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# Sex and Age Associations With Vestibular Schwannoma Size and Presenting Symptoms

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**Objective:** To assess the association of sex and age with presenting symptoms and size of vestibular schwannoma at clinical presentation to our clinics.
**Study Design:** Retrospective chart review.
**Setting:** Academic medical center.
**Patients:** Approximately 1,269 subjects diagnosed with unilateral vestibular schwannoma between 1997 and 2010.
**Intervention:** Demographic information, tumor characteristics, and treatment strategy were recorded.
**Main Outcome Measure:** Tumor size, patient-reported presence of hearing loss or dizziness at presentation.
**Results:** Male subjects had significantly larger tumors than female subjects at presentation (18.23 versus 16.81 mm, $p = 0.031$); this difference was particularly pronounced in patients younger than 40 years. Patient-reported symptoms at baseline also differed by sex: the prevalence of hearing loss was 95.1% in male subjects versus 90.3% in female subjects ($p = 0.001$), and the frequency of dizziness was 74.3% in female subjects versus 59.0% in male subjects ($p < 0.0001$). In multivariate analyses, male subjects continued to have a borderline significant positive association with tumor size ($p = 0.066$) and were 2-fold more likely to have hearing loss (odds ratio [OR], 2.082; 95% confidence interval [CI], 1.300–3.336) but half as likely to have dizziness (OR, 0.501; 95% CI, 0.387–0.649) than female subjects. Additionally, for every 1-mm increase in tumor size, patients were more likely to report hearing loss by 14.7% (OR, 1.147; 95% CI, 1.106–1.191) and dizziness by 2.8% (OR, 1.028; 95% CI, 1.016–1.041).
**Conclusion:** We observed significant sex differences in the presentation and size of unilateral vestibular schwannomas. As management and treatment strategies are predicated on presenting symptoms and patient factors, these observations merit further study to further understand tumor biology, improve risk stratification, and optimize tumor management. **Key Words:** Age—Dizziness—Sex—Hearing loss—Presenting symptoms—Vestibular Schwannoma—Treatment—Tumor size.

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Vestibular schwannomas (VS) are benign nerve sheath tumors arising from the VIIIth cranial nerve with an estimated incidence of about 1.0 per 100,000 per year in the United States (1,2). Tumor size at presentation varies among individuals, as do the presenting signs and symptoms, which include hearing loss, tinnitus, vertigo, facial paresthesia, or paresis (3,4). The pursuit of imaging studies for vestibular schwannoma are typically prompted by unilateral sensorineural hearing loss, although the incidental discovery of tumor has become more frequent with the increasingly widespread use of magnetic resonance imaging (2,5–7). A key concern addressed by the present study relates to the need for patients to present for a medical evaluation of symptoms potentially relating to vestibular schwannoma.

The association of patient characteristics with tumor size and symptoms at presentation has not been fully established (8–13). Tumors have been reported to present differently by sex, particularly with respect to tumor size. Evidence suggests that estrogen may accelerate vestibular schwannoma growth (14–16), such that larger tumors may occur more often in women particularly during pregnancy (17,18). Age has also been shown to be an independent predictor of tumor size at presentation or over time, with smaller tumors reportedly occurring in older compared with younger individuals (1,19). The predictive value of both age and sex on tumor size and symptoms at presentation has not been simultaneously evaluated in a rigorous fashion. Tumor treatment has become increasingly guided by the risk of future tumor growth as indicated by serial imaging or symptom progression (20). Tumor size

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at presentation and symptoms may be indicative of future growth (21) and have increasing relevance as patients, and their physicians jointly weigh the risks and benefits of surgical resection, stereotactic radiosurgery, and serial imaging.

The aim of this study was to assess the relationship of sex and age with unilateral vestibular schwannoma size and symptoms at presentation at our institution over the last 14 years. This knowledge may lead to a better understanding of patterns of tumor growth and improve risk stratification of patients with vestibular schwannoma.

## MATERIALS AND METHODS

A retrospective chart review was conducted for all patients who presented with the diagnosis of unilateral vestibular schwannoma between January 1, 1997, and December 31, 2010. These patients were seen in the departments of Otolaryngology–Head and Neck Surgery and Neurosurgery. This study was approved by the hospital institutional review board.

