PREVENTION OF DEMENTIA BY INTENSIVE VASCULAR CARE - OBSERVATIONAL EXTENSION STUDY

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Primary Objectives: • To continue observational data collection for the main clinical outcomes of the research subjects who participated in the preDIVA trial between 2006-2015.• To assess the effects of long-term vascular risk factor modification on...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Dementia and amnestic conditions
Study type	Observational non invasive

Summary

ID

NL-OMON42949

Source
ToetsingOnline

Brief title
preDIVA-POE study

Condition

- Dementia and amnestic conditions

Synonym
Dementia, forgetfulness

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Brain obduction, Cardiovasculair risk management, Dementia

Outcome measures

Primary outcome

The main study endpoint of the study is the clinical diagnosis of dementia (component 1).

For subjects participating in post-mortem brain autopsy (component 2), the main study parameter is clinical diagnosis of dementia and its relation to the extent and severity of (micro)vascular changes, neurodegenerative changes, neuroinflammation. Also, the effect of long-term vascular risk factor modification on neuropathological changes including (micro-)vascular damage and neurodegeneration and relation to changes on brain MRI will be studied. In exploratory analyses we will also assess the association between specific clinical variables (a.o. cognition, blood pressure) and neuropathological changes at autopsy.

For subjects participating in the qualitative interview study (component 3), the main study parameters are barriers and facilitators for participation in a brain donation program.

An independent and blinded outcome adjudication committee will be consulted to evaluate the primary outcome i.e. dementia. This committee will consist of neurologists, old age psychiatrists, geriatricians, general practitioners and cardiologists, who will evaluate all cases using available clinical

information.

Secondary outcome

Secondary outcomes, for all levels of the study, are mortality, myocardial infarction, cerebral infarction, transient ischaemic attack, peripheral vascular disease, AMC linear disability score (ALDS), score on mini mental state examination (MMSE) or Telephone Interview for Cognitive Status (TICS), (which can be interpreted in the same way as the MMSE which was used in preDIVA) and mood as assessed with the Geriatric Depression Scale. All these endpoints will be related to the microvascular changes of the brain tissue in subjects consenting to post-mortem autopsy. Medical records of participants can be requested via the general practitioner for additional information on medical status.

Other parameters collected in the study will be information on cardiovascular risk management over the past 2 years including visits to the general practitioner. Other variables will include living situation, new comorbidities, hospital admissions, smoking status, alcohol consumption and medication. Weight, height, blood pressure and heart rate will be collected in the participants of the component 2 study.

Study description

Background summary

The prevalence of dementia is about 180.000 in the Netherlands. In addition to the burden for patients and caregivers associated with this devastating

condition, the estimated increase in dementia prevalence will have an important impact on the health care system and on society at large. Despite tremendous research efforts, there are currently no options for effective prevention or treatment of Alzheimer's disease or dementia in general.
Vascular risk factors during life are associated with increased risk of dementia. A crucial question is whether these disease mechanisms can be influenced during life. If vascular changes play such an important role in the pathophysiology of AD, can treatment of vascular risk factors during life prevent cognitive decline and dementia? Several observations, suggest that intensive vascular care can reduce the incidence of dementia. Since neuropathological changes precede the occurrence of dementia by years or even decades, interventions should probably take place long before the clinical onset of cognitive impairment. Therefore, targeting modifiable vascular risk factors in a population aged 70-78 years, was the main focus of the recently conducted *prevention of dementia by intensive vascular care* (preDIVA) trial. In this trial, vascular risk factors associated with dementia that are directly amenable to intervention were addressed, such as hypertension, hypercholesterolaemia, obesity, smoking, lack of physical exercise and diabetes mellitus, in this trial. In total, 3526 participants were randomized to either intensive vascular care or standard care and 6-8 year follow up was completed. This trial provides a unique and well-defined cohort with valuable data in relation to dementia and vascular risk. The incidence of dementia during the trial was around 7%. Observational extension will increase the number of incident cases which will allow for additional analyses on factors that contributed to the development of dementia and aspects of the intervention that were most successful for the prevention of dementia.
Most patients clinically diagnosed as Alzheimer*s Disease (AD) have multiple cerebral pathologies at autopsy, including prominent cerebrovascular pathology. Vascular changes contribute in a synergistic way to cognitive impairment by lowering the threshold for plaque and tangle load to give rise to cognitive decline. Cerebral ischemia may even be an important process at the origin of the cascade of events leading to the development of Aβ and tau depositions. Abnormalities in vessel architecture, diminished cerebral blood flow, and altered oxygen utilization resulting in dysfunction of the cerebral microcirculation, may all lead to neuronal cell loss in AD. Additional interaction of vascular and neurodegenerative changes with systemic and neuro-inflammation might play a role in the final occurrence of clinical symptoms of AD. Chronic inflammation associated with atherosclerosis has been shown to precede Aβ deposition and Aβ in turn induces an array of pro-inflammatory responses24. Animal experiments have strongly suggested a causal relationship of hypertension and hypercholesterolemia with Aβ depositions, further fueling hypotheses about direct interaction between vascular factors and neurodegenerative changes. However, the interaction between cerebrovascular lesions, neuroinflammation and neurodegeneration is complex and exact mechanisms by which they contribute to cognitive decline and dementia are not yet fully understood.
The clinical implications of these pathophysiological mechanisms are largely

