Minimally invasive detection of early Alzheimer*s disease pathology at the eye clinic using blood tests and eye-scans: the BeyeOMARKER study

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Structural brain disorders
Study type	Observational invasive

Summary

ID

NL-OMON56662

Source
ToetsingOnline

Brief title
BeyeOMARKER

Condition

- Structural brain disorders

Synonym
Alzheimer's disease, dementia

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC

Source(s) of monetary or material Support: Alzheimer's Association;Health Holland,Optina Diagnostics,Quanterix

Intervention

Keyword: Alzheimer's disease, blood-based biomarkers, eye clinic, eye disease, hyperspectral retinal imaging, retinal imaging, visual impairment

Outcome measures

Primary outcome

The primary parameter of BeyeOMARKER is the predictive value of plasma p-tau and AI-based classification of the HS retinal scan to predict 1) clinical decline (cognitive changes between T0 and T2), and 2) AD pathophysiology (amyloid- and tau-PET visual read).

Secondary outcome

Secondary parameters include sociodemographic measures, medical history, blood-based outcomes including existing biomarkers (Aβ40, Aβ42, GFAP, NfL based on the Quanterix N4PE assay) and other existing or emerging biomarkers, standard retinal scan outcomes (e.g. thickness of retinal layers and vascular parameters), HS retinal scan outcomes (e.g. data-driven classification), cognitive and cortical vision performance, structural magnetic resonance imaging (MRI) outcomes (e.g. brain atrophy and neurovascular health), amyloid- and tau-PET (e.g. visual read and quantification), prevalence of PCA, prevalence of plasma p-tau positivity in an eye clinic, and participant experiences.

Study description

Background summary

Alzheimer*s disease (AD) is characterized by the presence of amyloid beta (Aβ) plaques and tau neurofibrillary tangles. The disease course of AD is increasingly recognized as a continuum in which pathophysiological changes occur up to around 10-20 years before the expression of clinical dementia. The window prior irreversible brain damage and cognitive decline is crucial to implement strategies that could slow the disease or could improve quality of life. However, intervention and diagnosis are intrinsically connected to each other: an accurate biomarker-based diagnosis is imperative to provide accurate prognostic information, appropriate intervention, access to possible clinical trials or, in the future, available disease-modifying medication. Currently, a biomarker-confirmed Alzheimer*s disease (AD) diagnosis requires expensive and sometimes invasive procedures that are only accessible in highly specialized clinics (i.e. a lumbar puncture or amyloid positron emission tomography (PET)). Consequently, the time to diagnosis in current clinical practice is relatively long and this contributes to the increasing societal and economic disease burden of AD. Hence, alternative methods and an infrastructure is warranted. Currently, plasma phospo-tau (p-tau) and eye-based hyperspectral (HS) retinal scanning are emerging as highly promising tools to distinguish between subjects with and without AD pathology. Thus far, studies on these biomarkers did not resemble *real-world* clinical application as these were mostly retrospective, included participants with high diagnostic certainty, few medical comorbidities and did not use a priori defined cut-offs. The BeyeOMARKER study aims to provide real-world proof-of-concept for early detection of AD pathology outside the memory clinic through prospective evaluation of plasma p-tau in an eye clinic with high patient-throughput. Eye clinics are an important setting with a high likelihood of early detection of AD given the high patient throughput of patients within the age-range where AD typically starts (i.e. 50-80 years old). Furthermore, eye patients may be at increased risk for AD based on epidemiological associations showing a higher risk on AD for certain eye conditions (e.g. HR=1.26 for cataract) and visual impairment (e.g. HR=1.47), and based on shared risk factors and pathological mechanisms between eye- en brain diseases. Importantly, visual impairment may mask cognitive complaints leading to significant diagnostic delays and underrepresentation of these individuals in clinical studies. Altogether, the BeyeOMARKER study utilizes this unique setting to assess whether these novel tools can facilitate early detection of AD and an accelerated diagnostic process in this clinically relevant group. Therefore, the BeyeOMARKER study will screen 700 healthy volunteers from the eye clinic using a bloodtest en short cognitive and visuoperceptive screening. Subsequently, 150 participants will be invited for the BeyeOMARKER+ cohort which entails more extensive assessment (neuropsychological testing, magnetic resonance imaging (MRI), amyloid- en tau PET). Based on these data we aim to determine which biomarkers are, in practice, most suitable for early detection of AD. The BeyeOMARKER study aims to provide proof-of-concept for implementation of these promising tools for AD

in eye clinics, with the ultimate goal of providing recommendations for minimally invasive detection of AD pathophysiology in alternative clinical settings.

