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# BMJ Open Evaluation of hearing levels and vestibular function and the impact on cognitive performance in (pre)-symptomatic patients with DFNA9: protocol for a prospective longitudinal study (Rosetta study)

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## ABSTRACT

**Introduction** Untreated hearing loss is the largest potentially modifiable risk factor for dementia. Additionally, vestibular dysfunction has been put forward as a potential risk factor for accelerated cognitive decline. Patients with Deafness Autosomal Dominant 9 (DFNA9) present with progressive sensorineural hearing loss and bilateral vestibulopathy and show significantly worse results in cognitive performance compared with a cognitively healthy control group. This highlights the need for adequate treatment to prevent further cognitive decline. This study aims to determine how hearing and vestibular function evolve in (pre)-symptomatic carriers of the p.Pro51Ser mutation in the *COCH* gene and how this impacts their cognitive performance and health-related quality of life.

**Methods and analysis** A prospective, longitudinal evaluation of hearing, vestibular function and cognitive performance will be acquired at baseline, 1-year and 2-year follow-up. A total of 40 patients with DFNA9 will be included in the study. The study will be a single-centre study performed at the ORL department at the Antwerp University Hospital (UZA), Belgium. The control group will encompass cognitively healthy subjects, already recruited through the GECKO study. The primary outcome measure will be the Repeatable Battery for the Assessment of Neuropsychological Status adjusted for the Hearing-Impaired total score. Secondary outcome measures include Cortical Auditory-Evoked Potentials, vestibular assessments and health-related quality of life questionnaires. The expected outcomes will aid in the development of gene therapy by providing insight in the optimal time window for the application of gene therapy for the inner ear.

**Ethics and dissemination** The ethical committee of UZA approved the study protocol on 19 December 2022 (protocol number B3002022000170). All participants have to give written initial informed consent in accordance with the Declaration of Helsinki. Results will be disseminated to the public through conference presentations, lectures and peer-reviewed scientific publications.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A neuropsychological test battery, developed and validated for a hearing-impaired population, will be used to assess cognitive performance.
- ⇒ The longitudinal study also includes pre-symptomatic carriers that will enable researchers to gain more insight into how the disease will evolve in the long term and what the exact time point of cognitive decline might be.
- ⇒ The use of Cortical Auditory-Evoked Potentials as an outcome variable is investigated to assess whether it can serve as an objective biomarker and serve as a prognostic indicator in the early stages of cognitive decline.
- ⇒ An extensive list of health-related quality of life questionnaires will be administered, which could have limitations related to self-reported data.

## INTRODUCTION

With more than 1.57 billion people affected worldwide, which could grow to 2.5 billion by 2050, hearing loss is the most frequently reported sensory deficit.<sup>1</sup> The WHO listed hearing impairment as one of the priority diseases for research into therapeutic interventions to address public health needs.<sup>2</sup> If unaddressed, hearing loss negatively impacts the patient's quality of life and society in general and leads to accelerated cognitive decline. Unaddressed hearing loss may be responsible for over 8% of cases of dementia among older adults.<sup>3 4</sup> It significantly increases the relative risk of dementia and cognitive impairment. Therefore, recent studies have identified hearing loss as the most significant potentially modifiable risk

factor for accelerated cognitive decline and age-related dementia.<sup>3–10</sup>

Not only hearing loss, but also vestibular dysfunction, and in particular bilateral vestibulopathy (BV) (bilateral vestibulo-ocular-reflex (VOR)-dysfunction) has been put forward as a potential risk factor for accelerated cognitive decline. Increasing evidence suggests that BV is associated with reduced spatial cognitive skills and may also be a risk factor for dementia.<sup>11–17</sup> This presumption has been strengthened by the fact that there is a high prevalence of vestibular dysfunctions in patients with Alzheimer's disease (AD) and vice versa. A study by Bosmans *et al*<sup>18</sup> found that individuals with BV demonstrated more cognitive deficits than healthy controls. This cognitive loss was found to be independent of concurrent hearing loss.

Deafness autosomal dominant 9 (DFNA9) is a non-syndromic dominant hereditary disorder caused by numerous mutations in the coagulation factor C homology (*COCH*) gene, which encodes for cochlin.<sup>19 20</sup> Several mutations have been described in all continents, but the p.Pro51Ser variant in *COCH* is the most prevalent in Belgium and the Netherlands.<sup>21 22</sup> Its exact prevalence is unknown, but DFNA9 has been reported in several families on four continents.<sup>23</sup> Patients affected with DFNA9 present with progressive sensorineural hearing loss (SNHL) with a high-frequency onset starting around the third life decade followed by vestibular dysfunction evolving towards BV, causing among other, oscillopsia, gait imbalance, increased risk of falling, spatial disorientation.<sup>24 25</sup> In contrast, homozygous loss-of-function mutations in *COCH* lead to autosomal recessive, early-onset, severe SNHL (DFNB110).<sup>21 26</sup> A recent cross-sectional study from Gommeren *et al*<sup>27</sup> found significantly worse results in patients with DFNA9 in cognitive performance compared with a cognitively healthy control group. This highlights the need for adequate treatment to prevent further cognitive decline and reduce dementia risk in this population.

