GENDER·NET Plus
Promoting gender equality in H2020 and the ERA

Final Dissemination Conference

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TIGER

The combined role of genetic and environmental risk factors in the gender-specific development of severe tinnitus

TIGER: Team presentation

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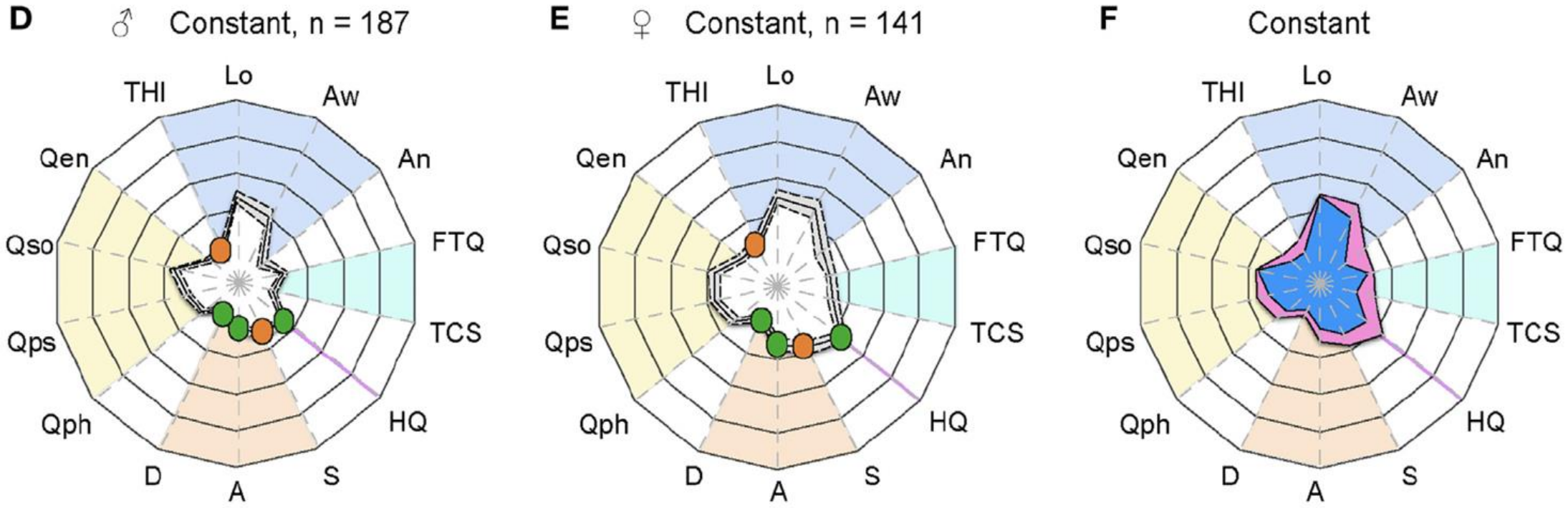
Tinnitus: highly unmet clinical need

- Tinnitus is a phantom perception with neural mechanisms similar to chronic pain
- Most often deriving from hearing loss
- Highly impacting in persons suffering from it
- Near 3’500€/year/person of healthcare costs, and 3’700/year/person of indirect costs
- Unknown sex/gender mechanisms

Sex differences in tinnitus burden



Schlee et al., *Frontiers in Medicine,* 2017

Science and societal impact

- 28 open access publications (*The Lancet, Lancet Public Health, JAMA Neurol, JAMA Otol, Ebiomedicine, AJHG, JCI*)
- Altmetric scores: 604, 224, 169, 149, 144 ..
- 2 international research Prizes
- 2 permanent positions
- Scientific advisors in two patient organizations
- 2 national recommendations
- 6 newspaper releases, 3 press releases, 4 podcasts

Aim 1:
Epidemiology

Cohorts

Whole Sweden

STR (DNA)
Total: 81,924
Tinnitus cases: 10,095

LifeGene (DNA)
Total: 26,282
Tinnitus cases: 7,618

SLOSH
Total: 19,992
Tinnitus cases: 6,021

Stockholm Region

SPHC
Total: 68,234
Tinnitus cases: 16,498

Public outreach
Total: ?
Tinnitus cases: ?

