Toward Genetic Screening for Glaucoma

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CHAPTER 5

Associations between tinnitus and glaucoma suggest a common mechanism: a clinical and population-based study

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Abstract

The purpose of this study was to determine if there is an association between tinnitus and glaucoma. We tested this by first completing a clinic-based cross-sectional questionnaire study in which we sent a series of tinnitus-related questions to glaucoma patients and healthy subjects, and then followed up with a large population-based cross-sectional study in which glaucoma and tinnitus were also assessed by questionnaire. For the clinical study, we received 209 responses from glaucoma patients and 109 responses from healthy subjects (primarily the spouses of the patients). For the population-based study, we evaluated 79,866 participants. Logistic regression models were used to test the relationship between glaucoma and tinnitus; the clinical study analysis was adjusted for age, gender, BMI, hypertension, and diabetes and the population-based study was adjusted for these same variables with the addition of socioeconomic status and subjective hearing loss. For the clinical study, glaucoma patients had an 85% increase in odds for tinnitus (adjusted OR 1.85, 95% CI 1.10 to 3.05). The effect did not depend on pretreatment intraocular pressure, and the associated symptoms were not pulsatile in nature. For the population-based study, glaucoma patients had a 19% increase in odds for tinnitus (adjusted OR 1.19, 95% CI 1.02 to 1.40). Overall, our results suggest that those with glaucoma are more likely to have tinnitus than those without glaucoma. These results provide hypotheses for a mechanism involved in both tinnitus and glaucoma. One possible mechanism could be vascular dysregulation due to impairment of nitric oxide production.

Introduction

Primary open angle glaucoma (POAG) is a chronic and progressive eye disease that is characterized by damage to the retinal ganglion cells and their axons and subsequent loss of visual function. If left untreated, it can eventually lead to blindness. Although POAG is often associated with a high intraocular pressure (IOP), a large proportion of patients will have a normal eye pressure. The underlying cause of POAG is therefore still not well understood (Janssen et al., 2013). There is a theory that, at least for some patients, glaucoma is an ocular manifestation of a wider problem of vascular dysregulation (Harris and Wirostko, 2013; Pasquale, 2016). Put simply, this means that the blood supply is not responsive to the shifting needs of various tissues. In this case, it is possible that organs other than the eye could be affected by insufficient blood flow as well.

In a previous study in our lab in which measurements of otoacoustic emissions were done in glaucoma patients (Loiselle et al., 2018), several subjects complained of tinnitus symptoms or wondered if their tinnitus would affect the test results. This anecdotal evidence led to a search of the literature, which yielded two articles that mentioned both glaucoma and tinnitus in the context of vascular dysregulation (Flammer et al., 2013; Konieczka et al., 2014). At least one possible disease mechanism associated with vascular dysregulation that is associated with both glaucoma and tinnitus is a decrease in bioavailability of nitric oxide (NO; see section 4). A third, recent article actually connected glaucoma and tinnitus (Konieczka et al., 2017); this questionnaire study showed that tinnitus occurred significantly more often in glaucoma patients with a normal eye pressure. To our knowledge there are no reports confirming the finding that tinnitus is more prevalent in glaucoma.

The aim of this study was therefore to determine if there is an association between glaucoma and tinnitus. We tested this by (1) performing a clinical cross-sectional questionnaire study with glaucoma patients and healthy subjects and (2) comparing this finding with the association between glaucoma and tinnitus in a large, population-based cross-sectional Dutch cohort study (Lifelines).

Methods

Clinical study population

The questionnaire (see section 3, original Dutch questions with translations) was sent to 371 patients with glaucoma, selected from the Groningen Longitudinal Glaucoma Study database (Heeg et al., 2005). The main tinnitus question was: "Do you hear a ringing or rushing sound in your ear?". In order to be eligible for the study, subjects had to be over 50 years of age, and have diagnosed glaucoma (as defined by Heeg et al (Heeg et al., 2005)). We sent two questionnaires to each patient, and the patient was asked to fill in the first and give the second to a friend or partner without glaucoma. As a result, the healthy subjects in our study were primarily the spouses of the glaucoma patients. Patients and healthy subjects were explicitly asked to complete the questionnaire independently. All healthy subjects confirmed that they had no family history of glaucoma and were not under regular supervision of an ophthalmologist. In this way, we assured a glaucoma prevalence below 1% in the healthy (Wolfs et al., 2000). The ethics board of the University Medical Center Groningen approved the study protocol. All patients provided written informed consent allowing data from their hospital files, such as IOP and visual field results, to be viewed. The study followed the tenets of the Declaration of Helsinki.