In 2015, around 47 million people worldwide were affected with dementia and this number is expected to triple by 2050.<sup>4</sup> While there is still no cure for dementia, it is important to adequately treat its modifiable risk factors, such as hearing loss. By doing so, the risk of developing dementia can be decreased by 9.1%.<sup>4 28–30</sup> While treatment is currently focused on hearing rehabilitation with hearing aids and cochlear implants, emerging alternatives are based on gene therapy to prevent or restore hearing permanently. They are considered to become part of successful future therapeutic interventions. However, such therapy is not available yet.<sup>31</sup>

Previous research already stressed using Cortical Auditory-Evoked Potentials (CAEP) as a neuropsychological indicator in the early stages of cognitive decline.<sup>32</sup> The P300 component, elicited by an oddball paradigm, reflects neural speed (P300 latencies) as well as cognitive resources (P300 amplitudes) and might therefore be a sensitive early-stage diagnostic marker for cognitive decline.<sup>33 34</sup>

In this project, a prospective evaluation of hearing level, vestibular function and cognitive performance will be acquired at different time points in both pre-symptomatic and symptomatic carriers of the p.Pro51Ser mutation in the *COCH* gene. This study aims to answer the following research question: 'How will hearing levels and vestibular function evolve in both pre-symptomatic and symptomatic carriers of the p.Pro51Ser mutation in the *COCH* gene and how will this impact their cognitive performance and health-related quality of life?'. The expected outcomes will aid in developing future gene therapy by providing more insight into the optimal time window, before the onset of hearing and vestibular dysfunction and cognitive decline, for the application of gene therapy for the inner ear.

## METHODS AND ANALYSIS

### Study design and setting

The present study will be a single-centre, prospective longitudinal study performed at the Department of Otorhinolaryngology—Head and Neck Surgery at the Antwerp University Hospital in Belgium.

### Eligibility criteria

In total, 40 confirmed p.Pro51Ser carriers will be included, all aged 18 years and older. The control group will encompass subjects without the DFNA9 disease, with different hearing and vestibular (dys)function levels as already recruited through the GECKO study at our department.<sup>35</sup> Inclusion and exclusion criteria are presented in table 1.

### Sample size and power

To obtain an estimation of the sample size needed to detect significant differences in the primary outcome variable—the Repeatable Battery for the Assessment of Neuropsychological Status adjusted for the Hearing-Impaired (RBANS-H) total score—a two-tailed paired t-test was carried out. The proposed sample size is 34 subjects, which holds a power of 80% to detect a mean of paired differences of 4 with an estimated SD of differences of 8 and a significance level of  $\alpha=0.05$ . When covering for

**Table 1** Inclusion and exclusion criteria of the patients with DFNA9

Inclusion	Exclusion
Adults aged $\geq 18$ years old	Known neurological disorders (eg, mild cognitive impairment or dementia)
Confirmed carriers of the p.Pro51Ser mutation in the <i>COCH</i> gene	Cochlear implantation or other implantable hearing devices
Dutch native speaking	Visual disability (not corrected for)
DFNA9, Deafness Autosomal Dominant 9.	

a possible drop-out of 15%, a sample size of 40 subjects will be required.

### Intervention description

This longitudinal study protocol will comprise of audiological, vestibular and cognitive assessments. Patients will undergo assessments at baseline, 12 months and 24 months follow-up. Before participation, all participants must give written initial informed consent per the Declaration of Helsinki. The clinical researchers involved in this study are all International Conference on Harmonisation—Good Clinical Practice accredited.

### Hearing assessment

Hearing assessment will consist of subjective (pure-tone audiometry) and objective measures (distortion-product oto-acoustic emissions, brainstem-evoked response audiometry). In case of hearing aid use, data logging and the duration of daily usage of the hearing aid will also be considered.

