

Original Article

Prevalence of Persistent Tinnitus and Dizziness in an Elderly Population in Southern Taiwan

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OBJECTIVES: Tinnitus and dizziness are common among the elderly. The conditions may increase depression, and patients may become susceptible to falls, thereby affecting the quality of life of the geriatric population. Investigating the prevalence of persistent tinnitus and chronic/recurrent dizziness in an elderly population and analyzing the association of certain comorbidities with tinnitus and dizziness in southern Taiwan were the main purposes of this study.

MATERIALS and METHODS: This was a cross-sectional study performed in a metropolitan hospital. Hearing tests were conducted in a total of 597 volunteers aged ≥65 years involving 322 (53.9%) men and 275 (46.1%) women recruited in the study. The pure tone average (PTA) and hearing handicap (HH) score were calculated. Patients completed questionnaires regarding the history of hypertension and diabetes and symptoms of tinnitus and dizziness. The association of gender, age, PTA/HH, body mass index (BMI), hypertension, diabetes, and metabolic syndrome (MetS) with tinnitus and dizziness were analyzed.

RESULTS: The prevalence of persistent tinnitus and chronic/recurrent dizziness was 32.0% and 24.1%, respectively. Tinnitus or dizziness were not associated with age, BMI, hypertension, diabetes, and MetS but was associated with hearing impairment. Women and those with fasting glucose levels <100 mg/dL were more likely to experience dizziness.

CONCLUSION: Persistent tinnitus and dizziness were common in an elderly population in southern Taiwan. These findings may help develop strategies to promote the quality of life in the elderly population.

KEYWORDS: Dizziness, elderly, metabolic syndrome, prevalence, tinnitus

INTRODUCTION

Aging of the population is a global phenomenon. The physiologic changes that accompany aging involving the body composition, skin, eyes, ears, cardiovascular or endocrine system, and metabolism may lead to the development of corresponding diseases or morbidities [1]. Ear and hearing disorders, epistaxis, and balance disorders are the leading complaints of the elderly during otorhinolaryngology visits, and tinnitus is the most common audiological disorder following hearing impairments [2].

The perception of sound or noise emanating from the ears or head that ranges from a barely noticeable to a debilitating chronic condition is termed a tinnitus ^[3]. The presence of tinnitus may impact the quality of life mainly through sleep disturbance and psychiatric distress (i.e., anxiety and depression) ^[4,5]. In Australia, the 5-year incidence of tinnitus in older adults was reported as 18.1% ^[6]. The prevalence of tinnitus in the elderly differs among different countries, ranging from 11.1% to 30% ^[7-12]. Several risk factors

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associated with tinnitus have been investigated, including hearing impairment, noise exposure, age, diet, obesity, smoking, and psychiatric distress ^[7-10, 13, 14]. However, the definite determinants remain unclear.

The older populations commonly complain of dizziness or vertiginous disorders. The most common complaints presented by the elderly in the emergency rooms are dyspnea, dizziness, and falls [15]. Dizziness may increase the risk of slipping and falling, leading to mobility limitations, anxiety, and depression [15, 16]. The reported prevalence of dizziness is diverse among studies, with a range of 17%-30% [17, 18] in the general population, and it has been reported to be higher in the elderly population [17-20].

Hypertension, diabetes, and metabolic syndrome (MetS) are common comorbidities in the elderly [21, 22]. These comorbidities are often associated with dizziness and vertigo [23, 24]. However, no report on the relationship between MetS and tinnitus could be retrieved yet from English literature. We conducted the present study to understand the epidemiology of persistent tinnitus and chronic/recurrent dizziness in an elderly population and investigate the relationships of the common comorbidities with tinnitus and dizziness. The aims of this study were (1) to obtain the prevalence of persistent tinnitus and chronic/recurrent dizziness in an elderly population in southern Taiwan, (2) to analyze the correlation between persistent tinnitus and chronic dizziness, (3) to analyze the associations of hypertension, diabetes, and MetS with tinnitus and dizziness, and (4) to identify risk factors related to tinnitus or dizziness.