Study objective

The BeyeOMARKER study*s primary aim is to (1) evaluate the real-world predictive value of blood- and eye-based biomarkers for detection of AD-related clinical progression and biological changes in eye clinics. Secondly, we aim (2) to assess the individual and complementary clinical predictive value of blood-based biomarkers and retinal scanning through multivariate modelling of clinical outcomes, (3) to provide head-to-head comparison of the accuracy of blood- and eye-based biomarkers for early detection of AD pathophysiology, (4) to explore the pathophysiological mechanisms linking AD and eye disease by comparing the clinical and neurobiological manifestation of AD in the BeyeOMARKER cohort against a traditional memory clinic cohort, (5) to investigate enrichment for AD in an eye clinic population based on a (relative) prevalence estimate of p-tau positivity, and (6) to ultimately provide a roadmap for future studies on minimally invasive early detection of AD in alternative diagnostic settings.

Study design

A prospective observational longitudinal cohort study.

Study burden and risks

Screening requires a single visit (~45 minutes) at the recruitment site (Bergman eye clinics) and includes collection of sociodemographic and medical information, blood collection (1x 6 mL EDTA blood) for plasma p-tau and N4PE analysis, optional blood collection for the BeyeOMARKER biobank (2x 6 mL EDTA blood for plasma, 1x 6 mL EDTA whole blood for genetic analyses), and a short cognitive and visuoperceptive screening battery. All screened participants (n=~700) will undergo annual cognitive screening (remote T1 and T2, 9-12 month interval) and are invited for annual questionnaires in collaboration with the *A Personalized Medicine Approach for Alzheimer's Disease* (ABOARD) cohort (METc 2022.0120). In addition, all plasma p-tau positive cases and matched negative controls (n=150) will be included in the BeyeOMARKER+ cohort for more extensive assessment at the on-site T0 (preferably 3, but max. 6 months after screening) and the on-site T2 (21-24 months after T0). This includes standard retinal imaging and HS retinal imaging using the Optina Mydriatic Hyperspectral Retinal Camera (MHRC) (T0; 60 minutes), brain MRI (T0 and T2; 30 minutes), amyloid- and tau-PET (T0; 70 and 100 minutes), and cognitive and cortical vision assessment (T0 and T2; 90 minutes) at the Amsterdam University Medical Center, location Vrije Universiteit medical center (VUmc). The study procedures of T0 will be split across minimally two visit days, adding up to a total of

three visit days and one remote assessment across two years of participation in the longitudinal subcohort. Potential burdens experienced by participants include mild discomfort during the blood draw, temporary photophobia and blurred view due to pupil mydriasis (tropicamide 0.5% drops) prior to retinal imaging, discomfort during the MRI, and burdens related to the PET-scan (i.e. radiation exposure, minimal risk on idiosyncratic reaction to the tracer and placement of the intravenous catheter). Risks related to the Optina MHRC are negligible according to the FDA 510(k) premarket notification of intent, and light exposure during scanning is below the recommended limits. All other study procedures are medical routine procedures with known and acceptable risks. There are no expected medical benefits to participation. The BeyeOMARKER study has a non-disclosure policy for personal study results and participants will be informed of the BeyeOMARKER disclosure protocol prior to participation to ensure that participants are supported in making informed decisions concerning their own biomarker data. However, participants will receive consultation in case of a clinically relevant incidental finding.

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

- >= 50 years of age
- No dementia diagnosis

Exclusion criteria

The eye condition only concerns:
- A traumatic insult
- A superficial inflammatory eye disease (i.e. in cornea and conjunctiva)
- A condition in a structure surrounding the eye that is not directly involved in visual processing (e.g. the tear-ducts and eye muscles)

Study design

Design

Study type:	Observational 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):	09-07-2024
Enrollment:	700
Type:	Actual

Medical products/devices used

Generic name:	Janssen SIMOA pTau-217 v2 Assay and Human Neurology 4-Plex E (N4PE) Assay
Registration:	No

Ethics review

Approved WMO Date:	19-03-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-10-2024
Application type:	Amendment
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	NL83157.000.23