### Pure-tone Audiometry

Hearing thresholds will be assessed using Pure-tone Audiometry for both air and bone conduction (AC and BC respectively) according to the current clinical standards (ISO 8253-1, 2010). To determine hearing thresholds in decibels Hearing Level (dB HL), the Hughson-Westlake methodology will be performed.<sup>36,37</sup> AC will be performed in a sound-proof booth at the following frequencies: 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 6000 Hz and 8000 Hz. A headphone type TDH-39P (Telephonics) and a two-channel AC-40 Audiometer (Interacoustics, Assens, Denmark) will be used. BC will be performed at frequencies between 250 Hz and 4000 Hz. AC and BC hearing thresholds will be collected from both ears separately for each participant.

### Distortion-Product Oto-Acoustic Emissions

Distortion-Product Oto-Acoustic Emissions (DPOAEs) will be elicited by use of a pair of two pure tone frequencies ( $f_1$  and  $f_2$ ) closely spaced and presented simultaneously at a level of 55 dB SPL for  $f_1$  and 65 dB SPL for  $f_2$  (frequency ratio= $f_1/f_2=1.22$ ). Non-linear intermodulation between the two frequencies in the cochlea evokes several new acoustic frequencies that can be measured. The most robust and largest distortion-product is  $2f_1-f_2$  which can be detected in almost all normal hearing ears. DPOAEs will be considered present when the signal-to-noise ratio (SNR) is equal to or larger than 6 dB SNR. DPOAEs are included in the test protocol as an objective measure of outer hair cell function.

### Brainstem-Evoked Response Audiometry

Auditory Brainstem Responses (ABR) will be recorded with the Neuro-Audio and Neurosoft Ltd. software system (V.1.0.105.0) (Neurosoft, Russia) in a sound-proof booth constructed as a Faraday cage to block external electrical fields to prevent them from interfering with the signal. ABR component amplitudes and latencies will be

determined by visual inspection of the waveforms I to V. Wave V is the most robust waveform in an adult population. A Nupreb gel will be used to lower skin impedance below 5 kOhm. Electrodes will be placed on both mastoids, one high on the forehead and the common electrode lower on the forehead. Patients lay down on a bed and the lights will be dimmed as well as patients are asked to close their eyes during recording to minimise muscle activity. To obtain the best possible outcome of the ABR testing, all recordings will be repeated two times to ensure reproducibility.

### Cortical Auditory-Evoked Potentials

To investigate auditory processing, CAEPs are measured. Patients wear a 32-channel electroencephalography (EEG) electrode cap, with 31 silver/silver chloride 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 an infrequent stimulus (2000 Hz, with a probability of 20%) is randomly presented 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 5 ms and are delivered using the software Presentation (Neurobehavioural Systems, Albany, California, USA). The EEG is recorded (Micromed SD LTM64 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 pre-processed using the Fieldtrip toolbox in MATLAB V.9.6.0.1150989 (R2019a) (Mathworks, Natick, Massachusetts, USA). 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 presenting excessive noise or low activity will be identified as a bad channel. An independent component analysis (ICA) will be performed to detect eye blinks. Based on their time course and localisation, components will be identified. If these components include eye blinks, they will be removed from the data using an inverse ICA procedure. Next, data will be segmented into 2 s epochs time-locked to the stimuli. Artefacts will be removed from the data set in a way that is based on the amount of variance as is determined by visual inspection of the data. The procedure will be formed by investigators blinded to subject groups to prevent bias. In the case of excluded channels, an interpolation of neighbouring channels will be performed using a weighted algorithm. The number of interpolated channels and the percentage of removed trials will be reported on a group level. Subsequently, a correction to a baseline period of 0.2 s preceding stimulus presentation will be applied to

all epochs. A detrending method will be used to remove linear trends from the data. Responses to target and non-target tones will be averaged separately because of the interest in the differences between them.

#### Vestibular assessment Electronystagmography

Electronystagmography (ENG) with a rotatory chair test and bi-thermal caloric tests will be performed in a semi-darkened room. At first, eye movements will be calibrated. Then, the rotatory chair test will be performed using sinusoidal rotation (0.05 Hz) with a peak velocity of 60°/s to evaluate low—to midfrequency vestibular function.<sup>38</sup> Next, bilateral caloric irrigation (with air insufflation) will be used to evaluate low-frequency lateral semi-circular canal (SCC) function. Air insufflation will be used instead of water irrigation due to equipment limitations. Air temperatures should be more extreme and the duration of the air insufflation longer to achieve responses comparable to water irrigation. A cold stimulus of 24°C and a warm stimulus of 47°C will be applied. A stimulus duration of 60 s will be used. A 10-min interstimulus interval is taken between two insufflations to reduce residual effects from the previous insufflation. The stimulation sequence will be as follows: cold right, cold left, warm right, warm left. The patients will be positioned supine, with their head elevated 30° to align the lateral SCC vertically for maximal stimulation. Finally, eye movements will be recorded using ENG (Nystagliner Toennies, Germany).

