kasanova. **Environmental reactivity for better or worse; The impact of stress and reward on neurochemistry, affect and behavior across the psychosis continuum.** Supervisor: Prof.dr. I. Myin-Germeyns, KU Leuven/UM; Co-supervisor: dr. D. Collip.
- Danielle Lambrechts. **Ketogenic diet therapies; treatment for children and adults with refractory epilepsy.** Supervisors: Prof.dr. H.J.M. Majoie; Prof.dr. J.S.H. Vles; Prof.dr. A.P. Aldenkamp; Co-supervisor: dr. A.J.A. de Louw, Kempenhaghe, Heeze.
- Frank van Bussel. **Advanced MRI in diabetes; cerebral biomarkers of cognitive decrements.** Supervisors: Prof.dr.ir. W.H. Backes; Prof.dr. P.A.M. Hofman; Co-supervisor: dr. J.F.A. Jansen.
- Lisa Schönfeldt. **Neurostimulation to treat brain injury?** Supervisors: Prof.dr. Y. Temel; Prof.dr. S. Hendrikx, Hasselt; Co-supervisor: dr. A. Jahanshahi.
- Rianne Geerlings. **Transition in patients with childhood-onset epilepsy; a long way to adulthood.** Supervisor: Prof.dr. A.P. Aldenkamp; Co-supervisors: dr. A.J.A. de Louw, dr. L.M.C. Gottmer, Kempenhaeghe.
- Nele Claes. **B cells as multifactorial players in multiple sclerosis pathogenesis: insights from therapeutics.** Supervisors: Prof.dr. V. Somers, Hasselt; Prof.dr. R. Hupperts Co-supervisors: Prof. dr. P. Stinissen, dr. J. Fraussen, Hasselt.
- Olaf Schijns. **Epilepsy surgery and biomarkers from history to molecular imaging.** Supervisors: Prof. dr. J.J. van Overbeeke; Prof.dr. H. Clustermann, Aachen; Co-supervisors: dr. G. Hoogland; dr. M.J.P. v. Kroonenburgh.
- Lizzy Boots. **Balanced and Prepared; development and evaluation of a supportive e-health intervention for caregivers of people with early-stage dementia.** Supervisors: Prof.dr. F.R.J. Verhey; Prof.dr. G.I.J.M. Kempen; Co-supervisor: dr. M.E. de Vugt.
- Wouter Donders. **Towards patient-specific (cerebro-) vascular model applications.** Supervisors: Prof. dr. T. Delhaas; Prof.dr.ir. F.N. van de Vosse, TUE; Co-supervisor: dr.ir. W. Huberts.
- Sizzle Vanterpool. **The implications of intrauterine invasion by microbes for placental Pathology and the occurrence of adverse pregnancy outcomes.** Supervisor: Prof.dr. B.W. Kramer. Co-supervisors: dr. J.V. Been, Erasmus MC Rotterdam, dr. U von Rango.
- Manuela Heins. **The Relationship between Social Adversity, Psychosis, and Depression across an Individual's Life Span.** Supervisor: Prof.dr. I. Myin-Germeyns.

