BMJ Open

# Impact of hearing loss and vestibular decline on cognition in Alzheimer's disease: a prospective longitudinal study protocol (Gehoor, Evenwicht en Cognitie, GECkO)

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**To cite:** Bosmans J, Jorissen C, Cras P, *et al*. Impact of hearing loss and vestibular decline on cognition in Alzheimer's disease: a prospective longitudinal study protocol (Gehoor, Evenwicht en Cognitie, GECkO). *BMJ Open* 2020;**10**:e039601. doi:10.1136/bmjopen-2020-039601

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-039601).

Received 20 April 2020
Revised 31 July 2020
Accepted 07 August 2020



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## ABSTRACT

**Introduction** Dementia is a prevalent disease affecting a growing number of the ageing population. Alzheimer's disease (AD) is the most common cause of dementia. Previous research investigated the link between hearing loss and cognition, and the effect of vestibular dysfunction on cognition. Hearing loss and, to a lesser extent, vestibular decline both result in a decreasing cognitive function. However, their interaction should not be underestimated. The aim of this study is to assess the effect of hearing loss, vestibular decline and their interaction on cognition in people suffering from mild cognitive impairment (MCI) and dementia due to AD (ADD).

**Methods and analysis** We designed a prospective longitudinal study to assess the effect of hearing loss and vestibular decline on cognition. A total of 100 cognitively impaired elderly (between 55 and 84 years of age), consisting of 60 patients with MCI due to AD and 40 patients with ADD will be included. The control group will consist of individuals with preserved cognition group-matched based on age, hearing level and vestibular function. A comprehensive assessment is performed at baseline, 12-month and 24-month follow-ups. The primary outcome measure is the change in the Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-impaired individuals total score, a cognitive test battery assessing different cognitive domains. Secondary outcome measures include additional neuropsychological assessments, cortical auditory-evoked potentials, and evaluation of general and disease-specific health-related quality of life. Variables include cognitive, audiological and vestibular evaluation. Variance analyses will assess the effect of hearing loss and vestibular decline on cognition. More precisely, the link between hearing loss and non-spatial cognitive functioning, the effect of vestibular decline on spatial cognition and the impact of both factors on the rate of conversion from MCI due to AD to ADD will be investigated.

**Ethics and dissemination** The study protocol was approved by the ethical committee of the Antwerp University Hospital on 4 February 2019 with protocol number B300201938949. The findings will be disseminated through peer-reviewed publications and conference presentations.

**Trial registration number** ClinicalTrials.gov Registry (NCT04385225).

## Strengths and limitations of this study

- To our knowledge, this longitudinal study is the first to assess both hearing loss and vestibular decline in a cognitively impaired elderly population.
- Cognition will be evaluated with a neuropsychological test adapted for a potentially hearing-impaired population.
- Expected outcomes will support prospective interventional studies assessing the potential benefit of customised hearing and vestibular rehabilitation.
- Expected outcomes will support the set-up of audiological and vestibular screening protocols in patients with Alzheimer's disease and those at risk.

## BACKGROUND

Cognition can be defined as the mental action of acquiring knowledge and understanding through experiences, thoughts and the senses. According to the Diagnostic and Statistical Manual of Mental Disorders, cognition encompasses six different domains.

These domains include learning and memory, language, perceptual-motor function, executive function, complex attention and social cognition. This article will focus on overall cognitive function and spatial cognition in particular. Spatial cognition is part of the perceptual-motor function domain. It is defined as the way the mind processes and understands two-dimensional and three-dimensional space, which includes spatial memory and spatial navigation. Spatial memory integrates information of

one's environment using several different components. These components include geometry, relative position, distance, size, orientation and coordinates.[1] Spatial navigation involves the ability of successfully moving through one's environment. This concept encompasses head direction, which refers to the awareness of the angle and direction of one's head and path integration.[1] Non-spatial cognition comprises the resulting cognitive domains. To assess one's cognition, multiple neuropsychological test batteries can be performed. However, available tests are often lengthy. Therefore, the Mini-Mental State Examination (MMSE), a simplified cognitive mental status examination is developed. This MMSE can be used as a first screening device for cognitive impairment. Currently, the MMSE is routinely used in daily clinical practice as it only takes 5–10 min to administer. Based on the MMSE score, a more extensive neuropsychological evaluation can be indicated. This quick screening and possible further evaluation of one's cognitive function gains importance since the world population is ageing rapidly. This progressive ageing of the population results in an increased amount of people suffering from dementia. Worldwide around 47 million people were affected with dementia in 2015, and this number is expected to triple by 2050.[2] Dementia is an umbrella term for diseases characterised by a decline in multiple cognitive function domains that affects a person's ability to perform daily activities. The most common type of dementia is Alzheimer's disease (AD), which, according to the WHO, accounts for 60%–70% of all dementia cases.