#### Video Head Impulse Test (vHIT)

The Video Head Impulse Test (vHIT) will be administered by a clinical audiologist in a well-lit room. Participants will be instructed to focus on a fixation dot placed at eye-level 1.5 metre in front of them while the clinical audiologist will stand behind the participant. Patients will undergo passive short, quick head impulses in the direction of all six SCC (lateral, superior and posterior). The head is moved randomly in both directions of the functional SCC pairs: right and left for the horizontal SCC (RL, LL), left anterior and right posterior SCC and right anterior and left posterior SCC. Ten valid head impulses are required for each canal. Eye velocity is determined using an infrared camera recording the right eye, angular head velocity by three mini-gyroscopes, all incorporated in vHIT goggles (Otometrics, Taastrup, Denmark). In addition, the ICS Impulse software (Otometrics, Natus, Pleasanton, California, USA) will be used in which the VOR-gain (by evaluating the relation between eye and head velocity), SD of VOR-gain, the velocity of the head (°/s), saccades (none, gathered, scattered) and Perez and Rey scores (PR-score) (as a measure to assess vestibular compensation) will be analysed.<sup>39 40</sup>

The inclusion of both vHIT and ENG, including a caloric test and rotatory chair test, is chosen to make it possible to define patients with acquired bilaterally

reduced vestibular responses in accordance with the diagnostic criteria of BV as established by the Barany Society.<sup>41</sup>

#### Cognitive assessment

##### *Repeatable Battery for the Assessment of Neuropsychological Status—adjusted for the Hearing-Impaired*

The Dutch RBANS-H instrument was developed and validated for a severely hearing-impaired population.<sup>42</sup> The RBANS-H is a modified version of the RBANS to minimise the effect of hearing loss on cognitive testing. It can also be used to detect mild forms of cognitive disorders.<sup>43 44</sup> By adding visual stimuli through an accompanying slideshow in addition to the oral instructions, it is possible to use this test in a hearing-impaired population to guarantee that the patient can understand the instructions correctly.<sup>42</sup> Assessment of the RBANS-H takes approximately 30 min on average. The RBANS-H consists of a set of 12 subtests each combined to assess five (cognitive domains): “List Learning”, “Story Memory” (Immediate Memory), “Figure Copy”, “Line Orientation” (Visuospatial Construction), “Picture Naming”, “Semantic Fluency” (Language), “Digit Span”, “Coding” (Attention), “List Recall”, “List Recognition”, “Story Recall” and “Figure Recall” (Delayed Memory). The raw total scores of the subtests are needed to convert to an index score for each cognitive domain. The sum of all index scores can be converted to an age-corrected standard score (total index scale) with a mean equal to 100 and an SD of 15. Suppose a patient obtained a scaled score (either total index scale or subtest index score) of below or equal to 85 (mean of 100–SD of 15). In that case, there is an indication of a lower-than-expected cognitive result, meaning that the subject is at risk to have mild cognitive impairment (MCI) or dementia.<sup>45 46</sup> If the cognitive decline is more significant than expected for the individual’s age and education level while being independent for activities of daily living, it is referred to as MCI.<sup>47</sup>

#### Questionnaires

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

The SSQ12 is a short version of the Speech, Spatial and Qualities of Hearing Scale and consists of 12 questions. It measures several aspects of hearing such as localisation of sound, distance and movement, listening effort and also the ability of speech comprehension in quiet and noisy environments. The ability to hear in different situations can be rated on a scale from 1 to 10 with 1 representing ‘not at all’ and 10 ‘perfectly’.<sup>48</sup>

##### *Dizziness Handicap Inventory (DHI)*

The Dizziness Handicap Inventory (DHI) is designed to assess the self-perceived effect of dizziness on the quality of life.<sup>49</sup> This 25-item questionnaire is divided into three subscales evaluating the subject’s performance along emotional, functional and physical aspects of daily life. It ranges from 0 to 100 meaning that the higher the score, the more symptoms the subject experiences and the lower its quality of life. A moderate self-perceived handicap is

present within a range from 30 to 60 points. A DHI score above 60 points at a severe handicap.<sup>50</sup>

#### *Activity-specific Balance Confidence Scale*

The Activity-specific Balance Confidence Scale is a self-perceived handicap questionnaire to investigate a patient's balance confidence in performing daily activities without falling. Based on an average score, a higher score indicates more confidence in not losing balance.<sup>51</sup>

#### *Falls Efficacy Scale International*

Another questionnaire investigating balance confidence is the Short Falls Efficacy Scale International. It comprises of seven statements, each being an activity of daily living, that can be scored from 1 (not at all concerned about falling) to 4 (very concerned about falling). The sum of all scores identifies the degree of concern and can be interpreted by 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).<sup>52</sup>

#### *Vestibular Disorders Activities of Daily Living Scale*

The Vestibular Disorders Activities of Daily Living Scale is a self-rated scale that can determine functional limitation or disability in people with vestibular disorders.<sup>53</sup> It assesses the patient's perception of autonomy in ambulation, functional and instrumental skills. A summed total and median score can be calculated for each of the subscales and the total.