- Christianus van Ganzewinkel. **NEONATAL PAIN; Out of Sight, Out of Mind?** Supervisor: Prof.dr. B.W.W. Kramer; Co-supervisor: dr. P. Andriessen, MMC Veldhoven.
- Anne-Hilde Muris. **Hype or hope? Vitamin D in multiple sclerosis; A clinical and immunological perspective.** Supervisor: Prof.dr. R.M.M. Hupperts; Co-supervisor: dr. J.G.M.C. Damoiseaux.
- Gerard Bode. **The link between ceramide transporters, innate Immunity and Alzheimer's disease.** Supervisor: Prof.dr. M.H.V. de Baets; Co-supervisors: dr. P. Martinez, dr. M. Losen.
- Jo Stevens. **Advanced diagnostics and therapeutics for Alzheimer's disease.** Supervisor: Prof.dr. M. de Baets; Co-supervisors: dr. M. Losen, dr. P. Martinez-Martinez.
- Rosan Luijckx. **Stress and pain in muscles and brain; developing psychophysiological paradigms to examine stress and pain interactions.** Supervisors: Prof.dr. J.J. van Os; Prof.dr.ir. H.J. Hermens, UT; Co-supervisor: dr. R. Lousberg.
- M.C. Haanschoten. **Towards efficient cardiac surgery – the integrating role of anesthesiology and intensive care.** Supervisors: Prof. dr. W. Buhre; Prof. dr. A. van Zundert (Queensland); Co-supervisors: Dr. M.A. Soliman Hamad; Dr. A. van Straten (Catharina zkhs).
- Harmen Jan van de Haar. **Microvascular and blood-brain barrier dysfunction in Alzheimer's disease.** Supervisor: Prof.dr.ir. W. Backes; Prof.dr. F. Verhey; Co-supervisor: Dr. J. Jansen; Dr.ir. M. v. Osch, LUMC.
- Coenraad Itz. **Chronic low back pain, considerations about: Natural Course, Diagnosis, Interventional Treatment and Costs.** Supervisor: Prof.dr. M. van Kleef; Prof.dr. F. Huygen, EUR; Co-supervisor: Dr. B. Ramaekers.
- Willemijn Jansen. **The Path of Alzheimer's disease: from neuropathology to clinic.** Supervisor: Prof. dr. F. Verhey; Co-supervisors: Dr. P.J. Visser; Dr. I. Ramakers.
- Ligia dos Santos Mendes Lemes Soares. **Phosphodiesterase inhibitors: a potential therapeutic approach for ischemic cerebral injury.** Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. R.M. Weffort de Oliveira, Brazil; Dr. J. Prickaerts
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- Sandra Schipper. **Extrasynaptic receptors as a treatment target in epilepsy.** Supervisor: Prof.dr. J.H.S. Vles; Co-supervisors: Dr. G. Hoogland; Dr. S. Klinkenberg; Dr. M.W. Aalbers, RUG.
- João Casaca Carreira. **Making sense of Antisense Oligonucleotides Therapy in Experimental Huntington's disease.** Supervisor: Prof.dr. Y. Temel; Co-supervisors: Dr. A. Jahanshahi; Dr. W. van Roon-Mom, LUMC.
- Dominique IJff. **Trick or Treat? Cognitive side-effects of antiepileptic treatment.** Supervisors: Prof.dr. A.P. Aldenkamp; Prof.dr. M. Majoie; Co-supervisors: Dr. J. Jansen; Dr. R. Lazeron, Kempenhaeghe.
- Alfredo Ramirez. **Neurogenetic approach in neurodegenerative disorders.** Supervisors: Prof.dr. B.P.F. Rutten; Prof.dr. H.W.M. Steinbusch; Prof.dr. M.M. Nöthen, University of Bonn.
- Nienke Visser. **Toric Intraocular lenses in cataract surgery.** Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisor: Dr. N.J.C. Bauer.

Jakob Burgstaller. **Prognostic indicators for patients with degenerative lumbar spinal stenosis.**

Supervisor: Prof.dr. M. van Kleef; Co-supervisors: Dr. M.M. Wertli, University of Zurich; Dr. H.F. Gramke.

Mark van den Hurk. **Neuronal Identity and Maturation: Insights from the Single-Cell Transcriptome.**

Supervisors: Prof.dr. H.W.M. Steinbusch; Prof.dr. B.P.F. Rutten; Co-supervisors: Dr. G. Kenis; Dr. C. Bardy, Adelaide.

Maria Nikiforou. **Prenatal stress and the fetal gut. Potential interventions to prevent adverse**

outcomes. Supervisors: Prof.dr. B.W. Kramer; Prof.dr. H.W. Steinbusch; Co-supervisor: Dr. T.G. Wolfs.