unknown. Can the neuropathological changes that underlie AD be slowed or even prevented? And if so, which neuropathological mechanisms are influenced? Several post-mortem studies have tried to address these questions. Hypertension, being one of the most important vascular risk factors, is associated with increased presence and severity of Aβ and tau neuropathology in older individuals without dementia. Treatment of hypertension has been associated with less severe neurodegenerative changes. This knowledge is, however, derived from cohort studies, precluding causal inference. Neuropathological outcomes in randomized controlled trials (RCTs) are generally not possible. Although clinical outcomes are the basis of most RCTs, knowing whether an intervention to prevent cognitive decline affects neuropathological changes would substantially increase our understanding of the etiology of AD. This could also guide in the design of new interventions to prevent cognitive decline and dementia. Such *interventional neuropathology studies* are rare, and we will, for the first time, obtain neuropathological outcomes of a long-lasting dementia prevention RCT.
PreDIVA offers an excellent opportunity to study the effect of the intervention on neuropathological changes. In other words, can longstanding vascular care protect against neuropathological changes associated with dementia, including microvascular changes, neurodegenerative changes and neuroinflammation? Due to the high age at recruitment, resulting in a cohort aged 79-89 in 2016, a relatively high mortality rate can be expected which can result in a considerable autopsy cohort in a relatively short period.
In most Western countries, including the Netherlands, autopsy rates have been declining for decades. Especially in old age autopsy rates are low. The reasons for this are probably multifactorial, but an important contributor may be changes in patients* or their relatives attitude towards post-mortem examination. Understanding barriers and facilitators to participate in a brain donation program can lead to adjustment of recruitment strategies to improve the participation rate. This will decrease inclusion bias and increase the external validity of future autopsy-cohorts. By Integrating 1) evaluating the effect of a clinical intervention to prevent dementia with 2) the building of a new autopsy cohort from an RCT and 3)qualitative research on brain donation, we aim for a comprehensive approach to improve clinic-pathological research into Alzheimer*s Disease.

Study objective

Primary Objectives:
• To continue observational data collection for the main clinical outcomes of the research subjects who participated in the preDIVA trial between 2006-2015.
• To assess the effects of long-term vascular risk factor modification on the extent and severity of (micro)vascular changes, neurodegenerative changes, neuroinflammation and the interaction between them, by setting up a unique autopsy cohort derived from a large long-term dementia-prevention trial.

Secondary Objectives:

• To build a state of the art brain bank from a well-defined/characterized older population.
• To use this cohort for association studies on specific participant characteristics in relation to neuropathological changes to further advance the understanding of the relation between vascular risk factors and dementia in order to guide the development of better-targeted interventions to prevent dementia
• To relate the neuropathological findings to changes on MRI during life, to improve understanding of brain changes as can be visualized on MRI during life.
• To explore barriers and facilitators for participation in a brain donation program.