### Study Population

A query was conducted of all hospital admissions and outpatient visits associated with the diagnosis code of a benign neoplasm of the cranial nerve between January 1, 2007, and December 31, 2010. The patients must have had at least 1 clinical visit with members of the departments of Neurosurgery or Otolaryngology–Head and Neck Surgery.

Patients were excluded if they had the following: 1) bilateral vestibular schwannomas or a diagnosis suggestive of neurofibromatosis Type 2 based on family history, 2) schwannomas arising from sites other than the VIIIth cranial nerve, or 3) lesions believed to be other than a schwannoma (e.g., meningioma, epidermoid) based on imaging characteristics or final surgical pathology. Approximately 1,269 patients met the final criteria.

### Variables and Outcomes

Medical records were reviewed to extract demographic information, tumor characteristics, presenting symptoms, and treatment at initial presentation. The main predictors of interest were sex and age. The main outcomes of interest were tumor size and the initial, patient-reported symptoms at presentation categorized as follows: 1) hearing loss, 2) tinnitus 3) facial weakness, 4) dizziness/vertigo/imbalance (collectively termed *dizziness*), or 5) tumor side. The secondary outcome of interest was the elected treatment categorized as follows: 1) surgery, 2) observation with serial magnetic resonance imaging, or 3) stereotactic radiosurgery.

### Statistical Analysis

Data were initially analyzed using bivariate analyses to compare the outcome variables between male and female patients. The association of binary variables (tumor side, hearing loss, tinnitus, facial weakness, and dizziness) with sex was tested with a $\chi^2$ statistic. The association of mean age and mean tumor size with sex was tested with the independent sample $t$ test.

The cohort was then stratified by age. Descriptive statistics were used to analyze the 2 samples (male and female subjects) by age group for any statistically significant variable outcomes found in the initial analysis. These results were compared using $\chi^2$ or $t$ tests.

Multivariate linear regression was used for analyses involving continuous dependent variables, and multivariate logistic regression was used for models involving categorical outcome variables. All statistical analyses were conducted with SAS version 9.2 (Cary, NC, USA).

## RESULTS

### Patient Characteristics

Approximately 1,269 patients presented to the departments of Otolaryngology–Head and Neck Surgery and/or Neurosurgery for the diagnosis of a unilateral presumptive vestibular schwannoma and fulfilled inclusion criteria for the study. Seventy-nine patients (6.2%) had missing information on tumor size, 26 patients (2.0%) on hearing loss, 232 patients (18.2%) on tinnitus, 264 patients (20.8%) on facial weakness, 123 patients (9.7%) on dizziness, and 50 patients (3.9%) on tumor management.

Patient characteristics by sex are presented in Table 1. Male patients had significantly larger tumors than female patients, with the mean tumor size of 18.23 mm in male subjects versus 16.81 mm in female subjects ($p = 0.031$). Hearing loss was a prevalent presenting symptom but more so among male subjects than female subjects. Hearing loss on the tumor side was a presenting complaint in 95.1% of male patients and 90.3% of female patients ($p = 0.001$). By comparison, dizziness was a more prevalent complaint among female subjects (74.3% versus 59.0%, $p < 0.0001$). Most patients underwent surgery for the management of their vestibular schwannoma (62.8% of male subjects and 62.7% of female subjects), and there were no statistically significant differences in management strategy, mean age, tumor side, or other presenting symptoms between male and female subjects.

