

**The European Tinnitus Survey: a cross-sectional observational study on tinnitus prevalence in 12 European countries**

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## **BACKGROUND AND RATIONALE**

Tinnitus is a common symptom of clinically heterogeneous pathologies and is defined as the conscious perception of an auditory sensation in the absence of a corresponding external stimulus.<sup>1</sup> Tinnitus, in its debilitating form, negatively affects emotional health and social well-being<sup>2</sup>, and can precipitate psychological distress severe enough to cause self-harm and suicidal ideations<sup>3,4</sup>, while exerting substantial individual and societal financial burden.<sup>5,6</sup> Therefore, it becomes crucial to take adequate preventive measures and health interventions. According to population-based studies from Western Europe and US, tinnitus prevalence lies between 10% and 15%.<sup>1</sup> Nonetheless, there is a lack of clear understanding of global prevalence of tinnitus. Inherent methodological drawbacks and between study differences hinder deriving a global estimate by pooling data from studies conducted in different countries and world regions.<sup>1,7,8</sup> Therefore, uncertainties with regards to the prevalence of tinnitus remain.

Being a subjective condition, the impact of tinnitus symptoms depends on its perceived bothersomeness or severity. Therefore, "bothersome" or "severe" tinnitus symptoms are a better predictor for the emotional, societal and financial burden of tinnitus than "any" tinnitus.<sup>5,6</sup> The economic burden is directly related to the severity of the tinnitus symptoms, with increased healthcare costs in people with severe tinnitus. In a study conducted in the Netherlands, the mean annual costs per patient was €767 for mild, €1329 for moderate and €2218 for severe tinnitus.<sup>5</sup> A similar pattern was noted in a study in USA, where medical costs were reported to be directly proportional to severity of tinnitus.<sup>9</sup> While epidemiological studies have attempted to distinguish any and severe tinnitus, both these concepts are troubled by heterogeneous prevalence estimates.<sup>8</sup> Hearing difficulty is a major risk factor for tinnitus and often co-occur in an individual.<sup>1</sup> However, not many studies have measured the prevalence of tinnitus in a population with hearing difficulty.

## **OBJECTIVE**

The primary objective of this population-based cross-sectional study is to estimate the overall and country specific prevalence of any tinnitus, bothersome tinnitus, and severe tinnitus in 12 European Union (EU) countries.

The study data have been analyzed to fulfil the following secondary objectives:

- To examine inter-country differences in prevalence of tinnitus by making the following comparisons:
  - Comparing prevalence estimates in countries with relatively low versus high gross domestic product (GDP) per capita
  - Comparing prevalence estimates in countries within different European regions (i.e., Northern, Southern, Eastern and Western Europe)
- To understand the effect of sex, age, socio-economic variables, body mass index (BMI), and marital status on overall prevalence of tinnitus
- To assess the effect of hearing difficulty on tinnitus prevalence
- To explore the effect of tinnitus severity on use of healthcare resource for tinnitus

## METHODS

### Study design

To achieve the aims of this study, we conducted face-to-face population-based cross-sectional survey in 12 strategically selected EU28 countries (Bulgaria, England, France, Germany, Greece, Ireland, Italy, Latvia, Poland, Portugal, Romania, and Spain). The study methodology is similar to another Pan-European survey on second-hand smoking and e-cigarettes, the TackSHS Project (“Tackling secondhand tobacco smoke and e-cigarette emissions: exposure assessment, novel interventions, impact on lung diseases and economic burden in diverse European populations”; [www.tackshs.eu](http://www.tackshs.eu)) conducted in the same 12 countries in 2017-2018, funded by the European Commission (EC) within the Horizon 2020 research grants (grant agreement number: 681040).<sup>10</sup>

For each country, the study sample is representative of the general population aged 18 years and above in terms of age, sex, geographic area, and socio-economic characteristics. Multi-stage methodology was used as the preferred sampling methodology. In the first stage, the primary unit of selection was geographic area or voting center. In the second stage, households or municipalities were selected. In the last stage, respondents were chosen randomly, in order to be representative of the population. Other methods, including stratified or simple sampling or quota methods, were also accepted wherever it is not possible to conduct a multistage random sampling.

### Selection of countries

For the present study, an appropriate sample of 12 European countries—all EU28 Member States (MS)—representing geographical, legislative and cultural variations across the EU, have been selected. The selected European countries are as follows: Bulgaria (BG), England (UK), France (FR), Germany (DE), Greece (GR), Ireland (IE), Italy (IT), Latvia (LV), Poland (PL), Portugal (PT), Romania (RO), and Spain (ES). These countries were selected after taking into account several aspects, including: i) different geographical distribution; ii) different level of per capita income. According to geographic area, we considered countries from northern (IE, UK), central/western (DE, FR), central/eastern (BG, LV, PL, RO), and southern Europe (ES, IT, GR, PT). Moreover, the selection includes the 7 most populated EU28 MS (DE, ES, FR, IT, UK, PL, RO), and, among less populated countries, we prioritized middle-income countries (BG, RO). Overall, the 12 selected EU MS represent 78.8% of the EU28 overall population.