Study design

This current study is designed as a single-centre, multi-site, prospectively observational cohort study and will be an extension of the randomized controlled preDIVA trial12 (METC MEC 05/093 # 06.17.0420 ; ISRCTN29711771), a single-centre, multi-site, open, randomized, parallel group trial, conducted in the Netherlands from 2006-2015. In this trial it was investigated whether intensive vascular care could lead to the prevention of dementia. Participants in the control group received care as usual. Participants in the intervention group consulted a practice nurse every 4-months, who addressed all vascular risk factors and unhealthy lifestyles. Participants were between 70 and 78 years at baseline and were not demented when the study started in 2006. All individuals in this age-range in 116 general practitioner (GP) practices were invited, of whom 53.3% agreed to participate.
In the current observational follow up study, all participants from the preDIVA trial, now between 79-89 years of age, will be asked to participate in the preDIVA-extension study, through a new informed consent procedure. Those preDIVA participants who indicated they were willing to consider participation in future research or extended follow-up, are deemed eligible. At the final follow-up visit of the preDIVA in 2015, 578 participants had died, leaving 2948 participants alive at that moment. Considering the high age, we expect that approximately 200 more participants have died since mid-2015, leaving around 2700 preDIVA participants still alive in mid-2016. Of all preDIVA participants we will carefully check whether they are still alive using the Dutch death registry, before contacting them. Those participants still alive will be informed about the outcome of the preDIVA trial by a newsletter. In this newsletter the possibility for participation in the extended data collection and brain donation will be raised. Participants will be contacted by phone and a visit will be scheduled (at their own home or at an easily accessible location in the area, provided by the researchers) during which the participants will be further informed about the observational extension and the possibility for brain donation. Participants will be contacted based on age, starting with the oldest participants and the possibility of participation in various components of the current study will be discussed (figure 1):
1. Two yearly clinical data collection (component 1).

2. Post-mortem brain autopsy with optional MRI-scan (component 2).
3. Participation in a qualitative sub-study on fears and expectations on the subject of brain autopsy (component 3).

Figure. Overview of the project. In the preDIVA RCT clinical data have been collected since 2006. This is all considered preliminary work. During the current project, subjects can agree to multiple components of participation: Component 1; two yearly clinical data collection in all participants will start in 2016 and will continue until the subject has passed away. Component 2; registration for post-mortem brain donation. Component 3; qualitative study on barriers and thoughts on brain donation will start in 2016 and will continue until the study has reached saturation. Neuropathological analyses in relation to clinical information will start when the first brain tissue is available and will be continued in the future.

In case home visits are not feasible for informing eligible participants about the preDIVA extension, information on the observational data collection (component 1) can be provided by phone and informed consent can be send by mail using a return envelope.

Component 1
All participants agreeing to exclusively participate in the data collection part (component 1) of this study will be subjected to questionnaires until death or request to end participation. This is preferably conducted during home visits (or at a site easily accessible provided by the researchers). However, if home visits are deemed not feasible, these may be replaced by telephone calls. To be able to identify any potential registration bias, reasons for decline of brain autopsy (component 2) will be recorded in all eligible subjects. When communication (or other) difficulties occur during telephone call, a visit (at their own home or at site provided by the researchers) will be suggested to overcome these problems.

Component 2/3
When subjects express interest in component 2 and/or 3 of the study, a visit at their own home or at a site provided by the researchers (e.g. at the AMC or at their primary care practice if feasible) will be scheduled. During this visit the subject will be informed about the current study and the possibility for brain donation. A careful, step-wise approach will be used to thoroughly address all the potential barriers and provide comprehensive information on the procedures leading to registration as a brain donor. We will build upon the experience of the Netherlands Brain Bank (NBB) for psychiatry (www.nhb-psy.nl) and the Cognitive Functioning an Ageing Study (CFAS) in Cambridge in the personal approach of potential donors. The consultants conducting the visits will be extensively trained using the CFAS experience and familiarized with all brain donation logistics of the NBB.
Participants agreeing to participate in both clinical data collection and post-mortem brain autopsy (component 2) will be subjected to two yearly visits

