Title: Potential Autoimmune Association between Benign Paroxysmal Positional Vertigo and Immune-mediated Skin Conditions: Population-based Cohort Study

Hyung Jin Hahn, MD, Ph.D[1,7], Sang Gyu Kwak PhD[2], Dong-Kyu Kim, MD, PhD[3,4], Jong-Yeup Kim MD, Ph.D[5,6,7]

[1]Department of Dermatology, College of Medicine, *Konyang* University, *Daejeon*, Republic of Korea

[2]School of Medicine, Department of Medical Statistics, Catholic University of *Daegu*

[3]Department of Otorhinolaryngology-Head and Neck Surgery, *Chuncheon* Sacred Heart Hospital and

[4]Institute of New Frontier Research, *Hallym* University College of Medicine, *Chuncheon*, Republic of Korea

[5]Department of Otorhinolaryngology–Head and Neck Surgery, College of Medicine, *Konyang* University, *Daejeon*, Republic of Korea

[6]Department of Biomedical Informatics, College of Medicine, *Konyang* University, *Daejeon*, Republic of Korea

[7]*Myunggok* Medical Research Institute, College of Medicine, *Konyang* University, *Daejeon*, Republic of Korea;

Corresponding authors:

Dong-Kyu Kim, MD, Ph.D

Department of Otorhinolaryngology-Head and Neck Surgery, *Chuncheon* Sacred Heart Hospital,

Hallym University College of Medicine (200-704), 77, *Sakju-ro*,

Chuncheon-si, *Gangwon-do*, Republic of Korea

Telephone: 82-33-240-5180

Email: doctordk@naver.com

Jong-Yeup Kim MD, Ph.D

Department of Biomedical Informatics, College of Medicine, *Konyang* University, 158 *Gwanjeodong-ro*, *Seo-gu*,

Daejeon 35365, Republic of Korea

Telephone: 82-42-600-9215

Email: jykim@konyang.ac.kr

Keywords: Benign Paroxysmal Positional Vertigo (BPPV), atopic dermatitis, vitiligo, autoimmunity, big data

ABSTRACT

Background: Benign paroxysmal positional vertigo (BPPV), an idiopathic disorder of sudden sensorineural hearing loss and vertigo, shares many similarities with two common skin conditions, atopic dermatitis (AD) and vitiligo. Recent studies have suggested that BPPV may be related to or triggered by autoimmune conditions, notably hypothyroidism and giant cell arteritis (GCA).

Objective: These evidences prompted the authors to entertain the possibility of immunological bridge between BPPV and the two skin conditions. The authors have tested this hypothesis with population-based cohort from the National Health Insurance Service Database of Korea.

Methods: A cohort of 1.1 million patients was extracted from the DB. Using χ^2 tests, prevalence of the two skin disorders in terms of BPPV status was analysed.

Results: In AD patients, the prevalence of BPPV was 30% lower, while there was no statistically significant relationship between BPPV prevalence and vitiligo. The relationship between vitiligo and BPPV was significant in younger subgroup only. Socio-economic subgroup analysis revealed the observed patterns are primarily a middle-upper class phenomenon.

Limitations: Uncertainty regarding temporal sequence of onset, and lack of detail on disease severity and subtype might have kept the authors from drawing more refined conclusion.

Conclusion: AD and vitiligo might be linked to BPPV through the action of certain components of cellular immunity, but follow-up studies based on large population cohort would be needed to add more substance to our findings.

Introduction

Benign paroxysmal positional vertigo (BPPV), along with *Ménière* disease (MD) and labyrhinthitis, is one of the most commonly encountered forms of vertiginous disorder. Accounting for almost 50% of all individuals with peripheral vestibular dysfunction [1], one-year and lifetime prevalence of this largely idiopathic entity is believed to be around 1.6% and 2.4% respectively, with a slight predilection for females [2,3,4]. The vertigo of sudden onset, that is characteristic of BPPV, is thought to be instigated by displacement of inner ear crystals (otoliths), with the stones lodging within the lumen of the semi-circular canals [5], which in turn culminates in perturbed rotational balance. While postural or head position changes as precipitating factors of BPPV symptoms is reasonably well established, whether there are other factors accounting for the stimulation of labyrinthine receptors is a matter of ongoing debate. Traditional views have held that the phenomenon is primarily of