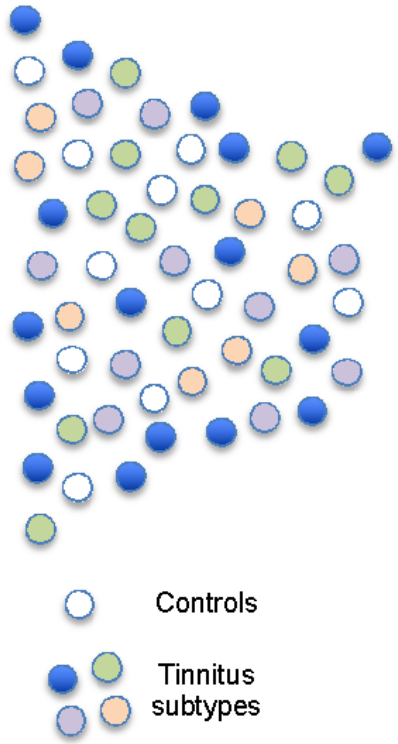
Aim 2:
Subtyping in STOP

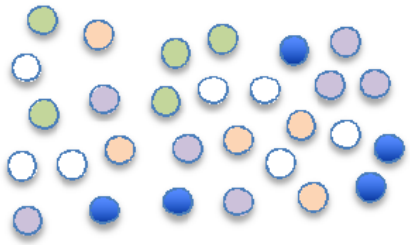
Questionnaires

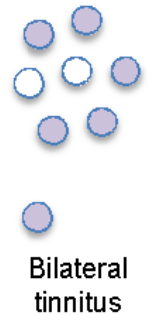
Control : 2,728
Occ Tin: 1,223
Con Tin: 1,901

Audiometry

Control : 168
Occ Tin: 177
Con Tin: 248

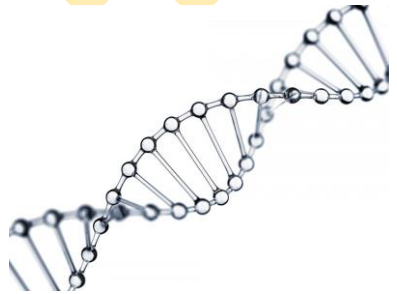


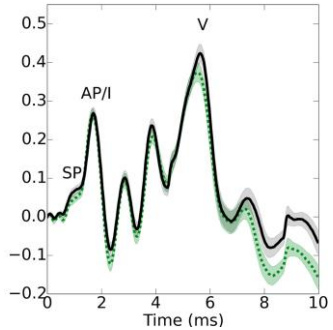




Aim 3:
Biomarkers

Genomics
Proteomics
Electrophysiology





Suicide attempts in women

Stockholm population: N=71’542 individuals

Tinnitus status	Total	Men	Women
Any tinnitus	1.15 (1.03-1.28)	1.08 (0.90-1.30)	1.19 (1.03-1.36)
Severe	1.32 (1.04-1.66)	0.98 (0.67-1.44)	1.57 (1.17-2.10)
With previous clinical care	0.92 (0.67-1.26)	0.97 (0.58-1.63)	0.87 (0.58-1.29)