**TABLE 1.** *Descriptive statistics of groups*

| | Sex | | |
|---|---|---|---|
| | Male (n/%) n = 608 | Female (n/%) n = 661 | Test statistic ($p$ value) |
| Age in years (mean ± SD) | 52.84 ± 13.00 | 53.67 ± 13.53 | 0.262 |
| Size in mm (mean ± SD) | 18.23 ± 11.99 | 16.81 ± 10.57 | **0.031** |
| Tumor side | | | |
| Right | 286 (47.0) | 318 (48.1) | |
| Left | 322 (53.0) | 343 (51.9) | 0.703 |
| Hearing loss | | | |
| Yes | 566 (95.1) | 585 (90.3) | |
| No | 29 (4.9) | 63 (9.7) | **0.001** |
| Tinnitus | | | |
| Yes | 431 (86.0) | 442 (82.5) | |
| No | 70 (14.0) | 94 (17.5) | 0.116 |
| Facial weakness | | | |
| Yes | 17 (3.5) | 32 (6.1) | |
| No | 463 (96.5) | 493 (93.9) | 0.061 |
| Dizziness | | | |
| Yes | 318 (59.0) | 451 (74.3) | |
| No | 221 (41.0) | 156 (25.7) | <**0.0001** |
| Treatment | | | |
| Surgery | 368 (62.8) | 398 (62.7) | |
| Serial imaging | 192 (32.8) | 199 (31.3) | |
| Stereotactic radiosurgery | 26 (4.4) | 38 (6.0) | 0.452 |

$p$ values in bold indicate significant differences.



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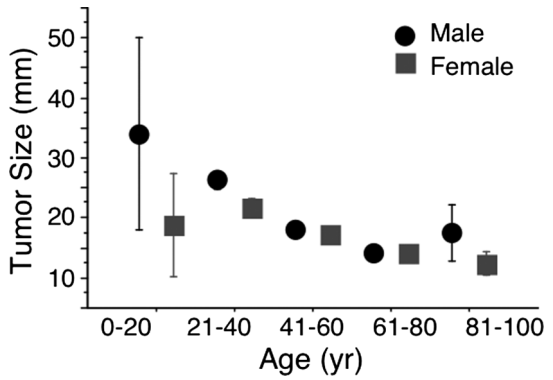


**FIG. 1.** Tumor size at presentation diminishes with age. Sex differences are more consistently seen in patients younger than 40 years. Both sexes present with similar tumor size at older ages.

### Age Stratification of Tumor Size, Hearing Loss, and Dizziness by Sex

We further considered sex-differences for tumor size and the prevalence of hearing loss and dizziness at presentation using analyses stratified by younger and older age categories. When the patient population was stratified by age into 20-year intervals, the mean tumor size at presentation declined with increasing age (Fig. 1). Additionally, there was a significant difference in mean tumor size between male and female subjects for age groups up to 40 years. We therefore chose age 40 as the cutoff between younger and older cohorts to further investigate the impact of sex and age on tumor size and the prevalence of symptoms reported at presentation.

#### *Mean Tumor Size*

There was a significant difference in mean tumor size between male and female subjects age 40 years or younger as depicted in Table 2. The mean tumor size in male subjects was 4.35 mm larger than that in female subjects (25.29 versus 20.94 mm, $p = 0.022$). There were no statistically significant differences in tumor size between sexes for the older age group.

#### *Hearing Loss*

There was a significant sex difference in the proportion of patients older than 40 years who reported hearing loss as shown in Table 3. The proportion of male subjects with hearing loss was 95.4% versus 90.5% for female subjects ($p = 0.004$). There was no sex difference for the older age group.

**TABLE 2.** *Mean tumor size (mm) by gender and age group*

| Age (yr) | Male size ± standard deviation (n) | Female size ± standard deviation (n) | *p* value |
|---|---|---|---|
| ≤40 | 25.29 ± 13.72 (100) | 20.94 ± 13.01 (100) | **0.022** |
| >40 | 16.75 ± 11.06 (477) | 16.01 ± 9.85 (513) | 0.266 |

*p* values in bold indicate significant differences.

**TABLE 3.** *Percentage of hearing loss and dizziness by sex and age group*

| | Hearing loss | | | Dizziness | | |
|---|---|---|---|---|---|---|
| Age (yr) | Male (n/%) | Female (n/%) | *p* value | Male (n/%) | Female (n/%) | *p* value |
| ≤40 | 94 (94.0) | 98 (89.1) | 0.227 | 59 (66.3) | 75 (70.8) | 0.303 |
| >40 | 472 (95.4) | 487 (90.5) | **0.004**[a] | 259 (57.6) | 376 (75.0) | <**0.0001**[b] |

[a]Greater proportion of hearing loss in male subjects older than 40 years.
[b]Greater proportion of dizziness in female subjects older than 40 years.
*p* values in bold indicate significant differences.