A different kind of cognitive decline is mild cognitive impairment (MCI). In this case a person experiences a decreased cognitive function but can still autonomously perform their activities of daily life (ADL).[3] Within 5 years more than half of the cases progresses into a dementia syndrome.[4] Especially the amnestic subtype of MCI could be a prodromal stage of AD, because of its high risk of conversion. The diagnosis of dementia and its subtypes, like AD, is currently based on the patients' medical history, physical examination, neuropsychological assessment, their performance in ADL and biomarkers. These biomarkers include (hippocampal) atrophy on brain MRI, fluorodeoxyglucose/positron emission tomography (FDG-PET), cerebrospinal fluid biomarkers and amyloid PET. Apart from these reliable biomarkers for diagnosing AD, other objective parameters may be of added value in the early detection of cognitive decline and the evaluation of conversion from prodromal AD to dementia due to AD (ADD).[5] One promising objective parameter is the measurement of cortical auditory-evoked potentials (CAEPs). Three major CAEPs are classified by latency from the P1-N1-P2 complex. Their latencies lie between 80 ms and 200 ms, and P300 latencies lie between 150 ms and 1000 ms.[6] The P1-N1-P2 complex is an obligatory CAEP response and is therefore always present in a healthy auditory system. The P300 component is obtained with an oddball paradigm, where standard stimuli are presented most of the time (80%) but occasionally (20%) a deviant stimulus is presented, which elicits the P300 response. The latency of the P300 component can be linked to processes involved in perception and cognition. Since dementia is an example of cognitive decline, it may alter the characteristics of the P300 response.[7] CAEPs provide objective information about the auditory system and reliable temporal resolution. But still little is known about its promising possibilities. Thus, CAEPs can possibly be used as an early-stage diagnostic marker for cognitive decline and may predict the conversion from prodromal AD to ADD, thus could therefore have the potential of being an important objective parameter.

Hearing loss gradually increases with old age and affects approximately one-third of the ageing population. Multiple studies have shown that hearing impairment is associated with an increased risk of cognitive decline.[8] One of these studies, performed by Harrison Bush *et al*, states that peripheral hearing accounts for significant, but small, changes in processing speed, executive function, memory and global cognitive status.[9] Consistent with these results, multiple studies found significant, though also small, associations between hearing loss and cognitive function in older adults, independent of age, sex, education or other confounding variables.[10–13] Most often, these studies found an impairment in overall cognitive function, as well as a more pronounced decline in memory and executive function. However, various studies could not replicate these findings.[14–16] A systematic review and meta-analysis performed by Loughrey *et al* found a significant association between age-related hearing loss and a decreased performance on all domains of cognitive function.[17] Furthermore, they state that hearing loss is related to cognitive impairment and dementia, while vascular dysfunction and impaired verbal communication may also contribute to this association. Lin *et al* demonstrated that hearing loss is independently associated with accelerated cognitive decline and cognitive impairment. In addition, a 24% increased risk of cognitive impairment in individuals with hearing loss was found, with more severe hearing loss resulting into an accelerated cognitive decline and greater risk of cognitive impairment.[18] Furthermore, patients with dementia show greater degrees of hearing loss.[19] In summary, hearing loss is a modifiable risk factor and possible biomarker for cognitive decline, cognitive impairment and dementia.[17] While assessing cognitive function in subjects with hearing loss, one has to keep in mind that the subject may perform worse because of not receiving the instructions clearly. Hence, their hearing loss can bias the results of the predominantly verbal tests. A possible solution is to simultaneously present the instructions and stimuli in an oral and visual manner. An example of a cognitive test adapted for hearing-impaired subjects is the Repeatable Battery for the Assessment of Neuropsychological Status adapted for Hearing impaired persons (RBANS-H).[20] This comprehensive neuropsychological assessment investigates cognitive function in a reliable manner in hearing-impaired subjects by using an accompanied

PowerPoint presentation shown on an external computer screen. This presentation supports all oral instructions and stimuli with written explanations and stimuli. Therefore, the participant can understand all instructions and should be able to reproduce presented stimuli even when auditorily deprived.