MATERIALS AND METHODS

Participants

The participants of this study were clients who received national annual health examinations performed by a health management center in a metropolitan hospital from March 17, 2015, to May 19, 2015. The national annual health examinations were free of charge for participants older than 65 years of age. The financial assistance was provided by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan. We recruited volunteers who were 65 years of age or older and who agreed to participate in the study. A brief questionnaire regarding the existence of persistent tinnitus for more than 6 months, chronic/recurrent dizziness (including any disequilibrium, vertigo, and head-lightness) within 6 months, and a personal history of hypertension and diabetes was administered when the participants underwent the health examinations. Participants with dementia and those who could not sit independently to receive the audiometric tests were excluded from this study. Participants who incompletely answered the questionnaire were also excluded during the data analysis stage.

Procedure

Audiometric assessments

Pure tone audiometry was performed in sound-attenuating booths by trained technicians using standard procedures that met the requirements of the Council of Labor Affairs, Executive Yuan, Taiwan. The audiometric data were recorded at frequencies 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. The speech fre-

quency (500, 1000, 2000, and 4000 Hz) pure tone average (PTA) was calculated for each side. The high tone average (the average hearing level of bilateral 4000, 6000, and 8000 Hz) was also calculated to analyze the correlation of age-related hearing loss, which is initially presented as high tone sensorineural hearing loss, with tinnitus and dizziness. The PTA of the worse ear was used to analyze the association of hearing impairment with tinnitus and dizziness. The average of the bilateral PTA and hearing handicap (HH) score (percentage) was also computed to investigate the associations with tinnitus and dizziness. The HH formula is presented below:

Monaural impairment (MI) = 1.5 (PTA-25)

$$HH = [5 (MI_b) + (MI_w)]/6$$

 ${
m MI}_{
m b}$ denotes the MI of the better ear and ${
m MI}_{
m w}$ denotes the MI of the worse ear. The MI defines the percentage of function loss of monaural hearing; therefore, MI >100 is considered equivalent to MI=100, i.e., as a non-serviceable ear. This formula has been officially adopted by the Taiwan government for the evaluation of HHs.

Basic information and biochemistry data

The basic information and biochemistry data of the participant, which included age, gender, height, weight, systolic and diastolic blood pressures, waist circumference, fasting serum glucose level, serum triglyceride (TG) level, total cholesterol level, and highdensity lipoprotein cholesterol (HDL-C) level, were collected during the annual health examinations. The body mass index (BMI) was calculated. The existence of MetS was analyzed with gender adjustment.

Definition of metabolic syndrome

According to the modified definition stated by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan, MetS is diagnosed when the patient met at least three of the following five criteria: (1) blood pressure of at least 130/85 mmHg or receiving treatment for hypertension; (2) TG of at least 150 mg/dL; (3) HDL <40 mg/dL in men and <50 mg/dL in women; (4) fasting glucose \geq 100 mg/dL or receiving treatment for diabetes; and (5) waist circumference \geq 90 cm in men and \geq 80 cm in women.

Statistical Analysis

All data were entered into a computer and analyzed using the Statistical Package for Social Sciences (SPSS) statistics software package version 20.0 (IBM Corp., Armonk, NY, USA). The correlation between tinnitus and dizziness was investigated. The associations of gender, age, BMI, hearing level, hypertension, diabetes, and MetS and its parameters with tinnitus and dizziness were analyzed. Logistic regressions were also used to adjust the effects of gender and age on the potential factors associated with tinnitus and dizziness. The level of statistical significance was set at a p<0.05.

Ethical considerations

All participants provided written informed consent. Patients' personal information was de-identified. This study was approved by the institutional review board of our institute (IRB approval No.: KMUHIRB-G(I)-20150011).