#### *Hospital Anxiety and Depression Scale*

The Hospital Anxiety and Depression Scale is a screening tool consisting of 14 questions, of which seven relate to depression and seven to anxiety. A score of 11 or higher on either subscale indicates clinically elevated depression or anxiety levels.<sup>54 55</sup>

#### *Beck Depression Inventory*

To measure symptoms and severity of depression, the Beck Depression Inventory can be used. Each of the 21 questions has four answer options, indicating an ascending grade of depression. The total score and sum of all questions can be interpreted as: 0–13: minimal depression, 14–19: light depression, 20–28: moderate depression and 29–63: severe depression.<sup>56</sup>

#### *Type D Scale-14*

Type D Scale-14 is a validated 14-item questionnaire used to identify individuals with type D personality traits. It consists of two subdomains: negative affectivity (NA) and social inhibition (SI).<sup>57</sup> NA denotes the tendency to perceive negative emotions across time and situations. SI refers to inhibiting behaviours and emotions in social interaction to avoid disapproval by others. The 14 items are formulated as statements to which the respondent have four response options to indicate the degree to which the statement is true: (0) false, (1) rather false, (2) neutral, (3) rather true, (4) true. If both the NA and SI

total scores are equal or greater than 10, the person is classified as a type D personality.

#### *European Quality of Life-5 Dimensions Questionnaire*

Health-related and disease-specific quality of life are measured by the European Quality of Life-5 Dimensions Questionnaire, comprising of five dimensions: mobility, self-care, daily activities, pain/discomfort and anxiety/depression.<sup>58 59</sup>

#### *Health Utilities Index Mark-3 (HUI-3)*

The Health Utilities Index Mark-3 (HUI-3) is an extended version of the HUI.<sup>60</sup> It consists of three different types of outcome measures: attribute levels, representing health states of participants ranging from 1 (no disability) to 6 (severe disability); single-attribute utility scores and multi-attribute utility scores, varying from dead (0.00) to perfect health (1.00). The scored attributes are vision, hearing, speech, ambulation, dexterity, emotion and cognition.<sup>61 62</sup>

#### *Oscillopsia Severity Questionnaire*

The Oscillopsia Severity Questionnaire can assess the severity of oscillopsia in a population with BV.<sup>63</sup> Oscillopsia is a 'sensation that the visual environment is moving when it's not'. The questionnaire describes nine daily life situations, in which oscillopsia can be experienced, which can be scored as follows: (1) never, (2) seldom, (3) sometimes, (4) often or (5) always. Hence, the higher the score (range 9–45), the higher the self-perceived frequency of oscillopsia.

### **Data collection and management**

All patient-related information collected in this study is kept strictly confidential. The researcher will assign a personal code to all patient information and results of each participant. A secure web platform for building and managing online databases, RedCap, will be used to store raw data safely. Data are stored for 20 years. Data collection started in March 2023 and will continue till March 2026.

### **Statistical methods**

Statistical software such as SPSS V.25 and JMP Pro 16 (JMP, V.16. SAS Institute, Cary, North Carolina, USA, 2021) will be used for the statistical analyses. The appropriate parametric or non-parametric tests will be used to study the cross-sectional results. Longitudinal differences will be analysed at 12 and 24 months using a repeated measures design.

### **Patient and public involvement**

Patients and/or the public will not be involved in the research's design, conduct, reporting or dissemination plans.

### **Ethics and dissemination**

The study protocol is approved by the ethical committee of the Antwerp University Hospital on 19 December 2022



with protocol number B3002022000170. Before participation, all participants must provide written initial informed consent per the Declaration of Helsinki. Results will be disseminated to the public through conference presentations, lectures and peer-reviewed scientific publications.

## DISCUSSION

Although some studies investigated the evolution of the DFNA9 disease, none focused on including pre-symptomatic carriers. Performing this longitudinal study will enable researchers to gain more insight into how the disease will evolve in the long term and the exact time point of cognitive decline.