### Study population

In each of the 12 selected European countries, approximately 1000 individuals, representative of the general population aged 18 years and above in terms of age, sex, geographic area, and socio-economic characteristics, were enrolled in this cross-sectional study. The final sample therefore includes a total of 11,427 subjects.

### Inclusion criteria

- individuals aged 18 years and above
- individuals who are residents of the 12 selected countries
- individuals able to understand and answer the questions of the study questionnaire in the country-specific language
- individuals who formally accept to participate in the study

### Exclusion criteria

No specific exclusion criteria are considered

### Sample size computation

The sample size for each country allowed us to obtain prevalence estimates with a maximum standard error (SE) lower than  $\pm 1.6\%$ . Therefore, with such a sample size we have been able to provide stable prevalence estimates (with a relatively small 95% confidence interval), both overall and country-specific.

### **Data collection**

In each country, individuals were surveyed by trained interviewers through face-to-face interviews using a structured standardized questionnaire. Data collection was coordinated by DOXA, a leading market research organization and Italian branch of the Worldwide Independent Network/Gallup International Association (WIN/GIA), and performed in collaboration with its European partners (see “Selection of the subcontract or performing data collection” paragraph). Data was collected within computer assisted personal interviews (CAPI). The fieldworks lasted two to three months in each country. The English version of the questionnaire has been developed by collaborators from University of Nottingham (UK) University of Regensburg (Germany), and Mario Negri Institute (Italy). Before fieldwork, the tinnitus-related questions were translated from English into various country-specific languages using the good practice guidelines for questionnaire translation. The details of the translation process have been published as a technical note.<sup>11</sup>

The country-specific information provided by DOXA and its European partners for each European country include information on sampling methodology (e.g., sampling method used, response rate, fieldwork dates, age range). The survey questionnaire is designed to collect individual-level information for each survey participant, and is divided in two sections. The first section provided information on: socio-economic and demographic characteristics (e.g., sex, age, level of education, and profession). The second section provided information on tinnitus prevalence, tinnitus severity, healthcare resource use for tinnitus, and hearing difficulty prevalence.

### **Statistical analysis plan**

#### Creation of the survey dataset

Once the fieldwork was completed, DOXA collected data from its European partners and after internal checks provided to Mario Negri Institute the 12 anonymous data files in text format, with the corresponding codebook in English language. The 12 data files were managed by the team at the Laboratory of Lifestyle Epidemiology, Department of Environmental Health Sciences of Mario Negri Institute. Using the statistical package SAS, version 9.4 (SAS Institute, Cary, NC, USA), they performed the input of the 12 textual data file into 12 corresponding SAS datasets, and then created a unique final dataset in SAS. This dataset was checked for coherence and for the presence of possible errors, cleaned, and finalized through the generation of queries which were addressed by DOXA and its European partners.

#### Statistical analyses

Statistical analyses required to achieve objectives has been conducted by the teams from the Laboratory of Lifestyle Epidemiology, Department of Environmental Health Sciences of Mario Negri Institute and the University of Nottingham, using SAS statistical package. Prevalence of three working definitions of tinnitus (any, bothersome and severe tinnitus) have been estimated through univariate statistical analyses (i.e., descriptive statistics for categorical data, including absolute or relative frequencies), overall, by country, and in strata of selected demographic and socio-economic (individual and country-specific) characteristics. Continuous variables have been summarized through the use of means and standard deviations. Alternatively, they have been categorized, and thus described through absolute or relative frequencies.

Multivariate analyses have been conducted to identify sub-groups of the population (e.g., based age-groups, low vs. high educated subjects) or clusters of countries (e.g., based on income levels and regional groups) where tinnitus is more frequent. Thus, odds ratios (OR), and the corresponding 95% confidence intervals (CI), were estimated through logistic regression models after adjustment for selected individual-level characteristics.

## **ETHICAL AND ADMINISTRATIVE ASPECTS**

### **Informed consent**

At recruitment, information on survey characteristics was given to all participants by suitably qualified professionals, who were able to provide answers to any possible questions and to eliminate any concern respondents may have. Information explaining the condition (i.e., tinnitus) was provided to survey participants in the country-specific language in a clear, jargon free manner, using fully understandable terms and language.