In addition, vestibular decline, affecting one-third of the older population, may influence cognitive performance.[21] The vestibular apparatus, located in the inner ear, is responsible for gaze stabilisation by coding rotation and translation of the head. This vestibular apparatus projects to the medial temporal cortex, which includes the hippocampus and entorhinal cortex. These brain structures are known for their strong involvement in spatial cognition and computation of the inner neural map.[22–24] Bilateral vestibulopathy (BVP), characterised by a bilateral vestibular function loss, leads to hippocampal atrophy, memory impairment, and a decline of spatial cognition and attention.[25–31] This may suggest that vestibular dysfunction is a risk factor for dementia, more specifically for AD. In addition, vestibular decline can predict a decrease in spatial cognition in patients with MCI and AD.[32 33] When comparing spatially impaired patients with AD with spatially normal patients with AD, a significantly higher prevalence of vestibular decline is present in the former group. Furthermore, patients with vestibular dysfunction experience an increased risk of falling and deficits in daily activities.[32] In addition, patients with AD show more often impaired saccular function in comparison with patients with MCI and preserved cognition, while semicircular canal function remains intact.[21]

Often sensorineural hearing loss (SNHL) and vestibular decline are concomitant. According to Dobbels *et al*, 85% of patients with BVP had abnormal hearing in at least one ear. Compared with literature, this prevalence was relatively high.[34] Vice versa, more than half of patients with hearing loss (26–80 dB HL of better ear) presented with vertigo and abnormal vestibular test results (including caloric irrigation and vestibular-evoked myogenic potential (VEMP) testing).[35] This underpins the importance of assessing both hearing and vestibular function in these patient groups. However, little research integrates both the scientific evaluation of hearing loss and vestibular dysfunction in their analyses. Therefore, to date this research question has not (yet) been systematically evaluated in an elderly population. The association between SNHL and cognitive impairment has been investigated thoroughly and appears to be robust. Nonetheless, vestibular decline as a potential cause of cognitive decline has been frequently overlooked.[17 36] Additionally, a systematic literature review evaluating the relationship between BVP and cognition concludes that the effect of vestibular decline on cognition is often established without considering hearing loss as a potential confounding variable.[31] This leaves the question whether the impact of hearing loss on cognition might be related to concomitant vestibular dysfunction (and vice versa) unanswered.

The objective of this longitudinal study is to investigate the impact of SNHL and vestibular decline on CAEPs, overall cognitive functionand spatial cognition in particular in patients with MCI due to AD and ADD. The study sample will be compared with cognitively healthy subjects group-matched based on mean age at baseline, mean hearing level of the better-hearing ear and mean vestibular function. It is hypothesised that SNHL will result in overall cognitive dysfunction and CAEPs deficits. In addition, vestibular decline will increase the spatial cognitive load in a population with MCI due to AD and ADD. Furthermore, it is hypothesised that SNHL and vestibular decline may result in an increased rate of conversion from MCI due to AD to ADD.

## METHODS

### Study setting

This study will be coordinated by the department of Translational Neurosciences of the University of Antwerp. The study will be performed at the departments of Otorhinolaryngology and Neurology of University Hospital Antwerp in collaboration with the memory clinic/department of Neurology of Hospital Network Antwerp Middelheim and Hoge Beuken, and University Hospital Brussels in Belgium.

### Eligibility criteria

A total of 100 cognitively impaired elderly will be included in the study. This group will consist of 60 patients with diagnosed MCI due to AD and 40 patients with diagnosed ADD, all between 55 and 84 years of age. The cut-off of 55 years was chosen because this age was the youngest mean age in which presence of hearing loss was shown to increase dementia risk.[37] As the prevalence of individuals with hearing loss, vestibular decline and cognitive impairment increases with age,[38–43] and in order to guarantee sufficient patient inclusion, the upper boundary of 84 years of age was chosen for patient inclusion. The control group will encompass individuals with preserved cognition group-matched based on mean age at baseline, mean hearing level of the better-hearing ear and mean vestibular function. The protocol will be executed by a trained psychiatrist, geriatrician or neurologist after proper neuropsychological examination. A diagnosis will be made according to the International Working Group-2 criteria.[44] Inclusion and exclusion criteria are presented in table 1. The MMSE is used as a short cognitive screening to obtain a first measurement of overall cognitive function. A total score greater than 12 is needed to enable vestibular assessment.

Participation will be discontinued when asked by the participant. When the researchers are convinced that further participation of the participant is adverse for the research or the participant's health, participation will be terminated.