mechanical nature, while some schools of thought have embraced the notion of autoimmune etiopathogenesis for BPPV. Studies over the past several years have reinforced the notion of the endolymphatic sac, where these "ear rocks" originate, as a vibrant hub of immunological interactions, rather than an inert structural locale [6]. The labyrinthine sac is known to harbour inner ear autoantigens of various molecular weights, which can trigger type II (surface antigens) or type III (antigen-antibody immunocomplexes) hypersensitivities [7,8]. One facet of the autoimmune hypothesis points to this type of immune-complex formation and diffusion of these complexes into the inner ear surface, as a direct cause of the triggering of the symptoms [9]. For the past couple of decades, there has been some debate raging over the issue of thyroid status with respect to BPPV pathogenesis. Some authors have found that there is a positive correlation between the chronic inner ear disorder and Hashimoto thyroiditis, which is the most common cause of hypothyroidism [10,11]. Furthermore, Papi *et al*. showed that BPPV is related to autoimmune chronic thyroiditis (ACT), and that the association is independent of thyroid status [12]. However, despite these reports, the issue remains unsettled. To explore the issue from a different perspective, the authors have tested how the chronic inner ear condition is related to two of the most prevalent inflammatory skin diseases, atopic dermatitis and vitiligo. The strong ties of these two conditions to a variety of autoimmune diseases are fairly well established, and in particular, their relationship to thyroid diseases has been explored in a wealth of previous literatures [13,14]. Also, because each of the two entities has distinctive immuno-pathological mechanism, they were deemed suitable for the purposes of comparison with BPPV.

The aim of the authors in the present investigation was to offer an alternative and complementary explanation for the controversial role of autoimmunity in BPPV, through analysis based on population-based cohorts from the National Health Insurance Service of Korea (NHIS) database.

Results

Baseline characteristics. Baseline demographic information is summarized in Table 1. The entire study cohort was made up of 1,113,656 individuals, with nearly equal sex distribution (M:F=50.1:49.9). Geographically, the highest proportion of the cohort was drawn from Seoul and *Gyeonggi* Province, a metropolitan area surrounding the nation's capital (at around 21% apiece). Other major cities and the metropolitan provinces of the country were evenly represented. Each eligible citizen is subject to either one of the two coverage plans, *i.e*., employee-insured or self employee-insured, or when applicable, the Korean Medical Aid program. The cohort was divided into ten income brackets (deciles), and then regrouped as *lower* (brackets 1 through 4), *middle* (brackets 5 through 7), or *upper* (brackets 8 through 10) income tiers. The study cohort was also divided from grade of 0 to 6 according to

the extent of their disability. For the entire cohort, the "baseline" prevalence of BPPV, AD, and vitiligo were computed at 0.69%, 0.72% and 0.11%, respectively.

Prevalence of BPPV in terms of skin disease status. The prevalence of BPPV in AD individuals was 0.72%. In non-AD patients, the prevalence was 0.50%. The finding was statistically significant (p=0.023). The prevalence of BPPV in vitiligo and non-vitiligo individuals was 0.11% and 0.14%, respectively. However, these relationships were not statistically significant (p=0.464).

Sex and age. A similar pattern prevailed after male and female cohorts were considered separately, although the relationship between BPPV and AD was not statistically significant in males (p=0.119). Age group analysis revealed that the higher prevalence of vitiligo in BPPV patients held true only for the younger individuals (p=0.000). Other findings were not statistically significant.

Socioeconomic subgroups. On χ^2 test, the BPPV-vitiligo relationship was valid only in the "middle" income tier (brackets 5 through 7, p=0.000). On the other hand, the lower BPPV prevalence in AD patients was seen only in the "upper" tier (brackets 8 through 10, p=0.037). Other relationships were not statistically significant.

Disability. The BPPV-AD/vitiligo relationship was also analysed by disability status. χ^2 analysis revealed virtually the same results for individuals without disability as the whole cohort (p-values of 0.026 and 0.000 for AD and vitiligo, respectively). Interestingly, there was a reversal of pattern in the subgroup with moderate (grade 1 & 2) disability, with a five-fold increase in AD prevalence in BPPV patients (1 of 56 *versus* 22 of 8,864 in non-BPPV patients; p=0.025).

Discussion

While many causes are cited as possible players in its aetiology, nearly 60% of BPPV cases are still idiopathic [15], and it would not be completely implausible that at least a part of this proportion may be attributed to autoimmune causes. The autoimmune aspect of BPPV pathogenesis is a relatively recent development, and it is not "officially" recognised and given serious consideration in most established text sources. Apart from the issue involving thyroid, another piece of evidence in favour of the autoimmunity theory may be the link between BPPV and giant cell arteritis (GCA) [16]. The pathophysiology of GCA involves dendritic cells (DC) in the vessel wall which attract T cells and macrophages to form granulomatous infiltrates. T helper 17 cells (Th 17), interconnected with interleukin (IL) 6, IL-17 and IL-21, play an essential role, and this pathway can be blocked by corticosteroids [17]. From the population-based cohort of the present study, it was revealed that individuals with AD, or history of AD (BPPV tends to affect senile individuals whereas the incidence of AD peaks at late-20's to mid-30's) is