Lifelines study population

Lifelines is a prospective, population-based cohort study based in the Northern Netherlands (Klijs et al., 2015). Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the north of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The cohort is fully described elsewhere. In brief, recruitment was done through self-recruitment or general practitioner between the years of 2006-2013, and the approximately 167,000 participants will be followed for at least 30 years, and regularly receive questionnaires on a range of topics (Scholtens et al., 2015). One such questionnaire, the National Eye Institute Visual Functioning Questionnaire (NEI-

VFQ-25), contains questions related to vision; we added questions regarding the presence of certain eye diseases as well as surgical, laser, or medical interventions for eye diseases; targeting age-related macular degeneration, cataract, diabetic retinopathy, dry eye disease, high eye pressure or glaucoma, refraction, and retinal detachment. The results from the first available 79,866 participants who completed the questionnaire were used in this study. We then investigated how this subsample responded to a different questionnaire in which questions about hearing and tinnitus were posed, specifically, the participants were asked "Do you ever hear a ringing or rushing sound in your ear(s)?" (Original in Dutch: "Hoort u suizen of fluiten in uw oor/oren?"). Response options were "never", "sometimes", and "always".

The glaucoma definition (proxy) was questionnaire based. Since glaucoma is often undiagnosed, and ocular hypertension (high IOP without damage to the visual system) is sometimes mixed-up with glaucoma, we combined self-reported glaucoma with the presence of glaucoma-specific visual complaints, in order to define glaucoma as accurately as possible with a questionnaire. For the assessment of visual complaints, we used the NEI-VFQ-25. Definite glaucoma cases were those who had a history of glaucoma surgery. Their visual complaint pattern was compared to that of healthy subjects, yielding the glaucoma-specific visual complaints (mainly complaints regarding peripheral vision and visual functioning in low luminance). Subsequently, probable glaucoma cases were those who self-reported glaucoma (without surgery) and displayed glaucoma-specific visual complaints. Possible glaucoma cases were those who self-reported glaucoma (without surgery) or displayed glaucoma-specific visual complaints, but not both. Unaffected were those who neither self-reported glaucoma nor displayed glaucoma specific visual complaints. Details will be described fully elsewhere (Neustaeter et al., unpublished results). For this study, glaucoma classification was binarized, where 'definites' and 'probables' were categorized as affected, the 'unaffected' was the same, and those classified as 'possible' were excluded.

Clinical study data analysis

Patients and healthy subjects were described with mean and standard deviation (SD) for normally distributed variables; means were compared using the Student's t-test. Proportions for demographics and for the questionnaire results were compared using a chi-square test. For the patients, disease severity was quantified as the standard automated perimetry (Humphrey field analyzer 30-2 SITA; Carl Zeiss Meditec, Jena, Germany) mean deviation (MD) of the worse eye.

A logistic regression was performed using a model with tinnitus as the outcome variable and glaucoma, age, gender, body mass index (BMI; categorical variable with "low" ≤ 18.5, "normal" = 18.6 - 24.9, "high" ≥ 25 kg/m^2), hypertension (antihypertensive medication use), and diabetes (use of Metformin or insulin) as explanatory variables. BMI, hypertension, and diabetes were added to the model as these have previously been associated with both tinnitus (Figueiredo et al., 2016; Gibrin et al., 2013; Janssen et al., 2013; Lavinsky et al., 2004; Lee et al., 2018; Shargorodsky et al., 2010) and glaucoma (Janssen et al., 2013). This was repeated after stratifying glaucoma into glaucoma with high and normal IOP, using a pretreatment IOP > 21 mmHg as cut-off (during treatment, virtually all glaucoma patients have a normal IOP; it is the pretreatment IOP that characterizes the patient). An odds ratio (OR) and 95% confidence interval (CI) were calculated to identify the likelihood of tinnitus when glaucoma was present.