### Sample size and power

A power calculation is performed to obtain an estimation of the needed sample size to detect significant differences in RBANS-H total score at baseline and at a 24-month follow-up.

Table 1 Inclusion and exclusion criteria

| Inclusion | Exclusion |
|---|---|
| ► MMSE >12 | ► Uncorrectable visual impairment |
| ► Between 55 and 84 years of age | ► Hearing implants |
| ► Diagnosis of MCI and dementia due to AD according to IWG-2 criteria | ► Hearing aids |
| ► Dutch-speaking | ► Conductive hearing loss |

AD, Alzheimer's disease; IWG-2, International Working Group-2; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

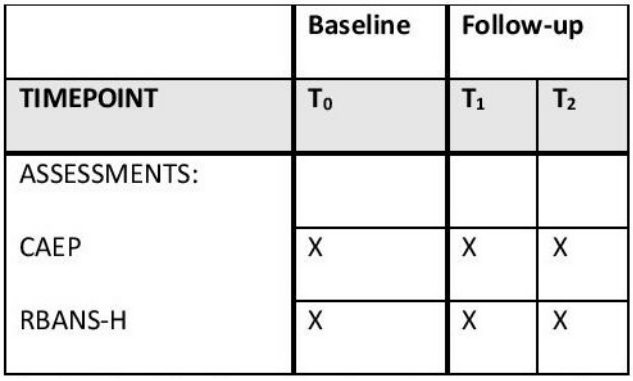


Figure 1 Schedule of enrolment and assessments in accordance with the Standard Protocol Items: Recommendations for Interventional Trials 2013 guidelines. CAEP, cortical auditory-evoked potential; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status adjusted for Hearing-impaired individuals.

A two-sided paired t-test is carried out to obtain a power of 80% to detect a mean of paired differences of 4 with an estimated SD of 8 and a significance level (alpha) of 0.05. A non-parametric calculation showed a proposed sample size of 34 subjects per group. These sample size calculations are based on the RBANS-H total score of cognitively healthy participants with SNHL. As the RBANS-H total score of cognitively impaired patients is expected to result in more differentiated outcomes, a smaller sample size should be sufficient to obtain statistical significance. As one of the aims of this study is to evaluate the rate of conversion from prodromal AD to ADD, a larger number of patients with prodromal AD will be required. When covering a possible drop-out and possibility of recruitment, 60 patients with MCI due to AD and 40 patients with ADD will be recruited. In conclusion, a total of 100 cognitively impaired patients will be recruited for the study.

## Intervention description

For this longitudinal study, an extensive protocol will be administered comprising audiological, vestibular and cognitive testing. The study protocol will be assessed at baseline, 12 months and 24 months. The schedule of assessment is displayed in figure 1. Prior to any test enrolment all patients fill out an informed consent. All researchers involved in this study are International Conference on Harmonisation–Good Clinical Practice certified.

### Cognitive assessment

► RBANS-H

The RBANS-H is based on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[45] The RBANS is a neuropsychological test used to detect mild forms of cognitive disorders. The RBANS-H is developed in order to examine cognitive function of individuals with hearing impairment.[20] This is done by presenting an accompanying PowerPoint presentation. Written explanations are given to support verbal instructions and to ascertain that the participant understands the instruction. Besides a visual support of the instructions, all relevant stimuli are not only presented verbally but visually as well. All adjustments were made in accordance to the RBANS guidelines.

The RBANS-H consists of 12 subtests: 'List Learning', 'Story Memory', 'Figure Copy', 'Line Orientation', 'Picture Naming', 'Semantic Fluency', 'Digit Span', 'Coding', 'List Recall', 'List Recognition', 'Story Recall' and 'Figure Recall'. It measures the cognitive domains of immediate memory, visuospatial/constructional, language, attention and delayed memory.

The cognitive domain of immediate memory is examined by subtests 'List Learning' and 'Story Memory'. In 'List Learning', a list of 10 words is repeated four times, while in 'Story Memory', a 12-item short story is presented two times. After each presentation, either a list of 10 words or a short story, the participant is instructed to recall as much of the words or story as possible. The visuospatial/constructional domain consists of the subtests 'Figure Copy' and 'Line Orientation'. In the former, a complex geometric figure is presented and the participant needs to copy this figure as exactly as possible. In the latter, the participant needs to match two lines according to their different degrees of orientation. To assess language, participants are asked to name 10 line drawings in the subtest 'Picture Naming', while in the subtest 'Semantic Fluency', they are asked to generate as many examples as possible from a certain semantic category in 1 min. The attention domain consists of the subtest 'Digit Span', where a string of digits is presented, after which the individual is asked to repeat the digits in the correct order. When doing so successfully, the string becomes longer and more digits need to be repeated. The subtest 'Coding' is also part of the attention domain, where the participant needs to complete a page of symbols as much as possible with the corresponding digits according to a key on top of the page in 2 min. To assess delayed memory, the participant needs to recall as many items as possible from the subtest 'List Learning' (free recall and recognition; where the latter 10 target words are presented from the to-be-remembered list, as well as 10 distractors, and the participant needs to indicate