#### *Dizziness*

There was a significant sex difference in the proportion of patients reporting dizziness among patients older than 40 years. As shown in Table 3, 75.0% of women reported dizziness at presentation versus 57.6% of men ($p < 0.0001$).

### Multivariate Analysis of Factors Influencing Tumor Size

Initial bivariate analyses demonstrated that tumor size was significantly associated with sex, but with further stratification by age, this relationship was only significant for the younger age group (≤40 yr). We then performed a multivariate analysis to determine if these observations still remained significant in a multiple linear regression model (Table 4). This analysis identified age as a significant predictor of tumor size at presentation. For each additional year of the age at presentation, mean tumor size declined by 0.244 mm (95% CI, 0.197 to 0.291 mm; $B = -0.244$, $p < 0.0001$). Male sex maintained a borderline significant effect on predicting larger tumor sizes ($B = -1.155$, $p = 0.066$).

### Multivariate Analysis of Factors Influencing Hearing Loss and Dizziness

Initial bivariate analyses revealed that hearing loss and dizziness were statistically significantly associated with sex. With further stratification, we observed that this association was present for patients in the older age group (>40 yr) for hearing loss and for dizziness.

We performed a multivariate analysis to determine if these observations still remained significant after controlling for age, sex, and tumor size in a multiple logistic regression model (Table 5). Sex remained a significant predictor of hearing loss, with male subjects 2-fold more likely to have hearing loss than female subjects (OR, 2.082;

**TABLE 4.** *Linear regression model for tumor size at presentation*

| Variable | | B (standard error) | *p* value |
|---|---|---|---|
| Age | | −0.244 (0.024)[a] | <**0.0001** |
| Sex | Male[b] | | |
| | Female | −1.155 (0.628)[c] | 0.066 |

[a]For every yearly increase in age, tumor size is decreased by 0.244 mm.
[b]Referent group.
[c]Male sex predicts larger tumor size.
*p* values in bold indicate significant correlation.



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**TABLE 5.** *Logistic regression model for primary outcome variables hearing loss and dizziness at presentation*

| | | Hearing loss | Dizziness |
|---|---|---|---|
| Variable | | Adjusted odds ratio (95% confidence interval) | Adjusted odds ratio (95% confidence interval) |
| Age | | 1.027 (**1.009–1.046**)[a] | 1.009 (**0.998–1.019**) |
| Sex | Male[b] | | |
| | Female | 2.082 (**1.300–3.336**)[c] | 0.501 (**0.387–0.649**)[e] |
| Tumor size | | 1.147 (**1.106–1.191**)[d] | 1.028 (**1.016–1.041**)[f] |

[a]For every yearly increase in age, hearing loss is more likely by 2.7%.
[b]Referent group.
[c]Male subjects are 2-fold more likely to have hearing loss than female subjects.
[d]For every 1-mm increase in tumor size, hearing loss is more likely by 14.7%.
[e]Male subjects are 50% less likely to have dizziness than female subjects.
[f]For every 1-mm increase in tumor size, dizziness is more likely by 2.8%.
Confidence intervals in bold indicate significant relationships.

95% CI, 1.300–3.336) when controlling for age and tumor size. We found that age still remained a significant predictor of hearing loss at presentation. For each additional year of age at presentation, patients were 2.7% more likely to report hearing loss (OR, 1.027; 95% CI, 1.009–1.046). Similarly, tumor size also remained a significant predictor of hearing loss. For every 1-mm increase in tumor size, patients were 14.7% more likely to report hearing loss (OR, 1.147; 95% CI, 1.106–1.191) independent of sex. Odds ratios were not significantly different in analyses stratified by sex.

Only sex and tumor size remained significant predictors of dizziness. Male subjects were 50% less likely to report dizziness than female subjects (OR, 0.501; 95% CI, 0.387–0.649). Also, for every 1-mm increase in tumor size, patients were 2.8% more likely to report dizziness (OR, 1.028; 95% CI, 1.016–1.041) independent of sex; the odds ratios was not significantly different in analyses stratified by sex. Age no longer remained a significant predictor of dizziness (OR, 1.009; 95% CI, 0.998–1.019).