Lifelines data analysis

A logistic regression was also performed for the Lifelines cohort with tinnitus as the outcome variable and glaucoma, age, gender, categorical BMI, hypertension, diabetes, socioeconomic status (SES), and subjective hearing loss as explanatory variables. SES and hearing loss data were available for Lifelines and were included in the model because both are associated with tinnitus (Eggermont, 2012; Hoekstra et al., 2014). SES is possibly also related to glaucoma (Oh et al., 2019; Ramdas et al., 2011; Shweikh et al., 2015), while the relationship between hearing loss and glaucoma is not clear for all glaucoma types (Tryggvason et al., 2016). For this analysis, tinnitus was binarized (never = no; sometimes or always = yes). Hypertension was defined as one of the following: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensives (ATC code C02), diuretics (ATC code C03), ACE inhibitors (ATC code C09) beta-blockers (ATC code C07), or calcium channel blockers (ATC code C08). Diabetes was defined as one of the following: 'yes' to the question 'Do you have diabetes mellitus?', or use of metformin (ATC code A10BA or A10BD) or insulin (ATC code A10A). Socioeconomic status was defined by highest educational level achieved, as per van Zon et al. (van Zon et al., 2017). Socioeconomic status was categorized into low, medium, high, and other (a text box where participants could fill in their own answer; in this study the responses were primarily vocational school). Hearing loss was defined using the question: "Are you limited by problems with your hearing in daily life?" (Original question in Dutch: "Wordt u in het dagelijks leven beperkt door problemen met uw gehoor?") and answer

options were “not at all”, “somewhat”, “severely” (in Dutch: “Nee, helemaal niet beperkt”, “Ja, een beetje beperkt”, “Ja, ernstig beperkt”). An OR and 95% CI were calculated in order to identify the likelihood of tinnitus when glaucoma was present and to compare the Lifelines data with the clinical study questionnaire.

All analyses were performed using R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria). A P value of 0.05 or less was considered statistically significant.

Results

For the clinical study, we sent 371 questionnaires and received 209 responses from glaucoma patients (response rate 56.3%) and 109 from healthy subjects (the actual response rate is not known, as we don't know how many patients gave the second questionnaire to a spouse or friend - see section 2.1). From the Lifelines cohort we included 390 participants as "affected" and 72,319 controls. Table 1 shows the characteristics and demographics of both study populations. For the clinical study, glaucoma patients compared with healthy subjects were similar in age and gender. The average age of participants within the Lifelines cohort was approximately 50, that is, significantly different from those that are affected with glaucoma (62 years, on average).

Table 1: Characteristics of the study populations

Clinical Study			
	Glaucoma n=209	**Healthy n=109**	**P-Value**
Age (years; mean[SD])	72.6 [8.7]	70.9 [7.5]	0.07
Gender (% female)	51.2	56.9	0.33
Pretreatment IOP (mmHg; median[IQR])	26.0 [16.0 to 36.0]	NA	NA
MD (dB; median[IQR])	-9.7 [-22.9 to -3.5]	NA	NA
Lifelines Study			
	Glaucoma n=390	**Healthy n=72,319**	**P value**
Age (years; mean[SD])	62.1 [11.7]	49.6 [12.3]	<0.001
Gender (% female)	60.3	59.1	0.69

SD = standard deviation; IOP = intraocular pressure; IQR = interquartile range; MD = standard automated perimetry mean deviation.

Table 2 presents the original questions and results from the clinical study tinnitus questionnaire. Glaucoma patients were more likely to have tinnitus (Q1; P=0.01), but, once present, the frequency of symptoms (Q6; P=0.47) and the prevalence of pul-

satile tinnitus characteristics (Q3; P=0.70) did not differ between groups. Only eight subjects had both unilateral glaucoma and unilateral tinnitus. In 3 out of these 8, glaucoma and tinnitus were on the same side, indicating no clear ipsilateral relationship.