which words needed to be remembered and which were not in the list). The participant also needs to recall as much items as possible from the subtest 'Story Memory' and is instructed to redraw the complex figure from memory which was presented in the subtest 'Figure Copy'. These subtests are called 'List Recall', 'List Recognition', 'Story Recall' and 'Figure Recall', respectively.

Total scores of the subtests are summed in order to calculate index scores. These index scores are normed based on the age of the participant. The sum of all index scores is used to determine the total scale and percentile.

### Audiological assessment

- CAEP

To investigate auditory processing, CAEPs are measured. Patients wear a 32-channel electroencephalography (EEG) electrode cap, with 31 silver/silver chloride (Ag/AgCl) electrodes placed according to the 10–20 Standard International Electrode System referenced to a chin electrode, with the ground electrode placed on the right mastoid. While wearing this EEG-electrode cap, patients are presented an oddball paradigm. They are instructed to press a button every time a rare stimulus (2000 Hz, with a probability of 20%) is presented in between frequent stimuli (1000 Hz, with a probability of 80%). These stimuli, presented through shielded headphones (Audio Technica ATH M30x Refaeds), have a rise and fall time of both 5 ms and are delivered by the use of the software Presentation (Neurobehavioral Systems, Albany, California, USA). The EEG is recorded (Micromed SD LTM 64 Express) using the interface 'Gilat Medical Event Related Potentials system'. One additional electrode is placed below the right eye to record the vertical electro-oculogram, which can later be used to distinguish eye blinks. After recording, the EEG is sampled at 1024 Hz with 22-bit A/D resolution.

EEG data will be preprocessed using the Fieldtrip toolbox in MATLAB V.9.6.0.1150989 (R2019a) (Mathworks, Natick, Massachusetts, USA).[46] First, using a default Butterworth IIR filter between 0.5 Hz and 45 Hz, offline bandpass filtering will be applied to continuous EEG data. A channel may present excessive noise or low activity and will therefore be identified as a bad channel. Next, to detect eye blinks, an independent component analysis (ICA) will be performed and components will be identified based on their time course and localisation. Components including eye blinks will be removed from the data using an inverse ICA procedure. Subsequently, data will be segmented into 2-second epochs time-locked to the stimuli. Based on the amount of variance determined by visual inspection of the data, artefacts will be removed from the data set. This procedure will be performed by investigators blinded to subject groups. The percentage of removed trials for each subject group will be reported. The signal of excluded channels will be interpolated based on the activity of neighbouring channels using a weighted algorithm. The number of interpolated channels will be reported on a group level. Furthermore, a correction to a baseline period of 0.2 s preceding stimulus presentation will be applied to all epochs. Linear trends will also be removed from the data, using a detrending method. Because of the interest in differences between responses to target and non-target tones, these responses will be averaged separately.

## Outcomes

### Primary outcome measure

The primary outcome measure is the change in total score of the RBANS-H,[20] from baseline to follow-up at 24 months.

### Secondary outcome measures

- CAEP

Grand averages for each subject group (MCI due to AD and ADD) and time point (baseline, 12-month and 24-month follow-ups) will be calculated. Next, differences in responses between subjects with MCI and dementia due to AD will be detected by the Fieldtrip toolbox. The evolution of responses within the MCI and dementia due to AD subject groups from baseline to 12-month and 24-month follow-ups will also be investigated. This will be done on a global and scalp level. Clusters with significant differences between time points or subject groups are detected with permutation testing, using the Monte Carlo method with 1000 iterations. Finally, important CAEP peaks will be located by visual inspection. Calculation of these peak values will be performed using peak finding functions provided in MATLAB. Standard t-tests ($p<0.05$, two-tailed) will be used to compare amplitudes and latencies of these peak values across subjects with MCI and dementia due to AD, and between baseline, 12-month and 24-month follow-ups. All reporting of preprocessing steps and analysis will be done according to publication guidelines.[47]

## Variables

Next tests will be performed to assess the participants' cognitive, audiological and vestibular function. These variables may influence cognition, the rate of conversion to ADD and CAEP.

