

# Hearing Impairment as a Risk Factor for Dementia in Older Adults

Mid-life Hearing Impairment As Risk Factor For Dementia In People Aged  $\geq 70$  Years. A Population-Based Prospective Cohort Study: The HUNT Study, Norway

*NCT Number: NCT04284384*

*Document Date: 2021/07/07*

# Statistical Analysis Plan

## Index

Main variables .....	3
All-cause dementia [diagcog_nt4eld_dem] dichotom .....	3
Hearing threshold level [nt2htl54best] continuous .....	3
Variables with missing information.....	3
Alcohol use [alcfmy_nt2blq1] categorical covariate (604 missing).....	3
Physical activity [parangul_nt2] continuous mediator (480 missing) .....	3
History of stroke [apoplev_nt2blq1] dichotomous mediator (3 missing).....	3
Hypertension [bpsystemn23_nt2blm] continuous confounder (21 missing) .....	4
Smoking [smostat_nt2blq1] ordinal categorical confounder (69 missing) .....	4
Traumatic brain injury [hospheadinju_nt2hearq1] dichotomous confounder (289 missing) .....	4
Body Mass Index [bmi_nt2] continuous confounder (26 missing).....	4
Cholesterol [sechol_nt2blm] continuous confounder (25 missing).....	4
Mental Health [hadstot_nt2blq1] continuous mediator (1,175 missing) .....	4
HADS total [hadstot_nt2blq1] .....	4
SCL-10 [scl10tot_nt2] continuous (502 missing).....	4
CON-MHI [conmhitot_nt2] continuous (1239 missing) .....	4
ADI-4 [adi4tot_nt2] continuous (798 missing) .....	4
Ischemic heart disease [carinfev_nt2blq1] dichotomous mediator (5 missing) .....	4
Variables with no missing information.....	5
(Hearing threshold level [nt2htl54best] continuous, main exposure (0 missing)).....	5
Age [partag_nt4blq1] continuous confounder (0 missing) .....	5
Sex [sex] dichotom covariate (0 missing) .....	5
Marital status [sivilstand_1996] dichotom covariate (0 missing) .....	5
Social isolation [live_alone_1996] dichotom mediator (0 missing) .....	5
Diabetes [diaev_nt2blq1] dichotom confounder (3 missing).....	5
Education [education] ordinal confounder (0 missing).....	5
Missing.....	5
Selection .....	5
Statistical methods .....	6

1. Missing is replaced with answers from other waves of the HUNT Study, e.g. is the answer in HUNT4 «I have never smoked» been used to replace missing on smoking status in baseline HUNT2 (logical imputation).
2. Next, missing is handled with multiple imputation.
3. The main analysis is modelled with logistic regression.

## Main variables

All-cause dementia [diagcog\_nt4eld\_dem] dichotom

Primary outcome.

Hearing threshold level [nt2htl54best] continuous

Primary exposure. The mean of the frequencies 0.5, 1, 2 and 4 kHz on the best ear measured in dB with automatic pure tone audiometry (PTA).

## Variables with missing information

Alcohol use [alcfmy\_nt2blq1] categorical covariate (604 missing)

- «How often do you drink alcohol?».
- 0 «Never»
- 1 «1-7 times/month»
- 2 «8-18 times/month»
- 3 «19-31 times/month»
- (604 missing after 794 is replaced by «never drink»-answer [alcnev\_nt2blq1]).

Physical activity [parangul\_nt2] continuous mediator (480 missing)

- The index is the sum of the score for low and vigorous PA:

Low physical activity? (Not out of breath/sweat)	Hours/week	Scores
None	0	0
Less than 1 hour	0,5	0
1-2 hour	1,5	0,5
3 hours or more	3	1
Vigorous physical activity? (Out of breath/sweat)	Hours/week	Scores
None	0	0
Less than 1 hour	0,5	0,5
1-2 hour	1,5	1,5
3 hours or more	3	3

History of stroke [apoplev\_nt2blq1] dichotomous mediator (3 missing)

- «Have you ever had stroke/bleeding?»

(3 missing after 21 is replaced by «never stroke»-answer in NT3-4).

Hypertension [bpsystmn23\_nt2blm] continuous confounder (21 missing)

- Systolic blood pressure is measured three times, and the variable is the mean of the second and third measurements.

Smoking [smostat\_nt2blq1] ordinal categorical confounder (69 missing)

- Categorised into 0 «Have never smoked» 1 «Former smoker» 2 «Current smoker»

(69 missing after 10 is replaced by «never smoked»-answer in NT3-4).

Traumatic brain injury [hospheadinju\_nt2hearq1] dichotomous confounder (289 missing)

- «Have you ever been hospitalised because of a head injury?»

29 «Don't know» is merged with «No».