Lugo et al., *JAMA Otol,* 2019

Sex and genetics give rise to severity

Twin
s

N = 10,464 twin pairs

Bilateral T -> H_2=67%

Maas et al., *Genetics in Medicine*, 2017

Adoptees

N = 11,060 adoptees

Sig T -> H_2=31%

Cederroth et al., *JAMA Otol.,* 2019

Familial aggregation

N = 3,240 relatives

Severe T -> λs = 5.03-10.25

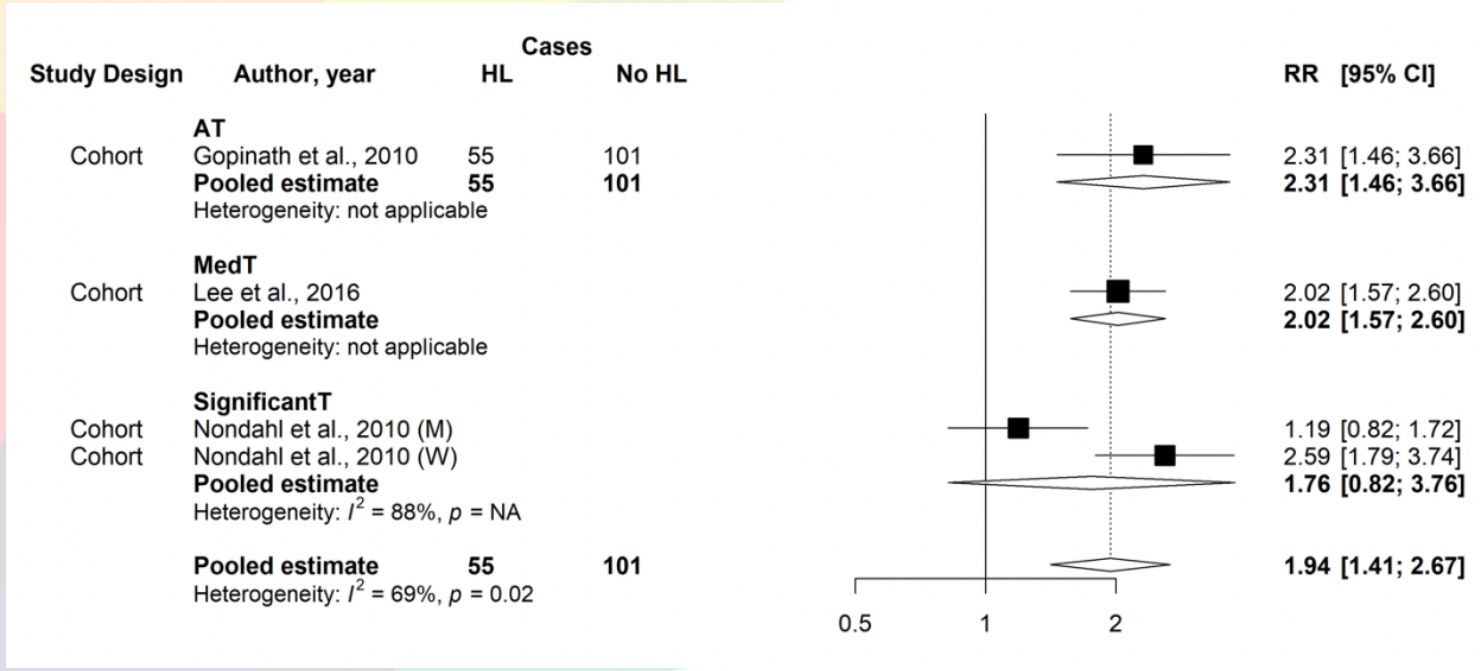
Trpchevska et al., *JCM,* 2020