### Cognitive variables

- MMSE

The MMSE is a cognitive test, which consists of 11 questions and requires 5–10 min to administer.[48] Questions cover temporal and spatial orientation, memory, attention, the ability to name, follow verbal and written commands, write a sentence spontaneously and copy interlocking pentagons. A maximum score of 30 can be obtained.[49]

### Audiological variables

- Pure tone audiometry

Pure-tone audiometry for air conduction will be performed at 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 6000 Hz and 8000 Hz using insert-earphones and a two-channel AC-40 audiometer (Interacoustics, Assens, Denmark). Bone conduction thresholds will be measured at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz and 4000 Hz when air conduction thresholds between 250 Hz and 4000 Hz exceed normality levels of 20 dB HL, so a distinction between sensorineural and conductive hearing loss can be made. Subsequently, the Weber test will be conducted to identify lateralisation.

- Speech-in-noise (SPIN)

The speech audiometry in noise is assessed by the Leuven Intelligibility Sentences Test using an adaptive procedure.[50] This SPIN test is conducted in free field using a loudspeaker at 0° azimuth at a distance of 1 m. The frequency spectrum of the noise matches the long-term average frequency spectrum of the speech signal. The noise level is constant at 65 dB SPL, while the speech level is adapted according to the response of the patient. A correct repetition of the keywords of a sentence results in a decreased speech level of 2 dB SPL, while an incorrect response results in an increased speech level of 2 dB SPL. Every list consists of 10 sentences, and minimally two lists are conducted in order to acquire the speech reception threshold (SRT). This SRT is calculated by averaging the speech levels of the last five sentences of the last list and the imaginary 11th sentence.

### Vestibular variables

- Video Head Impulse Test (vHIT)

The vHIT is a vestibular test. The patients are instructed to focus on a fixation dot placed at eye-level 1 m in front of them. The patients will experience short, quick head movements in the direction of all six (lateral, superior and posterior; left and right ear) semi-circular canals, performed by the researcher. The vHIT makes use of the ICS Impulse (Otometrics, Natus, Pleasanton, California, USA), which is a lightweight pair of glasses with a built-in accelerometer and video camera pointed at the right eye so it can analyse the vestibulo-ocular reflex. The eye and head movements of patients with a working vestibular system will overlap. When patients experience vestibular loss, a corrective saccadic eye movement ('catch-up' saccade) will be present. Measurements will consist of gain, SD, saccades (percentage and amplitude of covert and overt saccades), a classification of the saccades (normal, gathered, scattered) and the amplitude of the head. These measurements will be collected for all six semi-circular canals.

- Cervical VEMPs (c-VEMPs)

c-VEMPs are ipsilateral inhibiting muscle potentials measured at the level of the contracted sternocleidomastoid (SCM) muscle. These potentials are evoked by short tone bursts presented to the patient through insert-earphones. The patient is instructed to tilt his head to one side, thus tensioning the SCM muscle, while stimuli are presented in the contralateral ear. This procedure is repeated multiple times while decreasing the sound intensity and detecting the stimulation threshold. A typical c-VEMP potential is biphasic and characterised by two distinctive peaks (p13, n23). When this c-VEMP potential is present, it shows an intact reflex arc (sacculus–inferior vestibular nerve–vestibular nuclei–vestibulospinal tract). Besides a measurement of whether this reflex is present, also the threshold, the latency of p13 and n23, and the amplitude is assessed, for both the left and right ear. This test will be conducted using the validated neuroaudio device with electromyography feedback (Neurosoft).

### Questionnaires

- Edinburgh Handedness Inventory

This inventory is a quantitative assessment of handedness. Participants need to indicate for all 10 items if they prefer using their right hand, left hand or both. After calculations, it can be evaluated whether the participant is predominantly right-handed, left-handed or ambidexter.[51]

- Beck Depression Inventory (BDI)

The BDI is used to measure symptoms and severeness of depression. Participants must answer 21 questions. Every question has four answer options, which are displayed with an ascending grade of depression. The total score is the summed item score. A higher total score indicates a higher degree of depression (0–13=minimal, 14–19=light, 20–28=moderate, 29–63=severe depression).[52]

- Hospital Anxiety and Depression Scale (HADS)