RESULTS

A total of 602 participants who underwent the hearing tests and completed the guestionnaire were recruited. Five participants were excluded due to incompletely answered questionnaires. The remaining 597 participants comprising 322 men and 275 women, with an average age of 72.08±5.77 years (mean±standard deviation; range = 65-90), were included in this study. In total, 191 (32.0%) participants complained of persistent tinnitus, while 144 (24.1%) participants experienced chronic or recurrent dizziness. There was no relationship between the presence of tinnitus and dizziness (chi-square=1.479, p=0.224). The mean hearing level of the worse ear was 47.73±18.37 dBHL (range = 16.25-115.00). The mean level of bilateral PTA average was 41.75±16.77 dBHL (range=13.13-110.63), and the mean level of high tone average was 61.85±19.82 dBHL (range=16.67-115.00), and the mean HH score was 22.98±22.03% (range=0-100). The average BMI was 25.33±3.49 kg/m² (range=15.28-39.81). The average systolic and diastolic blood pressures were 139.51±15.52 mmHg (range=99-227) and 79.15±9.99 mmHg (range=56-129), respectively. The mean fasting serum glucose level was 108.28±29.32 mg/dL (range=74-360). Overall, 305 participants (51.1%) had a history of hypertension, while 123 participants (20.6%) had diabetes. The mean HDL-C levels were 45.80±12.48 mg/dL (range=25-91) in men, 58.21±14.35 mg/dL (range=32-100) in women, and 52.59±14.33 mg/dL (range=25-100) in total. The mean waist circumferences were 88.23±8.34 cm (range=63-114) in men, 83.09±9.39 cm (range=58-114) in women, and 85.86±9.20 cm (range=58-114) in total. Based on the definition described above, 299 participants (50.1%) had MetS.

Correlation between Tinnitus and Dizziness

In total, 52 out of the 597 participants (8.7%) had both tinnitus and dizziness. There was no significant correlation between persistent

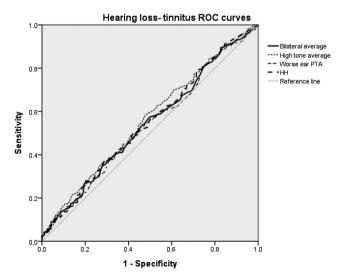


Figure 1. The ROC curves of hearing impairment and tinnitus. The optimal predictive value, sensitivity, specificity, and area under the curve (AUC) for each curve are listed below:

Bilateral pure tone average: optimal value=37.81 dB; sensitivity=57.6%; specificity=50.2%; AUC=0.541

High tone average: optimal value=61.25 dB; sensitivity=57.6%; specificity=52.5%; AUC=0.559

Worse ear PTA: optimal value=45.63 dB; sensitivity=45.0%; specificity=61.8%;

Hearing handicap score: optimal value=29.84%; sensitivity=36.6%; specificity=71.4%; AUC=0.546

tinnitus and chronic/recurrent dizziness in the present study (chi-square test, correlation coefficient=1.479, p=0.224). After the adjustment for age and gender, there was still no significant correlation (logistic regressions, odds ratio [OR]=1.274, 95% confidence interval [CI]=0.852-1.904, p=0.238).

Tinnitus and Comorbidities

The distribution of concurrent morbidities with tinnitus is presented in Table 1. There was no significant association of gender, age, BMI, hypertension, diabetes, or MetS and its parameters with persistent tinnitus. Hearing levels were associated with the existence of tinnitus. The participants with tinnitus had a higher PTA average (t-test, p=0.035), high tone average (t-test, p=0.013), worse ear PTA (t-test, p=0.047), and HH score (t-test, p=0.045). After adjusting for age and gender with logistic regressions, the PTA average (OR=1.012, 95% CI=1.001-1.023, p=0.036), high tone average (OR=1.014, 95% CI=1.004-1.024, p=0.008), and the HH score (OR=1.009, 95% Cl=1.000-1.017, p=0.047) were still related to tinnitus, while the worse ear PTA lost its significance relating to tinnitus (p=0.052). Based on the findings above, we plotted the receiver operating characteristics (ROC) curve and attempted to calculate the predictive levels of PTA average, high tone average, and HH score for persistent tinnitus. Figure 1 showed the ROC curve.

Dizziness and Comorbidities

There was no significant association of age, BMI, history of hypertension and/or diabetes, or MetS with dizziness. Women were more likely to experience dizziness than men (chi-square, p<0.001). Among the parameters of MetS, fasting serum glucose level was associated with dizziness (chi-square, p=0.024). The participants with fasting serum glucose levels ≥100 mg/dL were less likely to complain of dizziness. Among the participants with fasting serum glucose levels <100 mg/dL, 28.2% of them complained of dizziness, while 20.3% of the participants with the glucose levels ≥100 mg/dL had dizziness. However, there was no significant association of other MetS parameters with dizziness (Table 2). Logistic regressions were used to adjust the confounding effects of gender and age for the associations of MetS parameters with dizziness. Low fasting serum glucose levels were still significantly associated with dizziness after the adjustment for gender and age (OR=1.483, 95% CI=1.009-2.179, p=0.045). The other MetS parameters did not show significant associations with dizziness after the adjustments.

