

The effects on hearing function following hypoxia:  
A systematic review of animal studies

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ADMINISTRATIVE INFORMATION

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**Review Stage at time of this submission** - Data analysis.

**Conflicts of interest** - None declared.

**INPLASY registration number:** INPLASY202420122

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 February 2024 and was last updated on 29 February 2024.

INTRODUCTION

**Review question / Objective** The aim of this systematic review is to compare mice exposed to hypoxia and mice exposed to normoxia in terms of hearing function. To this end, the proposed systematic review will address the following question: What are the effects of hearing function following hypoxia in mice?

**Rationale** Chronic hypoxia murine models are used to investigate the influence of chronic hypoxia on hearing function with auditory brainstem response (ABR) tests and histological analysis. We aimed to conduct a systematic review assessing the effects of hearing function following hypoxia in mice.

**Condition being studied** To study the hearing function of mice exposed to hypoxia.

METHODS

**Search strategy** This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Page et al., 2021) (File S1 shows the PRISMA checklist) to explore the impact on the auditory system of mice after exposure to intermittent hypoxia. Four databases, including Embase, Ovid Medline, Cochrane Library, and Scopus, were systematically searched to identify relevant articles published from 1976 to September 2022. Reference lists of relevant articles were reviewed to identify additional studies. Three main concepts, mice, hypoxia, and hearing loss search strategy used in combination with controlled vocabulary (3 MeSH terms and 2 Emtree terms) and free-text terms (19 synonyms plus truncation symbols).

**Participant or population** Mice regardless of age and sex.

**Intervention** Mice were placed in a hypoxia chamber.

**Comparator** Controls were placed in an identical chamber with normal oxygenation conditions.

**Study designs to be included** Experimental study, Systematic review, Meta analysis.

**Eligibility criteria** Studies that met the following criteria were excluded: (1) Studies that used rats as an animal model instead of mice; (2) Studies that exposed mice to more than just hypoxia.

**Information sources** Information sources include trial registers, grey literature, citation searching, and electronic databases (including Embase, Ovid, Cochrane, and Scopus).

**Main outcome(s)** ABR thresholds increase in all four studies. Histological assessments showed extensive damage to outer hair cells in three layers of the organ of Corti in two of the included studies.

**Additional outcome(s)** As of December 14, 2022, a total of 196 articles were retrieved from four electronic databases, and 3 articles met the inclusion criteria and were included in the qualitative synthesis. Another article was included on October 5, 2023, via database search alert. For risk of bias assessment, all four were classified as having high or unclear risk of bias in domains like random sequence generation, baseline characteristics, allocation concealment, and random outcome assessment. As for the other 6 domains, all of the studies showed a low risk of bias.

**Data management** Two of the authors (CYL and KYY) independently screened all articles including titles, abstracts, and keyword which were imported into EndNote X9 for identification of duplicates study. After removing of duplication, the same two authors (CYL and KYY) extracted the following data from the selected articles: Author, year, study design, animal strain & species, sample size & sex, age, intervention type, intervention duration, daily hypoxia duration, O<sub>2</sub> nadir concentration, control, and relevant outcome measure.

**Quality assessment / Risk of bias analysis** The quality of eligible articles was assessed using the Systematic Review Center for Laboratory Experimentation (SYRCLE)'s risk of bias tool for animal studies. (Hooijmans et al., 2014). Any disagreements were resolved by consensus or consultation with a third author (YCC).

**Strategy of data synthesis** Given the high heterogeneity and low quality of included studies, a meta-analysis was not performed in this study. A narrative synthesis will be presented based on the evidence from the reviewed articles and in line with the goals and objectives of this systematic review.

**Subgroup analysis** No subgroup analysis was performed in this study.

**Sensitivity analysis** No sensitivity analysis was performed in this study.

**Language restriction** English.

**Country(ies) involved** Taiwan.

**Keywords** mice, hypoxia, hearing loss, systematic review.

#### **Contributions of each author**

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