PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of hearing loss and vestibular decline on cognition in Alzheimer's disease: a prospective longitudinal study protocol (Gehoor, Evenwicht en Cognitie, GECkO)
AUTHORS	Bosmans, Joyce; Jorissen, Cathérine; Cras, Patrick; Van Ombergen, Angelique; Engelborghs, Sebastiaan; Gilles, Annick; Princen, Eline; Moyaert, Julie; Mertens, Griet; Van Rompaey, Vincent

VERSION 1 – REVIEW

REVIEWER	Arianna Di Stadio University of Perugia
REVIEW RETURNED	26-May-2020

GENERAL COMMENTS	The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Yuri Agrawal Johns Hopkins, USA
REVIEW RETURNED	22-Jun-2020

GENERAL COMMENTS	GENERAL COMMENTS This paper lays a plan to conduct a prospective observational cohort study of the influence of hearing and vestibular function on cognitive function in patients with AD. This is an important area of study. It's not clear why the trial is focused on cognitively impaired rather than healthy older adults. Also, further methodological clarifications are requested per below. SPECIFIC COMMENTS Page 3 line 55: It's not clear why spatial and non-spatial cognition are specifically being considered. Hearing is not particularly associated with spatial cognition, it's unclear why the cognitive function associated with hearing loss are being lumped together. This study is also proposing to evaluate the use of CAEP in detecting cognitive decline, which is an unrelated aim. Will the study consider interactions between hearing and vestibular decline? The relationship between hearing loss and vestibular loss needs to be better explained, what is the reported association between these 2 variables. Why are the authors anticipating higher dropout rates in the MCI group compared to the AD group (i.e. why is the planned enrollment higher for MCI vs. AD)? It's unclear why the vWMT, Barthel index, frailty and QOL instruments are included in the study, they are not related to study

	hypotheses. Why is there an additional cognitive measure, the vWMT? What are the expected levels of hearing loss and vestibular decline in the study population? The power calculations and assumptions should be provided.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

- Methods and Analysis: You want to conduct a study on vestibular and hearing problems but you did not mention anything about testing these functions...So strange **We agree that the mentioning about vestibular and hearing evaluation is missing in the abstract. Therefore, we have added the following information.** Variables include cognitive, audiological, and vestibular evaluation.

- Methods and Analysis: I think that this number should be limited, i.e patients between 55 and 75 years **We agree that this number should be limited. Therefore, we have added the following paragraph to the manuscript.** 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 (Gallacher et al., 2012). As the prevalence of individuals with hearing loss, vestibular decline, and cognitive impairment increases with age (Agrawal et al., 2013; Colledge et al., 1994; Fernández et al., 2015; Hebert et al., 2013; Lin et al., 2011b; Tinetti et al., 2000), and in addition in order to guarantee sufficient patient inclusion, the upper boundary of 84 years of age was chosen for patient inclusion.

- Methods and Analysis: Why the number of patients is different? It seems that you already have these data. If you have to select a sample you should collect two balanced groups. **This is correct. Because we are additionally interested in evaluating the rate of conversion from prodromal AD to ADD, we will recruit more patients in the patient group with prodromal AD. Therefore, we have added the following information.** 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.

Reviewer #2: This paper lays a plan to conduct a prospective observational cohort study of the influence of hearing and vestibular function on cognitive function in patients with AD. This is an important area of study. It's not clear why the trial is focused on cognitively impaired rather than healthy older adults. **We agree that the group-matching procedure was not mentioned in the text and we**

therefore added the following line in the abstract. The control group will consist of individuals with preserved cognition group-matched based on age, hearing level, and vestibular function. **As well as the following sentence in the main text.** The study sample will be compared to cognitively healthy subjects group-matched based on mean age at baseline, mean hearing level of the better-hearing ear, and mean vestibular function

- Page 3 line 55: It's not clear why spatial and non-spatial cognition are specifically being considered. Hearing is not particularly associated with spatial cognition, it's unclear why the cognitive function associated with hearing loss are being lumped together. **We acknowledge that the association between hearing loss and non-spatial cognition is unclear. Therefore, we have changed "non-spatial cognition" to "overall cognitive function". This phrasing is more in line with the rest of the text, which states that recent studies found a significant association between age-related hearing loss and a decreased performance on all domains of cognitive function (Lin, 2011a; Lin, 2011b; Loughrey, 2018; Ray, 2018; Sugawara, 2011).**