Table 2: Tinnitus questionnaire for clinical study (with the original questions in Dutch)

Questions	Glaucoma (n=209)	Healthy subjects (n=109)	P-Value
Q1. Do you ever hear a ringing or rushing sound in your ear? (Q1. Hoort u ooit een suizen of fluitend geluid in uw oor?)	46.4% yes	31.2% yes	0.01
If yes on Q1	**(n=97)**	**(n=34)**	
Q2. If so, in which ear? (Q2. Zo ja, in welk oor?)	16.5% right 16.5% left 67.0% both	20.6% right 20.6% left 58.8% both	0.69
Q3. Does it pulsate? (Like the sound of your heart beat?) (Q3. Pulseert het? (Zoals het geluid van uw hartslag?))	16.5% yes	11.7% yes	0.70
Q4. Does it get quicker if you do exercise? (Q4. Wordt het sneller als u aan lichaamsbeweging doet?)	12.4% yes	2.9% yes	0.17
Q5. Does it get worse if you change body positions? (Q5. Wordt het erger als u van houding wisselt?)	3.1% yes	0% yes	0.53
Q6. How often do you hear it? (Q6. Hoe vaak hoort u het?)	8.2% rarely 53.6% sometimes 38.1% always	5.9% rarely 44.1% sometimes 50.0% always	0.47

Table 3 shows the multivariable logistic regression models. In the clinical study, after controlling for age, gender, BMI, hypertension, and diabetes, patients with glaucoma had an 85% increase in odds for tinnitus compared to those without glaucoma (binarized using Q1; adjusted OR 1.85; 95% CI 1.10 to 3.05; P=0.018). There was no

gender-specific effect of glaucoma (interaction term gender*glaucoma not significant; P=0.29). When analyzing the glaucoma subgroups split by normal IOP (48 patients) and high IOP (161 patients) separately, the relationship between normal IOP glaucoma and tinnitus (OR 1.77; 95% CI 0.85 to 3.69; P=0.12) appeared to be similar to that between high IOP glaucoma and tinnitus (OR 1.85; 95% CI 1.09 to 3.15; P<0.01) but did not reach significance, possibly related to the relatively small number of patients in the former group. The standard automated perimetry MD value (worse eye) did not differ between these subgroups (median [IQR] for high IOP glaucoma -9 (-23 to -5) dB and for normal IOP glaucoma -10 (-18 to -2) dB; P=0.84), indicating equal glaucoma severity amongst both subgroups.

Table 3: Logistic regression models for the clinical and Lifelines studies with tinnitus as outcome variable

	Clinical Study		Lifelines Study	
	Adjusted OR (95% CI)	**P-Value**	**Adjusted OR (95% CI)**	**P-Value**
Glaucoma (yes)	1.85 (1.10, 3.05)	0.018	1.19 (1.02, 1.40)	0.028
Age (yrs)	0.99 (0.96, 1.02)	0.59	1.01 (1.01, 1.02)	<0.001
Gender (female)	0.40 (0.25, 0.65)	< 0.001	0.83 (0.81-0.85)	<0.001
BMI (reference: normal)		0.61		0.042
Underweight	1.34 (0.44,4.10)		1.06 (0.90, 1.23)	
Overweight	0.69 (0.41, 1.13)		0.97 (0.95, 0.99)	
Hypertension (yes)	1.30 (0.77, 2.18)	0.32	1.09 (1.05, 1.12)	<0.001
Diabetes (yes)	0.94 (0.38, 2.33)	0.89	1.06 (0.99, 1.14)	0.087
SES (reference: high)				
Low	NA	NA		<0.001
Medium			1.42 (1.37, 1.47)	
Other			1.20 (1.16, 1.23)	
			1.35 (1.25, 1.47)	
Hearing loss (reference: not at all)	NA	NA		
Somewhat			3.52 (3.41, 3.65)	<0.001
Severely			6.13 (5.16, 7.28)	

BMI = Body mass index, SES = Socioeconomic Status

In Lifelines, the logistic regression showed that, when controlled for age, gender, BMI, hypertension, diabetes, socioeconomic status, and hearing loss, glaucoma

patients had a 19% increase in odds for tinnitus compared to those without glaucoma (adjusted OR 1.19; 95% CI 1.02 to 1.40; P=0.028). Again, there was no gender-specific effect of glaucoma (interaction term gender*glaucoma not significant; P=0.72). Figure 1 shows a comparison between the frequency of symptoms in the clinical study and Lifelines.

