# The role of inflammation in the pathogenesis of tinnitus

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Primary Objective: To evaluate cytokine levels in blood samples of human subjects with tinnitus and normal hearing, compared to healthy controls.Secondary Objective(s): To evaluate complete blood count measures (neutrophil count, platelet count etc...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Hearing disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON51359

**Source**
ToetsingOnline

**Brief title**
Inflammation in tinnitus

### Condition

- Hearing disorders

**Synonym**
ringing in the ears, Tinnitus

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Groningen
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** Cytokines, Inflammation, Tinnitus

## Outcome measures

### Primary outcome

The main study parameters are blood cytokine levels of TNF-α, IL-1β, IL-6,

IL-10 and IFN-γ.

### Secondary outcome

Complete blood count measures (neutrophil count, lymphocyte count, thrombocyte

count, Mean Platelet Volume (MPV), Mean Corpuscular Volume (MCV), Platelet

Distribution Weight (PDW), neutrophil-to-lymphocyte ratio (NLR) and

platelet-to-lymphocyte ratio (PLR)).

# Study description

### Background summary

Tinnitus is the perception of sound without an external source. Chronic tinnitus is prevalent among 5 to 15% of the general population and negatively affects quality of life in 20% of cases (Eggermont and Roberts, 2004). No curative treatment is available, making it a substantial medical and socioeconomic problem.
The exact pathophysiology of tinnitus remains unknown. It is thought that tinnitus is generated in the brain as a result of damage to the auditory tract somewhere between the cochlea and brain. Cochlear damage because of noise exposure is the major cause of such deafferentation in the onset of tinnitus (Agrawal et al., 2009, 2008). In the past decade several studies demonstrated an inflammatory response under various damaging conditions causing tinnitus, including noise exposure. In animal models of tinnitus, the expression of the proinflammatory cytokines Tumor Necrosis Factor-α (TNF-α) and interleukine-1β (IL-1β) was increased throughout the whole auditory tract (Mennink et al., 2022). In humans, results on complete blood count measures (mean platelet volume, platelet distribution width, platelet count and neutrophil-to-lymphocyte ratio) and cytokine levels were conflicting (Mennink et al., 2022). Szczepek et al. (2014) found a correlation between serum levels

TNF-α and tinnitus loudness. Only two studies evaluated cytokine concentrations in tinnitus patients. Weber et al. (2002) found an increase of IL-6 in tinnitus patients, and Haider et al. (2020) found a decrease in IL-10. However, neither study included tinnitus patients based on the degree of hearing loss, or accounted for hearing loss in the analysis, despite that inflammation has also been implicated in hearing loss (Frye et al., 2019; Fuentes-Santamaría et al., 2017). On the other hand, studies about inflammation in hearing loss did not (always) exclude tinnitus. Thus, it remains unclear whether the change in cytokine concentrations in Weber et al. (2002) and Haider et al. (2020) are specific to tinnitus, and whether potential effects remained unsignificant because the presence of hearing loss is a confounder. Therefore, the aim of this study is to evaluate the presence of inflammation in blood samples of tinnitus patients with normal hearing.

## Study objective

Primary Objective: To evaluate cytokine levels in blood samples of human subjects with tinnitus and normal hearing, compared to healthy controls.

Secondary Objective(s): To evaluate complete blood count measures (neutrophil count, platelet count etc.) in blood samples of human subjects with tinnitus and normal hearing, compared to healthy controls, and to assess the relation between tinnitus characteristics and inflammatory serum marker concentrations.

## Study design

This research protocol describes a cross-sectional study that will take place at the University Medical Center in Groningen at the department of ENT & Audiology. In this study, we intent to examine whether inflammation is present in tinnitus patients without hearing loss. Inclusion is planned from February/March 2022 to September 2022, or until the target number of inclusions is acquired. Patients who have been referred to the tinnitus consultation at the outpatient clinic will be asked to participate in this study. If a patient is eligible for the study, his/her primary caregiver will inform the patient orally and/or in writing. Normally, patients attending the tinnitus consultation complete a tinnitus questionnaire and undergo audiometric testing for standard care. For this study, we access this data and additionally, patients will have two samples of blood drawn. In these samples, cytokine concentrations and complete blood count measures will be determined. Moreover, the ENT department has a database with tinnitus patients that attended the tinnitus consultation previously. Eligible patients will be contacted by the audiologist (primary caregiver). If they give consent for being contacted for this study, they will be contacted by the researcher about this study and will be informed orally and/or in writing. Patients that attended the tinnitus consultation <= 5 years ago and still suffer of tinnitus are eligible, assuming they fulfill the inclusion criteria. These patients are asked to visit the UMCG

once to fill in a short version of the tinnitus questionnaire and to have two tubes of blood drawn by venipuncture. Additionally, we ask permission to review their audiogram if it is younger than 1 year, and audiometric testing is done if their audiogram is older than 1 year.
For controls, healthy volunteers will be recruited with flyers. When someone contacts the researcher that he/she is willing to participate, the researcher will make sure that he/she does not fulfill an exclusion criterium. If this is the case, a visit at the UMCG is planned. First, audiometric testing is performed to make sure the participant fulfills the inclusion criterium regarding hearing thresholds. If eligible, the participant will also complete a questionnaire and have two tubes of blood drawn by venipuncture.

**Study burden and risks**

There are no immediate benefits for patients to participate in this study. Complications of venipuncture are minor (bruising or hematoma, diaphoresis, hypotension, syncope, cellulitis and phlebitis). Except for bruising and hematoma, the other complications are uncommon. When they do arise however, they can be treated (Galena, 1992). Therefore, possible risks are minimal.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

- Adult, aged 18 years or older;
- Hearing threshold: average of 1000kHz, 2000kHz & 4000kHz <= 25 dB in both ears
- Hospital Anxiety and Depression Score (HADS), anxiety score <= 7
- HADS Depression score <= 7
- Participant has sufficient mastery of the Dutch language to fill out the questionnaires.

## Exclusion criteria

- Objective tinnitus.
- Presence of neurological disease (apart from tinnitus)
- Presence of inflammatory disease, or the use of anti-inflammatory medication.
- Presence or history of a malignancy
- Presence of a disease of the ear (e.g. chronic otitis media, otosclerosis, previous surgery etc).
- Presence of an coagulation disorder
- Presence of a serious psychiatric disorder.
- Pregnancy

# Study design

## Design

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|---|---|
| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Basic science |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 19-05-2022 |
| Enrollment: | 100 |
| Type: | Actual |

## Ethics review

Approved WMO

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| Date: | 18-05-2022 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| ClinicalTrials.gov | NCT05268770 |
| CCMO | NL80835.042.22 |