Risk factors for severe tinnitus

Limited knowledge from SR

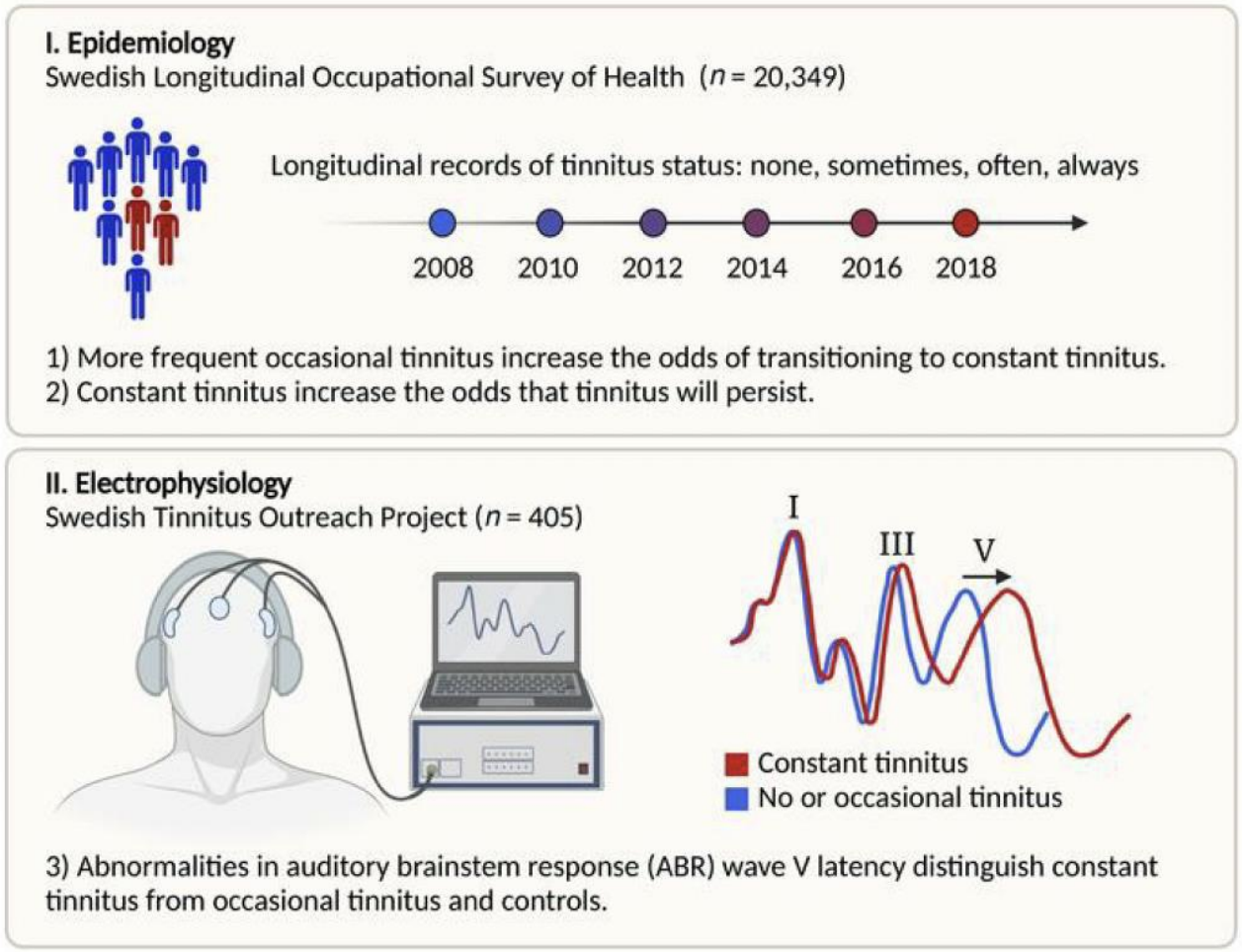
Associations with severe tinnitus

- **TMJD**
  - OR = 2.79 (1.59-4.91)
    - Edvall et al. *Front. Neurol*. 2019
- **Headache**
  - OR = 3.80 (2.4-5.9)
    - Lugo et al. *Scientific Reports*, 2020
- **Hyperacusis**
  - OR = 77.4 (35-171.3)
    - Cederroth et al., *J. Clin. Med.* 2020



