Aging and tinnitus: exploring the interrelations of age, tinnitus symptomatology, health and quality of life with a large tinnitus database - STSM Report

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1 Purpose of mission

The primary goal of the mission was to gain insights about the role of aging in the tinnitus population. Of special interest were putative protective and stabilization processes in healthy aging in large tinnitus cohorts. In order to study these phenomena, data from an European collaborative database `https://www.tinnitus-database.de` was selected. The choice of this data source was intended to maximize sample size for statistical analysis of the main variables of interest namely age, tinnitus distress, quality of life and health-related measures. The data was then evaluated and analyzed on supervision of the host in interaction with computer scientists (databases) as well as statistical experts within the TINNET research initiative. Finally, upon iteration of the research questions, hypotheses and analyses during and after the mission, it is planned to prepare a publication. Ideally, this publication will profit from 1) more data, 2) more variables to differentiate findings and validate analyses and 3) more in-depth and complex statistical models building on 1) and 2). To that end, a call is uttered to other centers to participate and share data towards the common goal of better understanding of tinnitus heterogeneity.

2 Methods and procedure

Given the heterogeneity and different input states (i.e. validation) and measurement time points (e.g. screening, baseline, treatment etc.) the selection, evaluation and cleansing of data can be not only seen as a necessary first step but also as a key and extensive task during the mission. Following on that, data was then visualized and analyzed with simple statistics (i.e. correlations) to probe for latent patterns in the data. Given the established research focus, namely interrelations of age, tinnitus, and quality of life, as well as preliminary data showing patterns of these interrelations worth looking at (e.g. age, quality of life, and tinnitus distress as seen in a component of a principal component analysis with the data the center of Zurich contributed to the database), the analysis procedure was directed and set up to evaluate these observations in 'big data' to both confirm their existence as well as studying them in more depth. A (counterintuitive) positive relation between health-related quality of life and tinnitus distress seems to exist alongside differential relations of age with the two aforementioned variables (i.e. slight positive correlation between age and physical quality of life and slight negative correlation between age and tinnitus distress). This observation therefore served as a hypothesis to be tested alongside the mentioned open analyses paths with various statistical approaches.

In a first phase the applicant selected, exported, cleaned out and evaluated data from `https://www.tinnitus-database.de`. As only the centre of Regensburg and Zurich provide relevant data in validated

		age	duration	tq	phys	psych	social	envir	global
N	Valid	3335	2516	2469	2061	2056	2022	2023	2096
	Missing	7	826	873	1281	1286	1320	1319	1246
Mean		57.82	168.68	41.31	54.52	60.68	66.36	75.39	55.04
Median		58.00	136.00	41.00	57.00	63.00	67.00	78.00	50.00
Std. Deviation		13.170	112.430	18.294	11.521	12.415	19.433	14.712	20.479
Range		80	801	82	97	83	92	87	87
Minimum		16	6	1	7	13	8	13	13
Maximum		96	807	83	100	96	100	100	100

Table 1: **Descriptive statistics of the sample (n=3342)**.

form at the moment, the analysis was centered around these data sets. Variables were chosen according to availability and number of cases. Furthermore the choice was set on total scores of questionnaires and relevant items from the tinnitus sample case history questionnaire (TCSHQ (Langguth et al., 2007)). Quality of life (WHOQoL Group, 1998) was taken into account with the 4 domains and the global score, tinnitus distress with the tinnitus questionnaire (TQ, (Goebel and Hiller, 1994). Unfortunately, further health questionnaires were either not available in sufficient numbers or input states. Age, sex and duration were included from the TCSHQ.

Counter to expectations and partly due to technical reasons, this first step was extensively time-consuming and required the required time well into the second week of the mission. Yet, in the meanwhile (e.g. while waiting for technical support by the database operators) the applicant performed first analysis with a clean data set from Zurich (n=188). Upon having been able to generate a clean data set with relevant variables and a maximized sample size from the database (n=3342, including incomplete cases), the statistical analysis began along two lines: First, a latent class analysis (LCA (Langguth et al., 2017)) on classes of quality of life was performed on the the small data set with no success (ceiling effect in the data). The application of this LCA pipeline on the larger dataset was able to produce classes but post hoc comparisons of the classes on common tinnitus and demographic variables did not produce significant differences. Resulting classes therefore were mostly meaning less with the data available.

Second, to probe the above mentioned observed interrelation between age, tinnitus distress, and quality of life, the second analysis focused on mediating or moderating effects of age on the relation between (high) quality of life, especially the physical domain, and (high) tinnitus distress. Mediation analysis was therefore performed using a toolbox by Hayes (2013). Results of this final analysis are presented and discussed in the following results and discussion section.