The responsiveness of the RBANS-H will allow the establishment of a cognitive trajectory in a population with an inevitable evolution towards SNHL and BV, and possibly also dementia due to its increased risk for it and accelerated cognitive decline observed in this population.<sup>27</sup>

CAEP will be used to study the neural correlates of the cognitive (dys)function in the DFNA9 population. Previous research stressed the use of CAEP as a neuropsychological indicator of early-stage cognitive decline.<sup>32</sup> CAEP morphology is known to be altered by dysfunctions being either from auditory or cognitive origin, and more specifically, its amplitude is decreased and its latency prolonged.<sup>34</sup> CAEP can therefore be an objective biomarker to link potentially increased N200 and P300 latencies (eg, cognitive decline) to the RBANS-H scores and serve as a prognostic indicator in the early stages of cognitive decline and predict the conversion from MCI to dementia due to AD.

Even though questionnaires are relatively quick and easy to administer, there are some self-report limitations. Questionnaires do contain subjective information and therefore might lead to socially desirable answers. On the other hand, the answers may be influenced by the participant's interpretation which could cause a high inter-individual variability.<sup>64</sup> Moreover, fatigue may occur due to the many questionnaires which can lead to less attentive responses.

Patients with moderate SNHL are often well rehabilitated with hearing aids to improve speech perception while cochlear implantation provides a solution for severely hearing-impaired patients. Unfortunately, this does not halt further progression to severe to profound SNHL. Since hearing aid use not only ameliorates hearing but might also contribute to the re-establishment of the patient's participation in society, it may positively affect the trajectory of cognition. Furthermore, cognitively well-functioning patients seek and obtain hearing aids more often.<sup>65</sup> It is therefore important to question hearing aid use and include it as a variable in the study protocol. Even though wearing hearing aids or a cochlear implant seems to have positive effects on cognitive performance and thus decreasing the risk of developing dementia,<sup>4 28–30</sup> there is currently no cure or disease-modifying therapy

available to prevent SNHL, BV and cognitive decline in patients with DFNA9.

This study allows to generate valuable knowledge on the effect of progressive SNHL and vestibular dysfunction on the different domains of cognitive functioning from the early pre-symptomatic stages (normal hearing) until the later stages with severe-to-profound SNHL because of the predictable evolution in DFNA9 (in contrast to presbycusis). Moreover, it will allow researchers to identify which tests (eg, CAEP, RBANS-H) can be used to screen for incident cognitive decline in DFNA9.

The expected outcomes will be important to society because they will provide data from a cognitive assessment protocol adapted for a potentially hearing-impaired population and objective outcome measures to identify patients at risk for cognitive decline. As such, this longitudinal study will further support screening and interventional studies that can assess the impact of otovestibular decline on cognition in patients with DFNA9.

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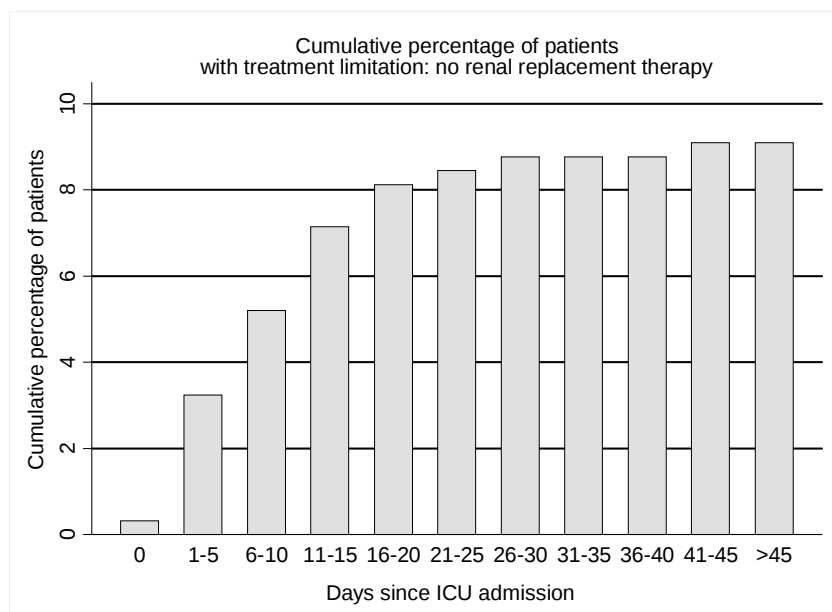