### Multivariate Analysis of Factors Influencing Treatment at Initial Presentation

Initial bivariate analyses revealed that the majority of subjects chose to undergo surgery after initial presentation of vestibular schwannoma, without differences between male and female subjects. We performed a multivariate analysis to determine which factors may influence the decision to choose surgery while controlling for age, sex, and tumor size (Table 6).

We found that younger age was a significant predictor of surgery. With every additional year of age, surgery was 5.1% less likely (OR, 0.949; 95% CI, 0.938–0.960). Similarly, larger tumor size was a predictor of surgery, with every 1-mm increase in tumor size associated with a 10.5% greater likelihood of surgery (OR, 1.105; 95% CI, 1.086–1.124). As suggested by the initial bivariate analysis, sex remained an insignificant predictor of treatment choice (OR, 0.936; 95% CI, 0.717–1.222).

## DISCUSSION

In this case series of more than 1,200 patients, we found significant sex and age differences in the presentation of unilateral vestibular schwannomas. Male subjects had significantly larger tumors than female subjects, particularly in the younger age group. When adjusting for tumor size, male subjects were twice as likely to have hearing loss at presentation but only half as likely to present with dizziness. With respect to age, we found that increasing age was negatively correlated with tumor size and positively correlated with hearing loss but did not predict the presence of dizziness.

Our results differ from what had previously been reported in the literature with regards to sex differences in tumor size but were similar with regard to age. Previous work had found that older individuals were more likely to present with smaller tumors (1,19), consistent with our results. Regarding sex differences, larger and more vascularized tumors have in the past been found in women (18) or in pregnant women (17). One population-based case-control study found that women who had previously given birth were 1.7 times more likely to develop a vestibular schwannoma than those who had never given birth (22). Some studies have suggested a possible role of estrogen in tumor growth rates with the demonstration of estrogen receptors in vestibular schwannoma (14,15,23) or significant tumor growth after the application of estradiol in vivo (16). However, other studies have found no expression of estrogen receptors in vestibular schwannomas (24–27), and another case series found that sex did not affect tumor size (28). Therefore, the etiology underlying these sex differences has not been fully established.

This is one of the first studies to show a predisposition for younger male subjects to present with larger tumors compared with female subjects and older adults. As this is a retrospective review, we can only hypothesize as to the causes underlying the influence of sex and age on tumor size and presenting symptoms. It is likely that this influence is multifactorial including behavioral confounds and physiological factors. Possible explanations for the predisposition of younger male subjects to present with larger tumors include the following: 1) larger cranium (29)

**TABLE 6.** *Logistic regression model for surgery after presentation*

| | | Surgery |
|---|---|---|
| Variable | | Adjusted[b] odds ratio (95% confidence interval) |
| Age | | 0.949 (**0.938–0.960**)[a] |
| Sex | Male[b] | |
| | Female | 0.936 (0.717–1.222) |
| Tumor size | | 1.105 (**1.086–1.124**)[c] |

[a]For every yearly increase in age, having surgery as treatment less likely by 5.1%.
[b]Referent group.
[c]For every 1-mm increase in tumor size, surgery as treatment is more likely by 10.5%.
Confidence intervals in bold indicate significant relationships.



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that can accommodate more tumor growth before symptoms prompt evaluation, 2) tumor growth that is of earlier onset, or 3) faster tumor growth in male subjects compared with female subjects. Several tumor growth studies have not demonstrated a sex difference in tumor growth rate (21,28,30,31). A greater lag time between symptom onset and diagnosis in men has been reported in 1 study (28) and may account for larger tumors in some cases. This finding has, however, been contradicted by Teppo et al. (32).

There may be several causes underlying the effect of age on tumor size. There has been a focus on increasingly frequent incidental discovery of vestibular schwannomas (2,5–7), which is perhaps secondary to the more widespread use of magnetic resonance imaging, particularly in older individuals (2). Incidental tumors on average tended to be smaller than those tumors found in symptomatic individuals (5). The negative correlation between increasing age and tumor size may therefore be a reflection of a higher proportion of incidental tumors among older individuals. Another consideration is the presence of a real difference in tumor growth rate as a function of the age at which the tumor develops. Some studies have found faster tumor growth rates in younger patients (33,34), which may explain why younger patients presented with larger tumors in our study. Other studies, however, have found no correlation between age and tumor growth rate (21, 28,31,35–37). Younger patients may tolerate more tumor growth because of greater neurologic reserve. It has been suggested that younger individuals may be less sensitive to cochleovestibular dysfunction because of greater reserves of baseline function; 1 case series found that younger patients often presented with large tumors but with signs and symptoms that were less severe than older patients (38).