Biswas et al., *JARO,* 2022

Novel biomarkers for tinnitus



Longitudinal study

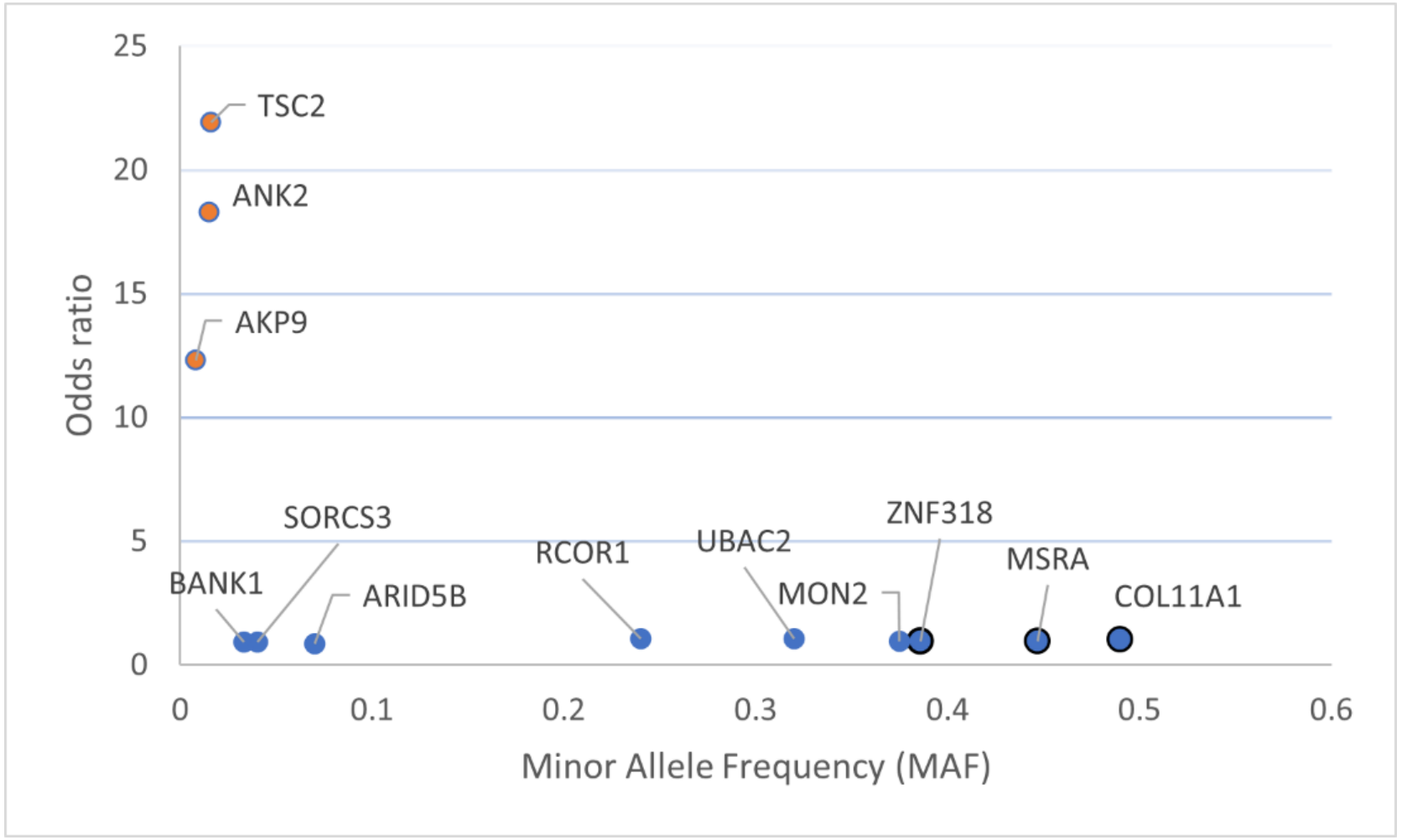
- Increased risk for getting constant tinnitus in men
- No changes with time in severity

Electrophysiological study

- Influence of sex on ABR
- No possibility of stratifying due to too low sample size
- Increased Wave 5 latency in constant tinnitus but not occasional tinnitus