Although in EU countries, according to their current legislation, written consent is not mandatory for this type of study (observational study collecting anonymized information), all participants were asked to sign the informed consent form for participation in the study. Since data was collected with CAPI method (using computer or tablet), participants had the possibility to tick an electronic document in order to express their willingness to participate in the study. No written signature was required.

### **Privacy observance procedures**

Survey data was stored in electronic format. Only a selected number of pre-designated members of the data collection team had access to the password protected laptops. Once data collection was complete, all data had been uploaded into a single database and reliably and completely deleted from the laptops. Selected personal data, including the names of respondents, was collected to enable quality assurance procedures and to allow participants willing to withdraw from participation in the survey to have their records deleted from the database. Once quality assurance procedures were complete (within 4 months of the completion of data collection), names and other unique personal identifiers (such as full address) were reliably and completely deleted. During the quality assurance procedures, Mario Negri Institute obtained an anonymous copy of the analysis database, i.e., without names of participants but with encrypted (not personally identifiable) codes. The encryption key is kept by DOXA and its European partners in a place separated from the research group. All access to the encryption key was logged. This encryption key was destroyed once quality assurance

procedures are complete. After this procedure, there was no possibility to identify the participant record and consequently to delete it from the database. The analysis database is held securely on a password protected file server at Mario Negri Institute, and only a limited number of researchers from the research team have access to this analysis database. All data is managed anonymously, in respect of the privacy regulations in force, only for scientific purposes, without any lucrative aim. Moreover, results of the study do not consist any individual-level data, but aggregated data, and summary results are disseminated, thus not allowing to identify the survey participants. These and other measures are in agreement with national and current or forthcoming EU (i.e., Directive 95/46/EC) regulations. The Ethics Committee of the study coordinator (Ethics Committee of Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy) notified that no preventative evaluation was required for the present study, since anonymous data was collected (File number 37/2017).

#### **Access to personal data and withdrawal from the study**

In this survey no sensitive personal data (e.g., health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction), genetic information, or data involving tracking or observation of participants was collected. According to other personal data, it was made clear that subjects are completely free to withdraw their records from participation in the survey, and that the consent given by participants in the study can be withdrawn, without any explanation or justification. In this case, all data pertaining to the subjects in question was destroyed.

#### **Selection of the subcontractor performing data collection**

The development of the questionnaire and the data managing, analysis and interpretation have been carried out by the Laboratory of Lifestyle Epidemiology, Department of Environmental Health Sciences of Mario Negri Institute, in collaboration with partners from University of Nottingham and University of Regensburg. For cost-effectiveness and efficient fieldwork, data collection of the European cross-sectional survey was delegated to a leading market research organization, DOXA, which was involved as a subcontractor of Mario Negri Institute. Mario Negri Institute has collaborated with DOXA in several national and international projects, including the annual national surveys on smoking since 2001 (in Italy), and in the PPACTE and the TackSHS project, involving 18 and 12 European countries, respectively. Therefore, the collaboration has been established before the beginning of the study.

#### **Ownership of the data**

Individual-level anonymous data sent from DOXA and its European partners, and stored at the Mario Negri Institute, are the property of the study coordinator.

### **RELEVANCE AND IMPLICATIONS**

One of the expected outcomes of this study is the first estimate of tinnitus prevalence from a Pan-European study. Given the lack of standardized tinnitus prevalence questions and a global prevalence estimate, this study provides both standard assessment measures and an estimate of how prevalent tinnitus symptoms are. McFerran and colleagues identified the lack of an agreed prevalence estimate as one of the most crucial hindrances to engaging the pharmaceutical industry in searching for a tinnitus cure.<sup>12</sup> In this study, we report the prevalence of any tinnitus using the same set of research questions in various languages. This measure

identifies the commonality of the condition. Furthermore, we assess the proportion of individuals having bothersome and severe symptoms, who exert the true burden on financial and personnel resources in the healthcare system. These estimates measured in a Pan-European study demonstrate the size of the problem. This can guide resource allocation for implementing effective measures and attract various stakeholders, including research funders, industrial and healthcare organizations, to engage in needful endeavors for tackling tinnitus.

## DISSEMINATION

The main channels of dissemination of the results of this survey will be international peer-reviewed open-access journals. Open access journals will allow the free dissemination of the study's results among the scientific community. The dissemination will be followed critically and professionally, to maximize the study's impact on both scientific knowledge and on public health. Key findings from this study have been presented in hearing and tinnitus related conferences, and other varied forms of communications have been used to promote awareness of the study results to organizations and stakeholders involved in the hearing and tinnitus research, health promotion, and public health.

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