- This study is also proposing to evaluate the use of CAEP in detecting cognitive decline, which is an unrelated aim. **We acknowledge that the use of CAEP in detecting cognitive decline is an unrelated aim, as the current diagnostic process is highly reliable. Therefore, we altered the paragraph to make it more clear that CAEPs can possibly be used in the detection of early-stage cognitive) decline and the evaluation of conversion from prodromal AD to ADD (Jiang et al., 2015).**

- Will the study consider interactions between hearing and vestibular decline? **Yes. The aim of the study is to assess the effect of hearing loss, vestibular decline, as well as their interaction on cognition in people suffering from prodromal AD and ADD. To our knowledge, this is the first research project that will look into the effect of both hearing loss and vestibular decline on cognition, including their interaction.**

- The relationship between hearing loss and vestibular loss needs to be better explained, what is the reported association between these 2 variables. **We agree that the relationship between hearing loss and vestibular loss is missing in the introduction. Therefore, we have added the following background information.** According to Dobbels et al. (2019), 85% of patients with bilateral vestibulopathy had abnormal hearing in at least one ear. Compared with literature, this prevalence was relatively high (Dobbels, 2019). 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 VEMP testing) (Niu et al., 2016). This underpins the importance of assessing both hearing and vestibular function in these patient groups.

- Why are the authors anticipating higher dropout rates in the MCI group compared to the AD group (i.e. why is the planned enrollment higher for MCI vs. AD)? **This is correct. Because we are additionally interested in evaluating the rate of conversion from prodromal AD to ADD, we will recruit more patients in the patient group with prodromal AD. Since another reviewer had the same correct comment, the following information has been added.** 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.

- It's unclear why the vWMT, Barthel index, frailty and QOL instruments are included in the study, they are not related to study hypotheses. **We acknowledge that these tests are not directly related to study hypotheses. Barthel index, frailty, and QOL instruments will provide useful information about possible confounding variables. Therefore, we have moved these parameters from "secondary outcome measures" to "variables".**

- Why is there an additional cognitive measure, the vWMT? **Originally, we aimed to use the vMWT as an additional cognitive measure of spatial navigation. However, as Dobbels et al. (2019) described, the vMWT is purely stationary. It does not rely on any vestibular input from real locomotion. It might therefore underestimate real-life spatial navigational abilities (Dobbels, 2019). Furthermore, our in-house analysis on our vMWT data of participants with preserved cognition revealed that these control patients were not able to adequately perform on this test, as they did not understand the instructions and often lacked experience with computer use. As we encountered this problem already with the control group, we expected the patient groups with impaired cognition to perform similarly or worse. Because the vMWT does not represent spatial navigation and because of the inadequate performance of our control subjects during our in-house analysis, we have therefore decided to remove the vMWT from our protocol.**

- What are the expected levels of hearing loss and vestibular decline in the study population? **We are expecting a greater degree of hearing loss in the patient group with ADD. According to Lin et al. (2011), two thirds of the population with dementia had hearing loss, compared to presence of hearing loss in only one third of the healthy population (Lin et al., 2011a; Organization, 2020). In addition, we expect a similar level of saccular impairment, as measured by absent cVEMP responses (25%), in the control group and the group with prodromal AD, but an increased level of saccular impairment in the ADD group (50%). Furthermore, we expect no significant difference in semicircular canal function, as measured by VOR gain, between groups (Harun, 2016). Therefore, we have revised the text accordingly.**

- The power calculations and assumptions should be provided. **This information is mentioned in the "methods" section of the manuscript. The revised version includes the rationale why the planned enrolment for subjects with MCI is larger that the planned enrolment for subjects with AD.**

VERSION 2 – REVIEW

REVIEWER	Arianna Di Stadio University of Perugia
REVIEW RETURNED	06-Aug-2020

GENERAL COMMENTS	Thanks for the correction

REVIEWER	Yuri Agrawal Johns Hopkins, USA
REVIEW RETURNED	03-Aug-2020

GENERAL COMMENTS	Responses satisfactory.