The significant sex differences in presenting symptoms may be explained by differences between men and women in the reporting of symptoms. Sex differences in the use of health-care services has been reported (39), which could lead to later presentation by men and differences in the frequency with which symptoms are reported. In this retrospective review, the providers did not use a standardized questionnaire that would limit the effect of sex reporting differences on symptom prevalence. Alternatively, the sex differences in presenting symptoms may reflect the differences in baseline prevalence of hearing loss and dizziness between male and female subjects. A population-based study (40) found that among adults in the United States, male subjects were 5.5 times more likely to have hearing loss than female subjects, and increasing age correlated with increasing odds of hearing loss. In our bivariate analysis, we found that male subjects older than 40 years had a higher prevalence of hearing loss as a presenting symptom of vestibular schwannoma than female subjects. Dizziness, conversely, has been found to be more prevalent in female subjects than in male subjects (41–48), and this difference has been found across all ages in 1 epidemiologic cross-sectional study (41). Similarly, we determined that there was a greater likelihood of dizziness as a presenting symptom in female subjects older than 40 years. The reason for increased susceptibility to vestibular dysfunction in women is unclear. Possible factors in need of investigation include impairment of central compensation because of less physical activity compared with men or a higher prevalence of migraine in women (49,50).

There may also be a role in tumorigenesis for epigenetics or differences in gene expression caused by mechanisms other than changes to the DNA sequence itself. For instance, DNA methylation of a tumor suppressor promoter region may silence that gene, leading to tumorigenesis (51). Lassaletta et al. (52) examined the methylation status of tumor-related genes in a series of 22 vestibular schwannomas. They found that the frequency of methylation of certain genes were associated with age, tumor size, and hearing loss. Epigenetic modifications, therefore, may have a role in influencing the patterns of vestibular schwannoma presentation.

This study does have several limitations. A retrospective review limited us to the information that was available in the patients' charts. Not all of the variables collected were documented for each patient. We also only included patients who were seen in either the departments of Otolaryngology–Head and Neck Surgery or Neurosurgery. Those patients who may have presented to other departments for management of their vestibular schwannoma (e.g., Radiation Oncology) were excluded, and therefore, our sample may not completely represent our target population. Additionally, not all tumors were histologically confirmed as some patients were followed as an outpatient for the presumptive diagnosis of vestibular schwannoma. It is possible that our sample included individuals with other diagnoses (e.g., meningioma or facial nerve schwannoma). Longitudinal analysis of severity of symptoms and tumor size was not possible, given the retrospective dataset available to us, and our observations are unadjusted and potentially biased by confounds described above. We also relied on subjective data of patient-reported symptoms, as a standardized intake questionnaire was not used by providers. Not all patients may have reported all relevant symptoms because of differences in the willingness to report certain symptoms or differences in provider interviews. The high prevalence of facial weakness, for instance, may not represent motor weakness but perceived facial asymmetries as reported by the patient. Additionally, the current study is limited to providing associations between demographic variables and clinical presentation and does not address causal relationships.

This study does generate hypotheses regarding differences in patient-reported, initial symptoms associated with a unilateral vestibular schwannoma and the influence of sex and age. We observed significant differences by sex in tumor size, hearing loss, and dizziness. These findings suggest heterogeneity in tumor biology because of, for example, hormonal influences but also implicate host factors, such as cranial size, which may differ by sex, and reserve of cochleovestibular function, which may differ by sex and age. This work has potential implications for understanding pathophysiology, improving risk stratification



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and optimizing treatment. Given that the evaluation for, and diagnosis of, vestibular schwannoma is typically dependent on an unforced medical evaluation that is elected by the patient, the patterns and sources of differences of patient-reported symptoms warrant further evaluation with prospective study designs.

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