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Overview

Tinnitus is the most frequent phantom sensation, affecting 70 million individuals in Europe. It dramatically increases with age, with nearly 40% of elderly persons experiencing tinnitus. It can be severely debilitating, increasing the risk for sick leave, disability pension and even suicide. While prevalence is higher in men, women, shows greater psychological burden and loss of life quality, suggesting that different coping mechanisms operate in the two genders. From a genetic perspective, we recently found that specific forms of tinnitus displayed significant heritability in men, albeit when segregated according to age, young women showed such high genetic influences. On this basis, TIGER aims to provide three major insights needed for long-lasting prevention and therapy for tinnitus through the principal goals: i) the identification of environmental risk factors to define non-genetic risks of developing severe tinnitus; ii) the identification of novel genetic and blood biomarkers. The insights from the two first aims will be used to iii) stratify disease risk and elaborate preventive medical recommendations for high-risk subgroups of tinnitus patients and to define molecular drivers/biological pathways relevant for the development of severe tinnitus that will be used to identify and validate new therapeutic targets. Here, we will use epidemiological lifestyle, nutritional, and medical analytical data from large Swedish longitudinal and Italian retrospective studies, and molecular genetics, coupled to in-depth tinnitus phenotyping beyond current clinical practice.

Main results

The conclusions from the Swedish project TIGER funded by the GENDER-NET Co Plus fund are clear: woman with severe tinnitus suffer more than men do and there could be an underlying genetic mechanism behind severe tinnitus. The first study on 2'156 subjects from the Swedish Tinnitus Outreach Project evidenced that woman with constant tinnitus have greater stress and anxiety. Constant tinnitus is the permanent perception of an uninterrupted beeping sound that is not physically present. It is often resulting from otological conditions, but evidence on the causal factors for tinnitus remain sparse). This guided a larger study on 71,542 individuals from the Stockholm region evaluating the relationships between tinnitus and suicide attempts, whereby women with severe tinnitus were shown to have greater odds of suicide attempts, whereas this was not found in men. Interestingly, analysis of medical registry data showed that women that had consulted medical support from specialty care prior the survey (been diagnosed for tinnitus and classified under the ICD10 code H93.1), the association with suicide attempts was no longer seen. This study highlighted that medical care, despite the lack of recognized medical treatment with the exception of cognitive behavioral therapy, also could impact on the well-being of tinnitus patients. Whether this medical treatment effect is sex or gender specific is however unclear, but an increasing body of research suggests that women could be more responsive to emerging treatments such as high-definition transcranial direct current stimulation (HDtDCS), orofacial therapy, transcranial magnetic stimulation or acoustic stimulation.

TIGER also started evidencing a sex-specific contribution of genetics on various tinnitus traits such as laterality or more importantly severity, where women with severe tinnitus were 10 times more likely to have a sibling with tinnitus than women with no tinnitus. These numbers are in the vicinity of what is found for schizophrenia or bipolar disorders, yet tinnitus has always been considered a symptom of conditions like hearing loss such that the familial transmission has never been questioned in the clinic. In fact, studies in adoptees have found that the familial transmission of clinically significant tinnitus (that is severe enough to be seeking medical care) is genetically mediated, and not due to share-environment. Thus, tinnitus as a primary complaint should be viewed as a disorder on its own, and not the mere symptom of another condition. Thus, it is now crucial to start considering severe constant tinnitus as a disorder (prevalence of 2%) and not as a symptom (prevalence of 15%), and emphasize the need for better treatments in particular towards women with high psychological burden.

Performance can also be evaluated in where TIGER is going? Together with the WHO, TIGER is currently establishing a working group to redefine the tinnitus classifications within the ICD code, which is inaccurate. Thanks to the results from the project, TIGER will contribute to a new guidance on tinnitus assessment, rehabilitation, taking sex and gender into consideration as psychological burden and response to treatments varies between gender.

Team members

	Woman	Man	Other
Gender balance in the whole consortium	8 (53%)	7 (47%)	0 (0%)
Presence of women as lead researchers/PIs	4 (50%)	4 (50%)	0 (0%)
Gender Experts in the team	1 (50%)	1 (50%)	0 (0%)
Subsequent team members trained (Gender equality and/or IGAR)	0	0	0

Contribution to the achievement of UN Sustainable Development Goals (SDGs)

So far not, but we hope to reveal that tinnitus is among the neurological disorders that have greater impact in women.

Differences/inequalities between women and men highlighted by the project

We have revealed a sex difference in the psychological impact of tinnitus, being more dramatic in women, increasing the risk for suicidal attempts. We however show that other factors (hyperacusis, headache, and temporomandibular joint problems), although more frequent in women, do not increase the risk for severe tinnitus. A striking observation in our studies, is that a sex effect is frequently found in our analyses, but when stratifying by sex, there is no significant differences observed. Thus, the conclusions on the role of sex/gender in disease risk depends highly on what statistical approaches are used.

Another aspect that was further evidenced, is that the familial transmission of tinnitus by genetics is greater when women report tinnitus. The risk of a woman with severe tinnitus to have another sibling with tinnitus is as high as what is found for schizophrenia. This calls to a major revision of the national guidelines to consider the genetic transmission of tinnitus, in particular when women with severe tinnitus come to the clinic.

Positive impact of the project on gender equality/scientific evidence on gender in the field

The project has revealed the lack of consideration of sex/gender aspects in tinnitus research, which stimulated research on the topic. This led us to create a Research Topic in Frontiers, where some research has shown gender effects in the response to treatments. <https://www.frontiersin.org/research-topics/9642/sex-and-gender-differences-in-tinnitus>

However, we believe this is not enough, and we plan to hammer this out in the next Tinnitus Research Conference in Dublin June 2021, hopefully post-COVID.

Due to COVID-19, the conference has been delayed until June 2023. The majority of the TIGER representatives will be present in Dublin to emphasize on the need for sex/gender research in the field.

Socio-economic impact; involvement of policy makers/civil society

The project has great potential of impact. TIGER members are currently in discussions with the WHO (Non-communicable disorders) to review the ICD definitions of tinnitus.