Janneke Peijnenborgh. **Assessment of cognition, time perception, and motivation in children.**

Supervisors: Prof.dr. J.S.H. Vles; Prof.dr. A.P. Aldenkamp; Co-supervisors: Dr. J. Hendriksen; Dr. P. Hurks.

Joany Millenaar. **Young onset dementia; towards a better understanding of care needs and**

experiences. Supervisors: Prof.dr. F. Verhey; Prof.dr. R. Koopmans, RUN; Co-supervisors: Dr. M. de Vugt; Dr. C. Bakker, RUN.

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Adriana Smits. **Perinatal factors and hearing outcome.** Supervisors: Prof.dr. R.J. Stokroos; Prof.dr. B.W.

Kramer; Prof.dr. B. Kremer.

Angela Bouwmans. **Transcranial sonography in parkinsonian disorders: clear window or blurred**

vision. Supervisor: Prof.dr. W.H. Mess; Co-promotores: Dr. W.E.J. Weber; Dr. A.F.G. Leentjens.

Björn K. Stessel. **Patient centred care after day surgery: scope for improvement.** Supervisors: Prof.dr.

W. Buhre; Prof.dr. B. Joosten. Co-supervisor: Dr. A.H. Gramke.

Jan Guy Bogaarts. **Quantitative EEG and machine learning methods for the detection of epileptic**

seizures and cerebral asymmetry. Supervisor: Prof.dr. W.M. Mess; Co-supervisor: Dr.ir. J.P.H. Reulen; Dr.ir. E.D. Gommer.

Martin M. Müller. **Pregnancy derived products for treatment of perinatal brain injuries.** Supervisors:

Prof.dr. B.W.W. Kramer; Prof.dr. D. Surbek, Bern; Co-supervisors: Dr. T. Wolfs; Dr. G. Gavilanes.

Daan Ophelders. **Novel treatment strategies for the protection of the preterm brain; Re-balancing**

inflammation and regeneration. Supervisor: Prof.dr. B. Kramer; Co-supervisor: Dr. T. Wolfs; Dr. R. Jellema.

Rosalie van Knippenberg. **Experience sampling in dementia care; an innovative intervention to**

support caregivers in daily life. Supervisors: Prof.dr. F. Verhey; Prof.dr. R. Ponds; Prof.dr. I. Myin-Germeys, KU Leuven; Co-supervisor: Dr. M. de Vugt.

Claudia Vingerhoets. **Investigating neurobiological mechanisms underlying comorbid cognitive**

symptoms in psychosis and substance use. Supervisors: Prof.dr. T. van Amelsvoort; Prof.dr. J. Booij, UvA; Co-supervisor: Dr. O. Bloemen

Dennis Oerlemans. **Evolution of Neuromodulation for Lower Urinary Tract Dysfunction; Past,**

Present and Future. Supervisors: Prof.dr. Ph. van Kerrebroeck; Prof.dr. G. van Koeveinge. Co-supervisors: Dr. E. Weil; Dr. T. Marcelissen.

- Marion Levy. **Evaluation of BDNF/TrkB signaling as a common target in the treatment of major depression and Alzheimer's disease.** Supervisors: Prof.dr. H. Steinbusch; Prof. L. Lanfumey, Université Paris Descartes, France. Co-supervisors: Dr. G. Kenis; Dr. D. van den Hove.
- Patrick Domen. **Stay connected: a family-based diffusion imaging study in psychotic disorder.** Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. M. Marcelis
- Geor Bakker. **Innovative Approaches to Understanding the Neurobiology of Psychosis.** Supervisors: Prof.dr. T. van Amelsfoort; Prof.dr. J. Booij, UvA. Co-supervisor: dr. M. Caan, UvA; dr. O. Bloemen.
- Wilma Boevink. **HEE! Over Herstel, Empowerment en Ervaringsdeskundigheid in de psychiatrie.** Supervisors: Prof.dr. J. van Os; Prof.dr. Ph. Delespaul. Co-supervisor: dr. H. Kroon.
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- Maurice Theunissen. **Understanding factors affecting postoperative Quality of Life.** Supervisors: Prof.dr. M. Peters, Prof.dr. M. Marcus. Co-supervisor: Dr. H. Gramke.
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- Alessandro Varrica. **S100B Protein and Congenital Heart Diseases: Brain Aspects.** Supervisors: Prof. dr. D. Gazzalo, Alessandria, Italy; Prof.dr. J.S.H. Vles; Prof.dr. L.J.I. Zimmermann. Co-supervisor: Dr. A.W.D. Gavilanes.
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Tamar van Veenendaal. **Neurotransmitters & Networks. An MR view on epilepsy and antiepileptic drugs.** Supervisors: Prof.dr.ir. W.H. Backes; Prof.dr. A.P. Aldenkamp. Co-supervisor: Dr. J.F.A. Jansen.