Discussion

In the current study we find that in both the clinical and Lifelines studies, those with glaucoma are more likely to have tinnitus than those without glaucoma. The symptoms are not pulsatile in nature, and there is no gender-specific effect of glaucoma. Pretreatment IOP also did not seem to affect the outcome.

There has only been one previous study investigating the association between glaucoma and tinnitus, in which questionnaires from 246 glaucoma patients with normal IOP and 1,116 controls were analyzed and showed these patients were more likely to have tinnitus (Konieczka et al., 2017). This is in agreement with our findings. In our study, however, we found this association for all glaucoma patients, including those with high pretreatment IOP.

We know that tinnitus is associated with hearing loss (Eggermont, 2012), so an obvious question is: Do glaucoma patients simply have more hearing loss than healthy people? There has been research that demonstrates a relationship between pseudoexfoliative glaucoma (PEX) and hearing loss, however this result is not found in POAG (Hayreh et al., 1999; Paliobei et al., 2011; Shapiro et al., 1997; Tryggvason et al., 2016), and we did not include PEX patients in our study. Hearing loss is more common with older age, but in the clinical study, the groups were similar in age and the analyses were adjusted for age in both the clinical and Lifelines studies. Additionally, in the Lifelines study we controlled for subjective hearing loss by including a question about the impact of hearing loss on daily life, and the relationship between glaucoma and tinnitus was still significant.

While it is possible that vascular dysregulation may play a role in both tinnitus and glaucoma, it is a broad term and could result from a multitude of causes. One possible specific cause of the relationship between glaucoma and tinnitus could be the inhibition of nitric oxide (NO) production. Interestingly, NO is reduced in the jugular vein of patients with tinnitus, which may lead to disruption of the microcirculation in the ear (Neri et al., 2006). It was also shown, in an animal model, that after noise exposure the modulation of NO producing enzymes in the cochlear nucleus determined whether or not the animal developed tinnitus (Coomber et al., 2015). It is known that *CAV1*, *CAV2*, and *NOS3* - genes that relate to NO production - can be affected in glaucoma (Emam et al., 2014; Kang et al., 2010; Logan et al., 2005; Thorleifsson et al., 2010).

These genes are crucial to the L-Arginine-NO pathway, and have been shown to alter ocular blood flow (Schmetterer and Polak, 2001). If this pathway is inhibited due to a deleterious change in the aforementioned genes - as in glaucoma - the body can utilize an alternative method whereby nitrates from the diet are converted to nitrites by commensal bacteria in the saliva, and then converted to NO in the stomach (the Nitrate-nitrite-NO pathway) (Lundberg et al., 2008; Weitzberg et al., 2010). Interestingly, it has already been shown that high levels of nitrates in the diet can reduce the risk of glaucoma by 20-30% (Kang et al., 2016). The Nitrate-nitrite-NO pathway may therefore be extremely important in glaucoma. However, in order to convert nitrites to NO in the stomach, a normal gastric pH must be present, therefore the use of any medications that raise the pH in the stomach, like proton pump inhibitors (PPIs) could hinder this pathway as well (Lundberg et al., 1994). In our clinical study, those taking PPIs had a 2.35 fold increase in odds for glaucoma (OR 2.35; 95% CI 1.26 to 4.39; $p<0.01$). The theory that NO could connect tinnitus and glaucoma needs to be confirmed.

There were some limitations in this study. We relied on self-reporting of tinnitus and not clinical evaluation in both the clinical and Lifelines data sets. However, the questions were phrased simply, and tinnitus is subjective by nature so there is no reason to suspect under or over-reporting in either group. Additionally, selective responses from patients who had tinnitus seem unlikely because the tinnitus questions in both the clinical and Lifelines studies were part of larger questionnaires on many different topics. Second, while in the clinical study we had a strict definition of POAG, in the Lifelines data we used a proxy for glaucoma. By using additional questions, secondary glaucoma was excluded as much as possible, but narrow-angle glaucoma could still confound the data. However, in a previous population-based Dutch cohort study where they did a thorough eye exam in all participants, it was shown that the majority of cases were POAG, with secondary or narrow-angle glaucoma as exceptions (Skenduli-Bala et al., 2005). The inclusion of 'probable' glaucoma cases in the proxy could mean that some subjects included as patients were actually healthy. Consequently, the difference between the patient and control group reported here presumably reflects a lower boundary to the actual relationship between tinnitus and glaucoma. One strong point is the high number of participants included in the Lifelines study. Additionally, the agreement between the clinical and Lifelines studies demonstrates that the association between tinnitus and glaucoma is a repeatable finding.