3 Results and discussion

Descriptive statistics of the final, large sample are reported in table 1. Note the missing values in some variables which lowered the effective sample size for the mediation analysis to n=1393.

Correlations between the variables of interest are listed in table 2. Notably, there seems to be a relation between age, tinnitus distress, and quality of life.

Results of the mediation analysis with TQ sum score as the dependent variable, physical quality of life as the independent variable, age as the (putative) mediator variable, and tinnitus duration, sex as well as the remaining WHO subscales as covariates are plotted in figure 1. Notably, the indirect effect of X on Y, namely through the mediating variable physical quality of life (phys) as well as the direct effects are significant. The 95%-confidence interval of the bootstrap results revealed that the indirect effect of physical quality of life on tinnitus distress through age was different from zero (lower level: 0.0588; upper level: 0.0187) indicating that

		age	duration	tq	phys	psych	social	envir	global
age	Correlation Coefficient	1.000	.295	-.139	.089	-.007	-.023	.001	.010
	Sig. (2-tailed)	.	.000	.000	.000	.747	.292	.982	.632
	N	3335	2512	2468	2057	2052	2018	2019	2092
duration	Correlation Coefficient	.295	1.000	-.080	-.017	-.041	-.050	-.060	-.053
	Sig. (2-tailed)	.000	.	.000	.463	.075	.032	.010	.021
	N	2512	2516	2154	1870	1862	1833	1834	1897
tq	Correlation Coefficient	-.139	-.080	1.000	.452	.502	.283	.407	.558
	Sig. (2-tailed)	.000	.000	.	.000	.000	.000	.000	.000
	N	2468	2154	2469	1788	1789	1755	1754	1808
phys	Correlation Coefficient	.089	-.017	.452	1.000	.594	.406	.465	.486
	Sig. (2-tailed)	.000	.463	.000	.	.000	.000	.000	.000
	N	2057	1870	1788	2061	1985	1948	1954	1997
psych	Correlation Coefficient	-.007	-.041	.502	.594	1.000	.520	.571	.584
	Sig. (2-tailed)	.747	.075	.000	.000	.	.000	.000	.000
	N	2052	1862	1789	1985	2056	1949	1952	1996
social	Correlation Coefficient	-.023	-.050	.283	.406	.520	1.000	.470	.405
	Sig. (2-tailed)	.292	.032	.000	.000	.000	.	.000	.000
	N	2018	1833	1755	1948	1949	2022	1913	1961
envir	Correlation Coefficient	.001	-.060	.407	.465	.571	.470	1.000	.437
	Sig. (2-tailed)	.982	.010	.000	.000	.000	.000	.	.000
	N	2019	1834	1754	1954	1952	1913	2023	1969
global	Correlation Coefficient	.010	-.053	.558	.486	.584	.405	.437	1.000
	Sig. (2-tailed)	.632	.021	.000	.000	.000	.000	.000	.
	N	2092	1897	1808	1997	1996	1961	1969	2096

Table 2: **Spearman correlations between variables of interest**. tq = tinnitus questionnaire sum score (Goebel and Hiller, 1994). phys(ical),psych(ological),social,envir(onmental),global(score) = subscales of WHObref questionnaire (WHOQoL Group, 1998).

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****************** TOTAL, DIRECT, AND INDIRECT EFFECTS ********************

Total effect of X on Y
     Effect         SE          t          p       LLCI       ULCI
      .2075      .0432     4.8002      .0000      .1227      .2922

Direct effect of X on Y
     Effect         SE          t          p       LLCI       ULCI
      .2439      .0426     5.7283      .0000      .1603      .3274

Indirect effect of X on Y
        Effect    Boot SE   BootLLCI   BootULCI
age     -.0364      .0101     -.0588     -.0187

Partially standardized indirect effect of X on Y
        Effect    Boot SE   BootLLCI   BootULCI
age     -.0027      .0007     -.0043     -.0014

Completely standardized indirect effect of X on Y
        Effect    Boot SE   BootLLCI   BootULCI
age     -.0224      .0062     -.0361     -.0114

Ratio of indirect to total effect of X on Y
        Effect    Boot SE   BootLLCI   BootULCI
age     -.1754      .0776     -.3890     -.0777

Ratio of indirect to direct effect of X on Y
        Effect    Boot SE   BootLLCI   BootULCI
age     -.1492      .0517     -.2800     -.0721

Normal theory tests for indirect effect
     Effect         se          Z          p
     -.0364      .0101    -3.6066      .0003
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Figure 1: **Results of the mediation analysis.**

age partially mediated the relationship between physical quality of life and tinnitus distress. As for effect sizes, the size of the indirect effect is rather low which may not be surprising given the small correlation coefficients (see table 2). On the other hand, when looking at the correlation matrix, it is evident that the chosen variables are clearly interrelated in contrast to the rest of the variable set.