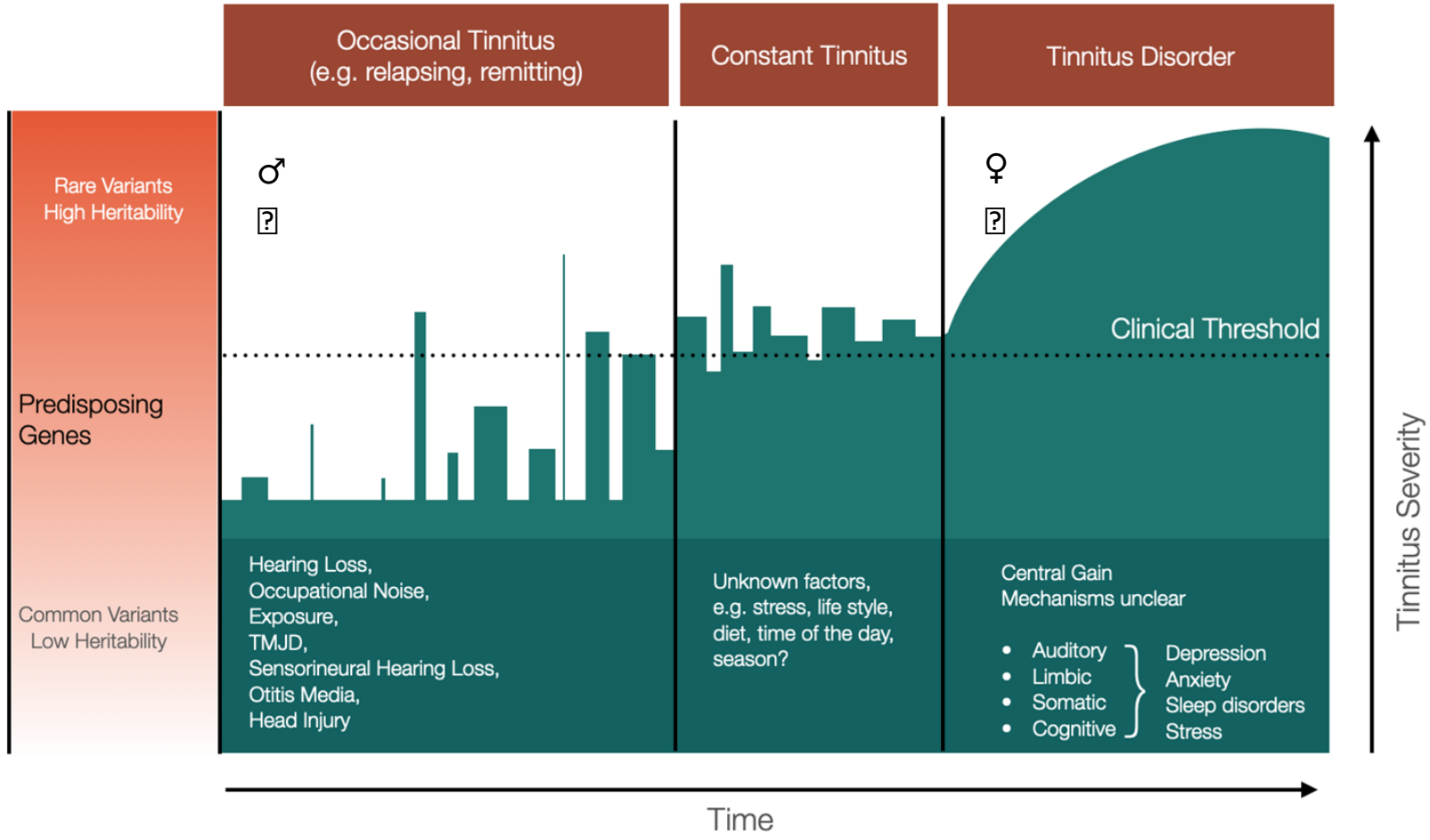
Edvall et al., *JCI,* 2022

First genes associated with severe tinnitus



Cederroth et al., *Tinnitus Textbook,* in production

Model for the development of tinnitus



Cederroth et al., *Tinnitus Textbook,* in production

Expected socio-economic impact

- Recognition of severe tinnitus as a neurological disorder
- Increased prevention and health care resources in ENT specialty care
- Increased funding for tinnitus research
  - **Fundamental mechanisms**
  - **Clinical research**
  - **Clinical care, development of new therapeutic interventions**
- Investment in innovation, R&D in pharma-industry, and bioengineering
- Increase fundraising for patient organization
- Changes in EU guidelines for better care at GP level and attention for women with severe tinnitus

Conclusions/Perspectives

Sex and genetics give rise to severity

- Increased risk in suicidal attempts in females with severe tinnitus, not in males
  - Psychological burden is greater in females than in males in Scandinavia
- Medical care abolishes this risk for females with severe tinnitus
- Medical treatments in general for tinnitus are more effective in women
- Transmission of severe tinnitus in the family is genetically driven, and more so in females
- Severe tinnitus has a global prevalence of 2% with no sex bias
- Severe tinnitus is associated with **rare genetic variants**, **altered midbrain function**, but no plasma biomarkers.

Directions for future research 1

- Increased subtyping by sex/gender and severity, leads to very small sample sizes.
  - There is a need for large ENT biobanks on tinnitus
  - Gender definitions need to be incorporated in current databanks and biobanks
  - Better tinnitus definitions need also to be included **(in progress with WHO)**
- Can the genetics tell whether severe tinnitus is similar to other neurological disorders – is it a neurological disorder?
- Is severity driven by male/female hormones, or is it related to gender identity?
- Are there genetic or social mechanisms that explain why women are better responding to treatments than men?

Directions for future research 2

- There is a need for more high quality studies on risk factors for severe tinnitus, taking sex/gender into account
- Development of objective measures that quantify tinnitus severity and/or loudness
- Research on biomarkers for inflammation in cerebrospinal fluids

THANK YOU GENDER-NET FOR ALLOWING US TO MAKE A DIFFERENCE FOR TINNITUS SUFFERERS