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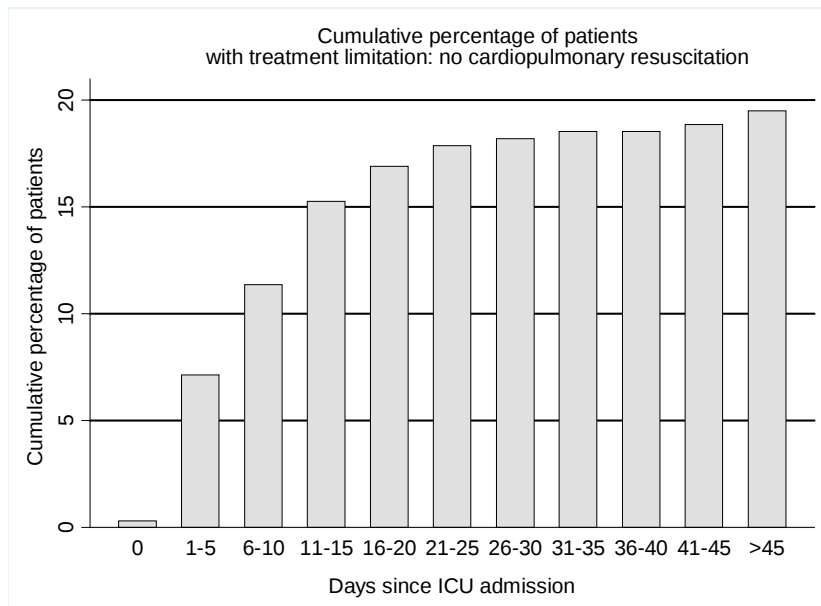
**Table S1: Post-hoc exploratory comparison between the subgroups for 90 days mortality and Renal replacement therapy**

Subgroups	90 day mortality		Renal replacement therapy	
	N (%)	p	N (%)	p
No chronic dysglycemia vs Prediabetes	9/61 (14.7) vs 28/114 (24.5)	0.17	17/61 (27.8) vs 22/114 (19.2)	0.25
No chronic dysglycemia vs Unknown diabetes	9/61 (14.7) vs 12/60 (20.0)	0.48	17/61 (27.8) vs 11/60 (18.3)	0.28
No chronic dysglycemia vs Controlled diabetes	9/61 (14.7) vs 7/25 (28.0)	0.22	17/61 (27.8) vs 1/25 (4.0)	0.01
No chronic dysglycemia vs Uncontrolled diabetes	9/61 (14.7) vs 15/48 (31.2)	0.06	17/61(27.8) vs 8/48 (16.6)	0.25
Prediabetes vs Unknown diabetes	28/114 (24.5) vs 12/60 (20.0)	0.57	22/114 (19.2) vs 11/60 (18.3)	1
Prediabetes vs Controlled diabetes	28/114 (24.5) vs 7/25 (28.0)	0.79	22/114 (19.2) vs 1/ 25 (4.0)	0.07
Prediabetes vs Uncontrolled diabetes	28/114 (24.5) vs 15/48 (31.2)	0.43	22/114 (19.2) vs 8/48 (16.6)	0.8
Unknown diabetes vs Controlled diabetes	12/60 (20.0) vs 7/25 (28.0)	0.41	11/60 (18.3) vs 1/25 (4.0)	0.1
Unknown diabetes vs Uncontrolled diabetes	12/60 (20.0) vs 15/48 (31.2)	0.18	11/60 (18.3) vs 8/48 (16.6)	1
Controlled vs Uncontrolled diabetes	7/25 (28.0) vs 15/48 (31.2)	0.77	1/25 (4.0) vs 8/48 (16.6)	0.01
No chronic dysglycemia and prediabetes vs unknown and known diabetes	37/175 (21.1) vs 34/133 (25.5)	0.41	39/175 (22.2) vs 20/133 (15.0)	0.14

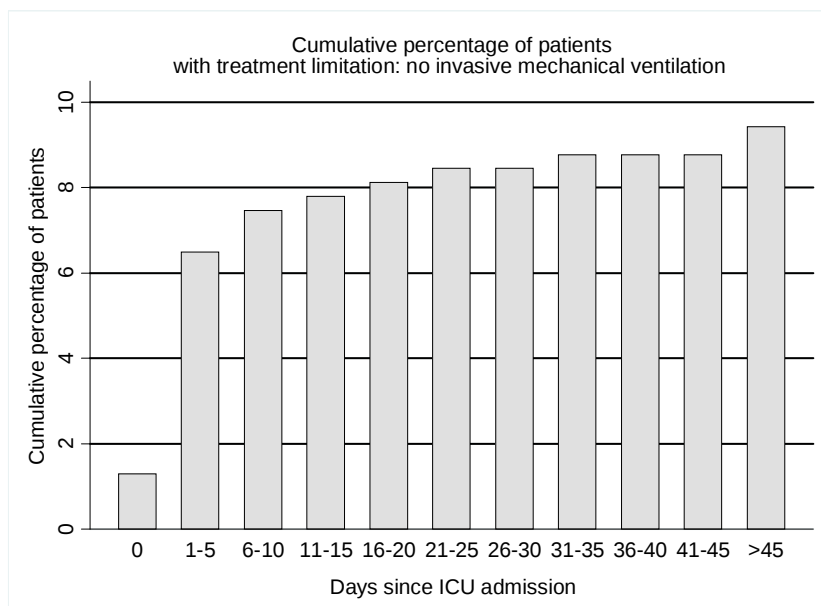
P values calculated with Fischer's exact test