The HADS screens states of anxiety and depression using a total of 14 questions.[53] Seven questions pertain to the subscale 'anxiety', whereas the other seven belong to the subscale 'depression'. A total score of 7 or less on each subscale indicates a non-case. A score of 8–10 is a borderline case, and a score of 11 or more indicates a case.[54]

- Type D Scale-14 (DS14)

The DS14 is used to assess negative affectivity, social inhibition and type D personality. The inventory contains 7-item negative affectivity and social inhibition subscales. A total score greater than or equal to 10 on either the negative affectivity or social inhibition subscale indicates a case. A type D personality is present when both subscale scores are greater than or equal to 10.[55]

- Dizziness Handicap Inventory (DHI)

This questionnaire measures self-perceived handicap resulting from dizziness and unsteadiness due to vestibular system diseases.[56] The DHI consists of 25 questions which can be divided into three subscales: functional, emotional and physical impacts on disability. A total score is calculated and indicates the level of handicap (0–14=no handicap, 16–34=mild handicap, 36–52=moderate handicap, >54=severe handicap).[57]

- Vestibular Disorders Activities of Daily Living Scale

This self-rated scale quantifies the effects of vertigo and balance disorders on independence in performing ADL by assessing the patient's perception about its autonomy in functional, ambulation and instrumental skills. The summed total and median is calculated for the total questionnaire, as well as for each subscale.[58]

- Activity-specific Balance Confidence (ABC) Scale

Seniors' balance confidence in their ability to perform daily activities without falling is investigated using the ABC Scale. This self-perceived handicap questionnaire includes a wider range of activity difficulty and items are described in more detail, compared with the Falls Efficacy Scale International (FES-I). The average score is calculated, with a higher score indicating more confidence in not losing balance.[59]

- Short FES-I

Balance confidence will also be evaluated by the short version of the FES-I. This questionnaire comprises seven statements which each is an activity of daily living commonly performed by seniors. Participants mark each item on a scale from 1 (not at all concerned about falling) to 4 (very

concerned about falling). The summed total score is used to identify the degree of concern, which can be done using the 2-item gradation (7–10=low concern, 11–28=high concern) or the 3-item gradation (7–8=low concern, 9–13=moderate concern, 14–28=high concern).[60]

- Speech, Spatial and Qualities of Hearing Scale-12 Questionnaire (SSQ12)

The SSQ12 consists of 12 questions and is a short version of the Speech, Spatial and Qualities of Hearing Scale. This questionnaire measures several aspects of hearing ability, such as: speech comprehension in quiet and noisy environments; localisation of sound, distance and movement; segregation and listening effort. Patients rate their ability to hear or experience different situations on a 1–10 scale (1=not at all, 10=perfectly). An average of all 12 scores is calculated.[61]

- Oscillopsia Severity Questionnaire (OSQ)

The OSQ is a questionnaire consisting of nine questions assessing whether the patient has an unstable view while performing different activities or engaging in different situations. The patient must mark whether he always/often/sometimes/seldom/never experiences unstable vision during the described activity or situation. These answers are converted to a 5–1 scale (5=always, 1=never) and an average score is calculated. An average score of greater than 3 indicates moderate to extreme oscillopsia severity.[62]

- Barthel Index

The Barthel Index is a questionnaire which consists of 10 questions and measures the level of independence in performing ADL. The Barthel Index is also used to define the dementia stage or conversion from MCI to dementia. A higher total score describes a higher level of independence (0–4=fully dependent, 10–14=needs help but can perform independently, 15–19=predominantly independent, 20=fully independent in basal ADL and mobility).[63]

- Comprehensive Frailty Assessment Instrument (CFAI)

This self-administered instrument measures frailty in four domains (physical, psychological, social and environmental frailty). The total score is calculated by summing the scores per domain and can identify three levels of frailty: no to mild frailty, moderate frailty and severe frailty. A higher total CFAI score indicates more frailty.[64]

- European Quality of Life-5 Dimensions Questionnaire (EQ5D-5L)

The EQ5D-5L is a questionnaire that measures health-related and disease-specific quality of life using five dimensions (mobility, self-care, daily activities, pain/discomfort, anxiety/depression).[65] Answers are converted into an EQ5D-5L profile, which is converted into an index value scaled from 0 (death) to 1 (perfect health). The questionnaire also assesses self-perceived health by using a Visual Analogue Scale. Participants need to report their perceived health status on a scale ranging from 0 (worst possible health status) to 100 (best possible health status).[66]

- Health Utilities Index Mark-3 (HUI3)

The HUI3 is a health-related and disease-specific quality-of-life measuring instrument.[67] This self-administered questionnaire comprises 15 questions, which can be divided into eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain). The total score ranges from 0 (dead) to 1 (perfect health).