DISCUSSION

The prevalence of tinnitus in the elderly may vary among different countries and regions. In the present study, we found that the prevalence of persistent tinnitus was 32.0% in the elderly population, which was similar to that of Korea ^[8]. In Korean studies, the prevalence of tinnitus was shown to be more that 30% in the elderly aged >70 years ^[7,8]. The prevalence rates of tinnitus in the elderly have been reported as 18.6% in Japan ^[10] and 13.5% in New Zealand ^[12]. Interestingly, in a Taiwanese study, the prevalence of persistent tinnitus in the elderly was reported as 13.9% in Taipei City ^[25]. The differences of the prevalence in the studies may be associated with the sample populations (community-based versus population-based), economic activities (industrial versus commercial), or ethnicities (European versus Asian). The prevalence of tinnitus in the elderly in Japan was reported to be 18.6% in a community-based study ^[10], while

Table 1. Associations of potential factors with persistent tinnitus

	Tinnitus	OR (95%CI)	р	OR (95%CI) (adjustedb)	p (adjusted)
Sex					
Male	101 (31.4%)	1.000	0.722		
Female	90 (32.7%)	1.064 (0.754-1.503)			
Total	191 (32.0%)				
Age (years; mean (SD))	72.34 (6.00)		0.466		
BMI (mean(SD))	25.12 (3.71)		0.304		
Hearing level (mean(SD))					
Bilateral average [dB]	43.88 (18.64)	1.011 (1.001-1.021)	0.035*	1.012 (1.001-1.023)	0.036*
High tone average [dB]	64.78 (20.18)	1.011 (1.002-1.020)	0.013*	1.014 (1.004-1.024)	0.008*
Worse ear PTA [dB]	47.26 (20.37)	1.009 (1.000-1.019)	0.047*	1.010 (1.000-1.020)	0.052
Hearing Handicap [%]	25.61 (23.92)	1.008 (1.000-1.016)	0.045*	1.009 (1.000-1.017)	0.047*
Hypertension					
Yes	101 (33.1%)	1.111 (0.788-1.568)	0.548	1.092 (0.771-1.546)	0.619
No	90 (30.8%)	1.000		1.000	
Diabetes					
Yes	39 (21.7%)	0.984 (0.642-1.506)	0.939	0.977 (0.638-1.498)	0.916
No	152 (32.1%)	1.000		1.000	
Metabolic syndromea					
Yes	88 (29.4%)	0.786 (0.556-1.109)	0.170	0.774 (0.548-1.095)	0.148
No	103 (34.7%)	1.000		1.000	
Metabolic syndrome parameters					
Elevated Blood pressure					
Yes	165 (32.4%)	1.144 (0.698-1.875)	0.594	1.131 (0.689-1.857)	0.626
No	26 (29.5%)	1.000		1.000	
Elevated fasting sugar					
Yes	93 (30.4%)	0.860 (0.609-1.213)	0.390	0.857 (0.607-1.211)	0.383
No	98 (33.7%)	1.000		1.000	
Elevated triglyceride level					
Yes	45 (30.8%)	0.931 (0.622-1.393)	0.727	0.938 (0.626-1.405)	0.755
No	146 (32.4%)	1.000		1.000	
Low HDL level					
Yes	61 (31.4%)	0.963 (0.667-1.392)	0.842	0.958 (0.663-1.386)	0.822
No	130 (32.3%)	1.000		1.000	
Large waist circumference					
Yes	102 (32.3%)	1.029 (0.728-1.454)	0.871	1.006 (0.707-1.431)	0.974
No	88 (31.7%)	1.000		1.000	

a: modified definition of metabolic syndrome by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan; some cases lost data of the waist circumference b: adjusted for age and sex *: p<0.05