Conclusion

Patients with glaucoma are more likely to have tinnitus than those without glaucoma. Future research should focus on the possibility that vascular dysregulation due to impairment of NO production - from both genetic expression and diet - could potentially lead to both of these diseases. Their chronology should also be characterized. Do they occur simultaneously? Or does one come before the other? If the latter is true, then one disease may be a predictor of the other. A causal relationship could be further explored by epidemiological studies, including longitudinal and case-control studies. Further research could also explore the relationships between glaucoma, tinnitus, and other diseases that have been associated with aberrant NO behavior, specifically type II diabetes (Assmann et al., 2016; Tessari et al., 2010), dementia (Austin et al., 2013; Katusic and Austin, 2016), and sleep apnea (Badran et al., 2015; Weiss et al., 2012). Investigation of these relationships could lead to an improvement in quality of life for the patients and a better understanding of the pathophysiology of both glaucoma and tinnitus.

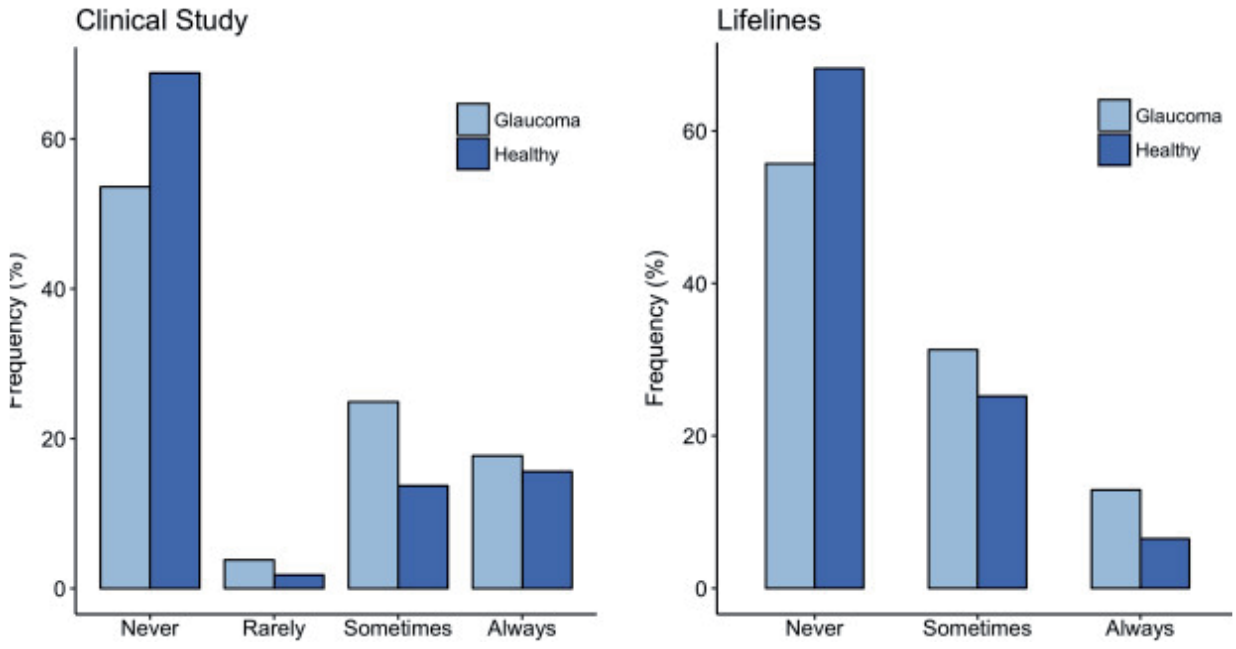

Figure 1: Frequency of tinnitus complaints. A comparison between the frequency of tinnitus complaints in the clinical study (left panel) and Lifelines study (right panel). In Lifelines there was no option to choose "rarely".

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