For illustration purposes, data of the mediation analysis showing the upper variable ranges of the sample is plotted in figure 2.

The mediation analysis demonstrates that the positive relation between physical quality of life and tinnitus distress is partly mediated by age. This observation may lead to one possible interpretation that age(ing) itself may act as a protective factor for both tinnitus distress and quality of life. Yet, analyses and results can only be interpreted with caution as it has to be dealt with issues of directionality and causality, among others. The causality between physical quality of life and tinnitus distress is unclear and only assumed through theoretical considerations or data from studies (e.g. (Milerova et al., 2013; Weidt et al., 2016)).
Taken together, results point to an interesting interaction between the domains of aging, quality of life and tinnitus distress while causal relations and further interactions have to be further studied.

4 Future directions and comments

The analysis performed on a large data set of clinical data in tinnitus seems to be suitable to detect and explore novel aspects of tinnitus: In recent times several studies with big data led to respective new insights to tinnitus and also its heterogeneity (e.g. (Probst et al., 2016; Langguth et al., 2017). With these studies or unpublished big data analyses, both genuinely novel insights were produced and, on the other hand, possible

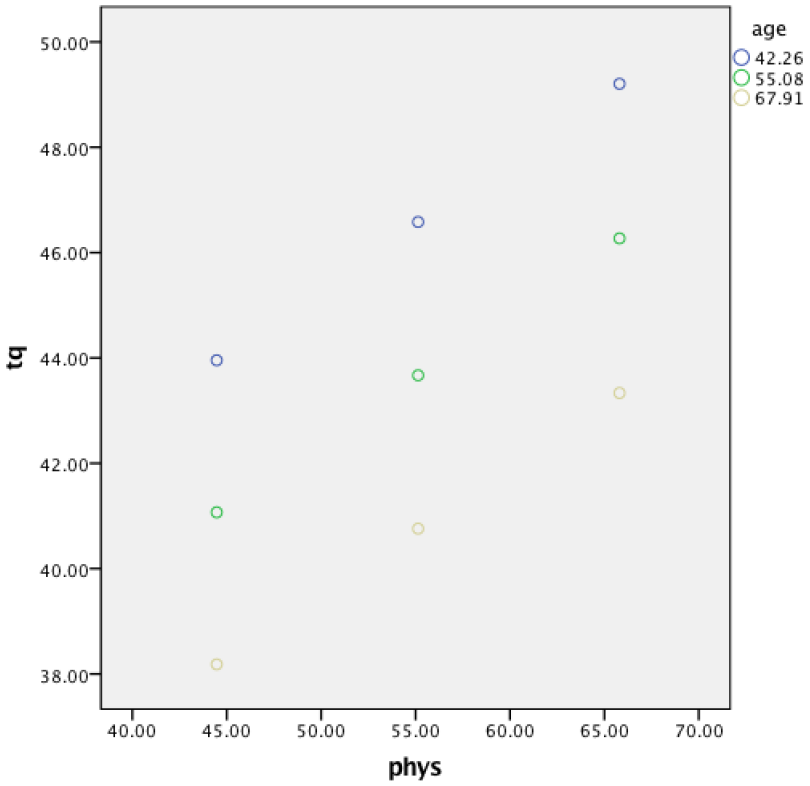

Figure 2: **Mean plot between the three variables of the mediation analysis.**

misconceptions derived from analyses from smaller samples discarded (e.g. an observed positive relation between tinnitus frequency and distress (e.g. (Meyer et al., 2014)) could not be replicated in big data (unpublished analysis)). In general, big data analysis is therefore highly effective to detect latent patterns and therefore enable tinnitus researcher to map out tinnitus heterogeneity.

In all honesty, I consider this mission as only partly successful. As mentioned in the beginning, data export and integrity issues overshadowed as well as hindered the main part of the 10 day mission, namely in-depth statistical analysis and modeling. This also reduced planned interaction with the hosts on site and supporting co-researchers within TINNET as basically time was running out. Certainly, this line of work will be continued and I am confident that a proper finalization of the efforts of studying the role of aging in big data of tinnitus will be reached soon. Consolingly, looking back at my other missions during the TINNET grant periods, mission goals were met and productive collaboration including follow-up experiments including a publication etc. was established. Still, I would have wished for more elaborate results of this mission during the actual stay and not being left with many open questions and tasks.

In conclusion, the preliminary analysis of the role of aging in tinnitus revealed possible mediating effects of age in the relation between of physical quality of life and tinnitus distress. Yet, data analysis and evaluation of analysis has to be reiterated to come to a fruitful conclusion in the aftermath of this mission.

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