Table 2. Associations of potential factors with chronic/recurrent dizziness

	Dizziness	OR (95%CI)	р	OR (95%CI) (adjustedb)	p (adjusted
Sex					
Male	54 (16.8%)	1.000	<0.001**		
Female	90 (32.7%)	2.414 (1.641-3.551)			
Total	144 (24.1%)				
Age (years; mean(SD))	71.86 (5.58)		0.595		
BMI (mean(SD))	25.10 (3.73)		0.355		
Hearing level (mean(SD))					
Bilateral average [dB]	41.18 (18.78)	0.997 (0.986-1.009)	0.639	1.004 (0.992-1.017)	0.509
High tone average [dB]	60.61 (8.82)	0.996 (0.986-1.005)	0.387	1.005 (0.994-1.016)	0.400
Worse ear PTA [dB]	44.60 (17.71)	0.998 (0.988-1.008)	0.723	1.004 (0.993-1.015)	0.478
Hearing Handicap [%]	22.35 (20.56)	0.998 (0.990-1.007)	0.694	1.003 (0.994-1.013)	0.480
Hypertension					
Yes	74 (24.3%)	1.016 (0.698-1.478)	0.934	0.949 (0.645-1.397)	0.791
No	70 (24.0%)	1.000		1.000	
Diabetes					
Yes	27 (22.0%)	0.858 (0.534-1.380)	0.528	0.887 (0.546-1.439)	0.627
No	117 (24.7%)	1.000		1.000	
Metabolic syndromea					
Yes	65 (21.7%)	0.767 (0.526-1.117)	0.166	0.721 (0.491-1.061)	0.097
No	79 (26.6%)	1.000		1.000	
Metabolic syndrome parameters					
Elevated Blood pressure					
Yes	119 (23.4%)	0.769 (0.463-1.276)	0.308	0.694 (0.412-1.167)	0.168
No	25 (28.4%)	1.000		1.000	
Elevated fasting sugar					
Yes	62 (20.3%)	0.648 (0.444-0.945)	0.024*	0.674 (0.459-0.991)	0.045*
No	82 (28.2%)	1.000		1.000	
Elevated triglyceride level					
Yes	42 (28.8%)	1.382 (0.907-2.105)	0.131	1.330 (0.865-2.043)	0.194
No	102 (22.6%)	1.000		1.000	
Low HDL level					
Yes	50 (25.8%)	1.141 (0.768-1.696)	0.513	1.097 (0.733-1.642)	0.652
No	94 (23.3%)	1.000		1.000	
Large waist circumference					
Yes	78 (24.7%)	1.053 (0.722-1.534)	0.789	0.898 (0.607-1.328)	0.591

a: modified definition of metabolic syndrome by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan; some cases lost data of the waist circumference b: adjusted for age and sex

HDL: High-Density Lipoprotein

^{*:} p<0.05

^{**:} p<0.001

the prevalence was lower at 6.7% in a populationbased study ^[11]. The primary economic activities of Kaohsiung (southern Taiwan) are industry-based, while those of Taipei (northern Taiwan) are commercial. Noise-related hazards are common in the industry, and tinnitus is known to be associated with noise exposures ^[7, 13, 14]. Ethnicity is another factor associated with tinnitus. In a report from New Zealand, the authors found that Europeans had a higher prevalence of tinnitus (7.7%), while Asians had a lower prevalence (1.2%) in an adult population ^[12].

Hearing impairment was the major factor associated with persistent tinnitus in the present study. This finding is not surprising because tinnitus itself is phantom auditory perception, and the hearing status may directly affect the generation of tinnitus. Hearing loss has also been reported as a risk factor related to persistent tinnitus in previous studies [7, 10, 13, 14, 26]. Although hearing loss is the major factor associated with persistent tinnitus, the small area under the curve (0.536-0.559) and the low sensitivity (36.6%-57.6%) and specificity (50.2%-71.4%) in the ROC curves in Figure 1 indicate that hearing loss may not be a good predictor for tinnitus. Other factors (e.g., depression, insomnia) may interact with hearing loss to cause tinnitus. Aging has been reported as a risk factor of persistent/chronic tinnitus [7-9, 11], and the prevalence increases more rapidly after the age of 50 years [7]. Although the prevalence of persistent tinnitus increases after 50 years of age, it seems stabilized after 65 years of age [7,10]. In the present study, the participants were ≥65 years of age, but age was not associated with persistent tinnitus. This condition corresponded to the stabilized prevalence of tinnitus after 65 years of age, which was similar to Japan [10]. Many risk factors associated with persistent tinnitus have been reported, such as being overweight, marital status, hypertension, diabetes, high cholesterol, diet, and stress, but they are still controversial [7-9, 11, 13]. To date, no report on the association of MetS with tinnitus could be found. In the present study, gender, BMI, hypertension, diabetes, HDL, fasting serum glucose, waist circumference, MetS, and dizziness were not found to be associated with persistent tinnitus.