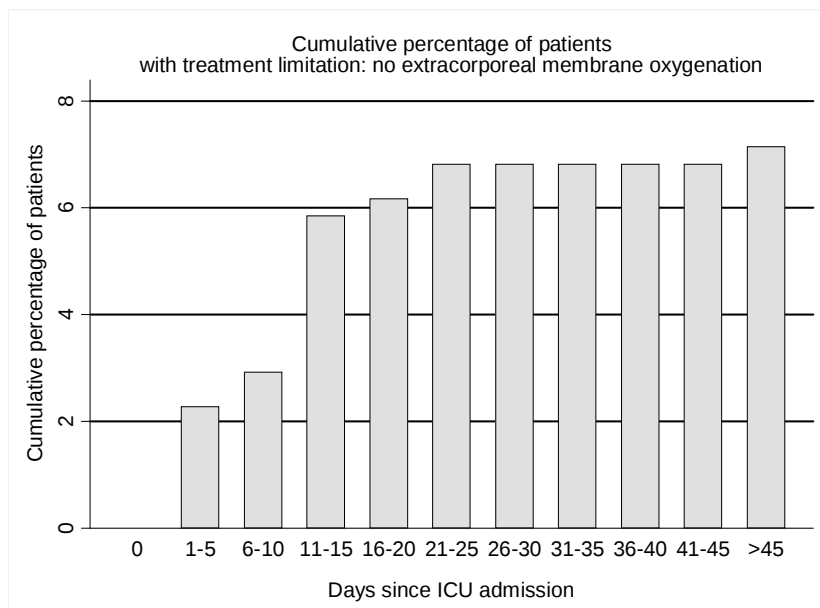
**Figure S1.** Cumulative percentage of patients with a treatment limitation: no renal replacement therapy. Day 0 (zero) denotes the day of admission to the intensive care unit.



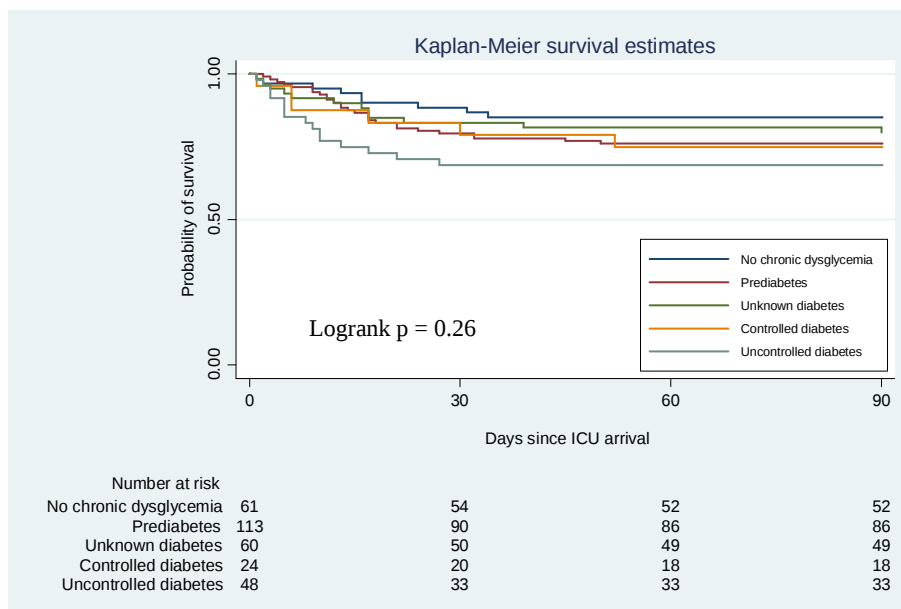
**Figure S2.** Cumulative percentage of patients with a treatment limitation: no cardiopulmonary resuscitation. Day 0 (zero) denotes the day of admission to the intensive care unit.



**Figure S3.** Cumulative percentage of patients with a treatment limitation: no invasive mechanical ventilation. Day 0 (zero) denotes the day of admission to the intensive care unit.



**Figure S4.** Cumulative percentage of patients with a treatment limitation: no extracorporeal membrane oxygenation. Day 0 (zero) denotes the day of admission to the intensive care unit.



**Figure S5.** Probability of survival in the study groups