(at their own home or at site provided by the researchers) to undergo more extensive questioning including a limited set of cognitive tests, until death. If participation in the brain donation program is higher than the anticipated 10-15%, the two yearly visits for data collection may be replaced by telephone calls for data collection. Subjecting large numbers of participants to home visits may not be feasible, since home visits are logistically challenging, time consuming and costly. Even so, home visits are preferred, since data collection via such visits can yield to the close contact that is considered necessary to sustain a donation program, and can therefore be of great value. In a subset (N ~ 20) of all participants interested in participating in component 2 and/or 3 who are informed about brain donation, an interview to address fears and expectations concerning brain donation will be planned. This interview will be semi-structured using a topic-list and will be conducted by a trained researcher in the subject*s own home. Participants will be encouraged to address perceived barriers (i.e. fears, preoccupations) and facilitators (i.e. altruistic motives) to participate in such a program. The topic list will be modified when new themes emerge from the data. Once data saturation is achieved (i.e. no new themes emerge during subsequent interviews), generally after 15 to 25 interviews, no further participants will be recruited.

Brain donation program
Post-mortem brain autopsy will be performed by the Netherlands Brain Bank (NBB). The existing infrastructure of the NBB will be used to allow for optimal expertise and efficiency. The current prospective cohort study among psychiatric patients (NBB-psy) will serve as an example for the current project. We will base ourselves on the best practices available at the NBB. The NBB is accessible 24/7. Whenever a donor has passed away, family members or the general practitioner will contact the NBB, who will initiate the logistics for autopsy. The existing rapid autopsy protocols of the NBB will be used (www.hersenbank.nl and www.brainbank.nl and appendix A), guaranteeing adequate tissue handling and storage. The donor is retrieved form their own home and transported to the VU medical centre, where brain autopsy will take place. The donor will be returned to the family or mortician/undertaker within 24 hours. Annually the NBB performs 90-130 autopsies and since its start the NBB has performed more than 3700 autopsies. In the current proposal, the neuropathological data will be linked to the data in the Case Report Form (CRF) of PreDIVA, containing prospectively and systematically collected clinical data, including vascular risk factors, medical history, medication use, cognition, depression daily and functioning.
Based on the literature we estimate that 10-15% will potentially consent to brain donation. It is expected that most participants have deceased after a decade considering the high age at the start of this project, resulting in a foreseen horizon of around 2026 for completion of this study, but a fixed date cannot be set at this moment.

General practitioners will receive notice of participation of their patient in the current preDIVA extension study. Medical records of participants may be

requested via the general practitioner for additional information on medical status and primary/secondary outcome measures.

An independent and blinded outcome adjudication committee will be consulted to evaluate the primary outcome i.e. dementia. This committee will consist of neurologists, old age psychiatrists, geriatricians, general practitioners and cardiologists, who will evaluate all cases using available clinical information. The procedure for independent outcome adjudication used in preDIVA will be used in the current study.

Study burden and risks

The burden of participation in either one of the three levels of the study is low and the risks are negligible. There are no direct benefits for the individual participants.

Clinical data collection
Participants will be subjected to data collection once every two years either by a phone call, or by a visit at their own home or at a site provided by the researchers if preferred and feasible. This phone call or visit can be relatively short and will be conducted by trained researchers and will be planned whenever suitable for the participant.

Qualitative study
For inclusion in the qualitative study, participation may be somewhat more demanding since an interview on thoughts and fears regarding brain donation may initiate a topic participants do not wish to think or talk about. We consider it therefore important to specifically ask informed consent for this substudy and train interviewers. For this component 3 of the study, no incapacitated subjects will be included.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Previous participation in the preDIVA trial
Previous consent to be contacted for future research or willingness to consider participation in future research or extended follow up

Exclusion criteria

Subjects of whom no contact information is present.
Subjects who have moved out of the country or out of reach for the consultants will not be asked for brain donation, but can be included in prospective data collection (level 1 of the study).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-04-2017
Enrollment:	2700
Type:	Actual

Ethics review

Approved WMO

Date:	03-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL57801.018.16