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Iris M.J. Lange. **Should I stay or should I go ? Brain mechanisms underlying fear and safety learning, and exposure therapy outcome.** Supervisors: Prof.dr. K.R.J. Schruers;

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Ruben G.F. Hendriksen. **Evidence for a dystrophin-associated encephalopathy in Duchenne Muscular Dystrophy.** Supervisor: Prof.dr. J.S.H. Vles. Co-supervisors: Dr. G. Hoogland; Dr. M.W. Aalbers, UMC Groningen.

Michael Gofeld. **Strengths and limitations of the lumbar spine ultrasound-guided interventions.** Supervisor: Prof.dr. M. van Kleef. Co-supervisor: Dr. M. Sommer.

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Maarten van Beek. **Spinal Cord Stimulation in Clinical and Experimental Painful Diabetic Polyneuropathy.** Supervisors: Prof.dr. E.A. Joosten; Prof.dr. M. van Kleef. Co-supervisor: Dr. S.M.J. van Kuijk.

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Mauro Pessia. **Brain K⁺ Channels: from molecular and physiological features to autism spectrum disorder and intellectual disability.** Supervisors: prof.dr. H.W.M. Steinbusch, prof.dr. M.B. Donati, It.

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Andrea S. Herrera Soto. **Aminochrome, an endotoxin for inducing a new rat model of Parkinson's Disease.** Supervisor: prof.dr. H.W.M. Steinbusch. Co-supervisors: Prof.dr. Juan Segura-Aguilar; prof. G. Diaz-Veliz, Santiago of Chile

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Sau May Wong. **Advances in Microvascular MRI Techniques: Breaking the Pathophysiological Barriers in Cerebral Small Vessel Disease.** Supervisor: Prof.dr. W.H. Backes, Prof.dr. R.J. van Oostenbrugge. Co-supervisor: Dr. J.F.A. Jansen

Mark B.N. van Winkel. **Lonely at heart and stressed in company of Others; the influence of daily life social experiences and emotions on depression.** Supervisors: prof.dr. F. Peeters; prof.dr. I. Myin-Germeyns, KU Leuven/UM; prof.dr. M. Wichers, UMC Groningen

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Ganne Chaitanya. **Epilepsy: A network disorder.** Supervisors: prof.dr. A.P. Aldenkamp; prof. P. Satishchandra, NIMHANS, Bangalore, India. Co-supervisors: Dr. J.F.A. Jansen; Dr. S. Zinger, TUE

Sumitha Rajendrarao. **New Insight into the Multifaceted Pathogenic Mechanisms of Sporadic Amyotrophic Lateral Sclerosis.** Supervisors: prof.dr. B.W. Kamer; prof.dr. H.W. Steinbusch. Co-supervisor: prof. T.R. Raju, NIMHANS, Bangalore, India

Suzanne Roggeveen. **Interference of mobile phone with electrophysiology and emotions; results from short-term experimental studies.** Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. R. Lousberg.

Matthias Walter. **Multi-methodological approaches to investigate lower urinary tract function in health and disease.** Supervisors: Prof.dr. Ph.E.V.A. van Kerrebroek; Prof.dr. G.A. van Koeveeringe; Prof.dr. A. Curt, Zürich, CH.

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