There is an abundance of literature concerning the disorders relating to dizziness. The prevalence of chronic/recurrent dizziness in the elderly was found to be 24.1% in the present study, corresponding to previous studies [16, 17, 19]. The prevalence of chronic dizziness in adults aged more than 50 years was reported to range from 6.5% to 23.4% in the European countries [16]. The prevalence of dizziness reportedly increases with age [17, 20, 27]. However, in the present study, age was not associated with chronic dizziness. The prevalence of dizziness may stabilize after 65 years of age. In previous studies, although the prevalence of dizziness increased with age, it may reach a peak between 65 and 75 years before decreasing [16, 20, 27, 28]. Females were more vulnerable to chronic dizziness. Nearly one-third of elderly women had chronic/recurrent dizziness. Similar to other studies, women were twice as likely to experience dizziness compared to men [17, 19, 20]. The possible reasons for this phenomenon include the hormone variations during menopause [20, 29] and a higher prevalence of migraines in females [17, 18].

There was no significant correlation between persistent tinnitus and chronic/recurrent dizziness in the elderly. The prevalence of coexisting tinnitus and dizziness was 8.7% in the present study. It accounted for

27.2% of the participants with tinnitus and 36.1% with dizziness. Coexistence of tinnitus and dizziness were found in syndromes, such as Meniere's disease and migraines. However, these conditions were relatively rare in general population. The estimated prevalence of migrainous vertigo and Meniere's disease was reported to be 0.98% and 0.2%, respectively [17, 18]. Although the prevalence of these disorders may increase with age, they are still the minor syndromes associated with tinnitus and dizziness in the elderly population. Therefore, persistent tinnitus and chronic vertigo were independent symptoms in the elderly.

Hypertension, diabetes, and MetS are common comorbidities in the elderly. In the current study, the prevalence of hypertension, diabetes, and MetS was 51.1%, 20.6%, and 50.1%, respectively. These comorbidities were not associated with tinnitus or dizziness. However, one parameter of MetS, the fasting serum glucose, was related to the risk of dizziness. In the elderly population, persons with fasting serum glucose levels <100 mg/dL had a nearly 50% higher risk of dizziness than those with higher serum glucose levels. Since hypoglycemia is commonly related to dizziness/vertigo in the elderly with or without diabetes, the higher risk can be justified [30]. The associations of obesity with dizziness have been reported in several studies [23, 28]. Neuhauser et al. [28] reported that persons with BMI ≥25 kg/m² had a higher risk of vestibular vertigo (OR=1.8) than those with BMI <25 kg/ m² in a general population. However, in the study by Corna et al. [23], dizziness did not seem to be related to the severity of obesity. Similarly, BMI and waist circumference were not associated with dizziness in the present study, indicating that obesity may not be a risk factor for dizziness in the elderly population.

The limitations of the present study included the lack of detailed characteristics of tinnitus and dizziness in the questionnaires. The phenotype, severity, duration, pitch of persistent tinnitus, and the of chronic/recurrent dizziness could not be retrieved, preventing further analyses on specific tinnitus and dizziness disorders in the elderly population. Because the administration of questionnaires and hearing tests were incorporated in the annual health examinations, there was less time for collecting information. The questionnaires had to be short and hence some details may have been lost. Another limitation is that the present study was a community based study, and the population may have different conditions compared to the general population. Conducting a multi-institutional study, specifically in geriatrics, may help provide more comprehensive knowledge on tinnitus and dizziness in the elderly population.

CONCLUSION

Persistent tinnitus and chronic/recurrent dizziness are common disorders in the elderly population in southern Taiwan, with a prevalence rate of 32.0% and 24.1%, respectively. Hearing impairment is an important risk factor of tinnitus, but it is not a good predictor for tinnitus. Women and persons with fasting serum glucose levels <100 mg/dL are more likely to have dizziness. Further studies on the different patterns of tinnitus and types of dizziness with their relevant risk factors should be conducted. The quality of life in the elderly population can be improved through strategies developed based on the results of the present study.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of Kaohsiung Medical University Hospital with IRB approval No. (KMUHIRB-G(I)-20150011).

Informed Consent: Informed consents have been signed by all participants.

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