### Data collection and management

Patient-level trial-related data will be collected using the participating site's electronic medical record and OpenClinica (V.3.13). OpenClinica is used to enter and store data in a clean, secure and efficient manner. This software package is developed especially for electronic data management in clinical research. Only the principal investigators have access to this password-protected database. Validation checks such as range checks for data values are programmed so that the number of mistakes is minimised. The information collected in this study is kept strictly confidential. Individual information and results are coded, with only the researcher knowing which code was assigned to each participant. The data are stored for 20 years.

### Statistical methods

Data will be analysed using SPSS statistical software V.25. Descriptive analyses will be expressed as mean values with SD or SEM. If the data is not normally distributed, median and median absolute difference will be reported. Cross-sectional results will be studied first using intended parametric or non-parametric tests, to provide insight in the correlation between hearing, vestibular function and cognition. Longitudinal differences will be analysed at 12 and 24 months using variance analyses (repeated measure design). A corresponding non-parametric test will be used to study the effect on conversion to dementia in patients with MCI. A significance level of 0.05 will be applied. The Holm-Bonferroni method will be used for multiple comparison correction.

## DISCUSSION

Because of the worldwide growing prevalence of dementia, identification of possible risk factors is prioritised. First of all, hearing loss is considered to be an independent risk factor for dementia. The evidence that a vestibular decline could also be a risk factor for cognitive decline continues to rise. Because of the close anatomical relationship between auditory and vestibular structures of the inner ear, hearing loss and vestibular decline are often presented jointly. Furthermore, previous studies often subjectively assess hearing and/or vestibular function. In this respect, subjects participating in this experiment will undergo extensive testing. This way, an objective and scientifically substantiated assessment of subjects' hearing, vestibular and cognitive function is performed.

To our knowledge, this is the first research project that will look into the effect of both hearing loss as well as vestibular decline on cognition, including their interaction. This study will go beyond the current state of art by using a neuropsychological cognitive test adapted for a potentially hearing-impaired population with MCI and dementia due to AD. This way hearing-impaired subjects will be able to understand the instructions clearly and perform conforming to their actual cognitive level. Furthermore, the study will be able

to objectively identify the impact of hearing loss and vestibular decline on both global cognitive function, as well as on specific (spatial and non-spatial) cognitive domains. Vestibular loss is expected to decrease the level of spatial cognitive function, whereas hearing loss is expected to reduce non-spatial cognition.

The expected results will gain important insights in the identification of risk of falling, unsteadiness, driving difficulties, which in turn can lead to major health concerns in people with ADD. Furthermore, vestibular rehabilitation is proven to be effective in balance improvement and reduction of fall risk in cognitively healthy subjects with vestibular deficits. On the contrary, the effectiveness of vestibular rehabilitation in cognitively impaired subjects, in this case subjects with MCI or dementia due to AD, has not yet been explored.[68] Future prospective interventional studies may look into the potential benefit of customised vestibular rehabilitation in subjects with varying degrees of cognitive decline, which will be supported by current research.

Hearing loss may be an early indication of ADD, and care management is primarily based on communication between the patient and its caregivers. However, the patient's hearing function is not taken into account during the diagnosis of ADD. As a result, hearing loss may be one of the most overlooked deficits in persons with ADD.[69] The expected results may alter this diagnostic process. In addition, current research would support future studies investigating whether individualised hearing rehabilitation could lessen cognitive decline, the rate of conversion to dementia and/or frailty. Finally, the set-up of audiological (eg, CAEP) and vestibular screening protocols in patients with MCI and dementia due to AD and those at risk will be strengthened by current research outcomes.

## Trial status

The present study protocol (V.1.1) was finalised on 30 January 2019. Patient recruitment was initiated in November 2019 and is expected to conclude in October 2020.

## Patient and public involvement

Patients or the public were and will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

## Ethics and dissemination

Written informed consent will be obtained from each participant and/or their legal guardian before baseline testing. The study protocol was approved by the ethical committee of the Antwerp University Hospital on 4 February 2019 with protocol number B300201938949. The findings will be disseminated through peer-reviewed publications and conference presentations.

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**Contributors** JB drafted the manuscript with support from CJ and EP. VVR, GM, AG, JM, AVO, PC and SE conceived and designed the study. All authors read and approved the final manuscript.

**Funding** This work was supported by an Applied Biomedical Research FWO grant number G042819N3.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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