Body Mass Index [bmi\_nt2] continuous confounder (26 missing)

Cholesterol [sechol\_nt2blm] continuous confounder (25 missing)

Mental Health [hadstot\_nt2blq1] continuous mediator (1,175 missing)

Because of a large number of missing total scores for HADS, we include the questions from SCL-10, CON-MHI and ADI-4 in the imputation model.

1. First, the score in the mood-question in ADI-4 need to be reversed so that the variables consistently reflects that «0» is the negative answer.
2. Then non-missing total scores are found for each of the three instruments
3. To strengthen the imputation of HADS, these scores are included in the imputation model

HADS total [hadstot\_nt2blq1]

Note: «In HUNT 2 the questions on mental distress, CONOR MHI included a question close to one of the HADS items; In the last two weeks, have you felt nervous and restless. Due to limited space in the questionnaire, the corresponding question in HADS “During the last week: I feel tense or wound up” was omitted» ([HUNT Database](#)). We, therefore, have only 13 of the 14 questions in HADS.

SCL-10 [scl10tot\_nt2] continuous (502 missing)

Note: For SCL-10, we only have 9 of 10 questions. «Have you, during the last two weeks, felt bothered or distressed by anything listed below? Suddenly scared for no reason» is missing.

CON-MHI [conmhitot\_nt2] continuous (1239 missing)

For CON-MHI, we have all 7 questions.

ADI-4 [adi4tot\_nt2] continuous (798 missing)

Note: For ADI-4, we only have 3 of 4 questions. The 4th question (“During the last month, have you suffered from nervousness (felt irritable, anxious, tense or restless)?”) is probably left out because of the similarity with one of the CON-MHI-questions («In the last two weeks, have you felt: Nervous and restless?). The score for the mood-question is reversed.

We do not believe that single items missing in SCL-10 and ADI-4 will affect the imputation or analysis outcome because of the broad spectre of mental health issues already covered.

Ischemic heart disease [carinfev\_nt2blq1] dichotomous mediator (5 missing)

- «Have you ever had a heart attack?»

(5 missing after 15 is replaced by «never heart attack»-answer in NT3-4).

## Variables with no missing information

(Hearing threshold level [nt2htl54best] continuous, main exposure (0 missing))

Age [partag\_nt4blq1] continuous confounder (0 missing)

Age at participation.

Sex [sex] dichotom covariate (0 missing)

Marital status [sivilstand\_1996] dichotom covariate (0 missing)

Social isolation [live\_alone\_1996] dichotom mediator (0 missing)

Diabetes [diaev\_nt2blq1] dichotom confounder (3 missing)

- «Have you ever had diabetes?»

(3 missing after 27 is replaced by «never diabetes»-answer in NT3-4).

Education [education] ordinal confounder (0 missing)

- 0 «Unspecified/none» 1 «Primary school» 2 «Secondary school» 3 «University, < 4 years» 4 «University, >= 4 years»

(11 missing from SSB is replaced with answers from NT2).

Data from connected register Statistics Norway (SSB).

Note: We leave premorbid cognitive ability out of the analysis because of a lack of data. “Race is a poor surrogate of social constructs and even more so, if not abjectly, of biology” (Ioannidis JPA, Powe NR, Yancy C. Recalibrating the Use of Race in Medical Research. JAMA. 2021;325(7):623–624. doi:10.1001/jama.2021.0003). We have no suitable way of measuring air pollution (Livingston). The use of hearing aid will be assessed in another paper (hypothesis V).

## Missing

We will perform a complete case analysis to compare demographics, main exposure and main outcome, and sensitivity analysis to compare results with and without multiple imputation.

## Selection

Systematic drop-outs (dementia Vs death) with competing risk and other biases will be assessed by focusing on risk factors in mid-life. To include death causes from a national register of diagnosis is discussed, but death cause is concluded not to be very valid in the registers.

Although all participants are 70-years old or more, they may not be in their «mid-life» at baseline (HUNT2). This will be discussed.

Analysis to compare eligible and not eligible participants will be performed.

## Statistical methods

The main analysis is a logistic regression model with baseline variables from HUNT2. Missing is first handled with logical imputation, then with multiple imputation. Multiple sensitivity analyses will be run, such as complete case analysis and analysis where missing are replaced with data from other waves of the HUNT Study. Inverse probability weighting will be performed.

Registered mediators are events with unknown times of debut, but which have always occurred before they are registered. This is also the case for both incidences of dementia and hearing impairment. E.g. is the mediator «reduced mental health» believed to be worsened by hearing impairment and next leading to even more dementia. We can not know for sure the chronology of incident mental health issues and hearing impairment. Mediators will be investigated by assessing direct, indirect and total effects on the outcome.

We will model logistic regression separately for all men and women aged 70 years or older with a hearing assessment in HUNT2 and cognitive test results in HUNT4 70+. Those without a PTA and with insufficient data for a cognitive test result will be omitted from the main analysis but will be interrogated in own analysis in regards to selection bias.