about 30% less likely to be affected with BPPV. Atopic dermatitis is a chronic, inflammatory disorder of the skin, in which thickening of the epidermis is one of the hallmarks [18]. The epidermal hyperplasia results from complex network of interactions between keratinocytes and T-cells, mediated by several cytokines and chemokines [19]. Several studies from recent years have found that systemic inflammatory disorders are more prone to developing inner ear diseases; in psoriasis, which is also a chronic inflammatory disease characterized by hyperplastic epidermis, there is an increased risk of sudden sensorineural hearing loss [20,21]. Given the systemic nature of AD inflammation [22], it is likely that the surface of the labyrinthine sac of the utricle is also affected in a way that secures the position of otoliths within the utricle. Meanwhile in subgroup analysis. there was a sharp contrast between younger and senile cohorts. The higher prevalence of BPPV in senile patients with AD may suggest that immune senescence plays a role in the pathogenesis of BPPV [23]. In the sub-analysis by socioeconomic status, the prevalence of vitiligo was three times higher in BPPV individuals that belong to the lower income tier (deciles 1 through 4). On the other hand, for the upper tier subgroup (deciles 8 through 10), the prevalence of AD in BPPV individuals was nearly one-half that of the non-BPPV cohort. This phenomenon may reflect unequal distribution of healthcare utilization across the socioeconomic hierarchy. Individuals lacking financial means and leisure are less likely to seek medical care for cutaneous signs of vitiligo at secondary or higher referral centres. However, they would be more compelled to take the trouble for symptoms of BPPV, which can seriously undermine the individual's day-to-day operation, and at larger centres this in turn would likely lead to the diagnosis of concurrent vitiligo.

The authors acknowledge that this study was subject to some limitations. Due to its cross-sectional nature, temporal relations between BPPV and skin disorders could not be established. Also, lack of information regarding disease severity and subtype (*e.g.*, anterior or horizontal canal *versus* posterior canal BPPV [24,25]) had impeded more detailed analysis, which would have allowed the authors to propose more elaborate disease mechanism. Finally, it was revealed by subgroup analysis that the relationship between the skin conditions and BPPV was statistically significant only for individuals *without* disability.

In conclusion, the present study represents a unique attempt to form a potential link between autoimmune conditions and BPPV, which has been considered to originate from mechanical/physical causes for the most part. Despite a few shortcomings, the study allowed the authors to glimpse through the underlying patho-mechanism of three puzzling conditions, and on the process gain some unique insights and perspectives. Further studies, with more thorough and sophisticated databases, would enable us to build upon this ground and yield more refined conclusions, including its therapeutic implications.

Methods

Database (DB). All study conduct adhered to the tenets of the Declaration of Helsinki. This study utilized KNHIS-NSC data (NHIS-2018-2-252), made by the National Health Insurance Service (NHIS) and was approved by the Institutional Review Board (IRB) of *Hallym* Medical University *Chuncheon* Sacred Hospital (IRB No. 2018-08-018). The need for written informed consent was waived because the KNHIS-NSC data set consisted of deidentified secondary data for research purposes. The NHIS is a compulsory healthcare plan for all Korean nationals; eligible citizens are covered either through community- or employee-based plan. The health care utilization DB, one of the main DB run by the Service, was used in the present study. The DB holds a vast amount (over 1.5 trillion cases) of inpatient and outpatient data, including diagnosis, length of inpatient admission, type of treatment, and prescription records.

Study Cohort. The following criteria were used in search query for extracting benign paroxysmal positional vertigo (BPPV) individuals from the DB; those who 1) had been diagnosed with KCD (Korean Standard Classification of Diseases) Diagnosis Code 'H811', and 2) had undergone canalith repositioning procedure (CRP, prescription code 'MX035'). Atopic dermatitis (AD) individuals were defined as those who 1) had been diagnosed *at least* twice with KCD Diagnosis code 'L20' with any two consecutive visits separated by at least 6 months, and 2) had been prescribed topical calcineurin inhibitors (TCI)-tacrolimus (Protopic®) 0.03% 10g/0.1% 30g, or pimecrolimus (Elidel®) 1% 30g-on the day of diagnosis. Vitiligo individuals were defined as those who 1) had been diagnosed with KCD Diagnosis Code 'L80', and 2) had been prescribed topical calcineurin inhibitors, topical corticosteroids-methylprednisolone aceponate 1mg/g (Advantan®) 10g, prednicarbate 0.025% (Dermatop®) 10mg, *etc.*-or topical calcipotriol 50μg/mL (Daivonex®).

Statistical analysis. A summary of demographic and baseline characteristics was constructed using descriptive analysis: quantitative variables were represented by the mean, maximum, minimum and standard deviation (S.D), while qualitative variables were described by the frequency and proportions (%). Potential associations of BPPV to atopic dermatitis and vitiligo were analysed by χ^2 tests. Potential disease associations, by sex (male and female), age (≤60, >60), age (≤65, >65), income deciles (0~4, 5~7 and 8~10) and severity grade (normal, moderate and severe), were analysed by χ^2 tests. The data analysis was performed by a medical statistician. All statistical analyses were performed using SAS Enterprise Guide 6.1 M1 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS software package for Windows (version 19.0, Chicago, IL). All tests were 2-sided and *p*-values less than 0.05 were ruled statistically significant.

ACKNOWLEDGEMENTS: This research was supported by a grant of the Clinical Research infrastructure Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare (H17C2412 to Jong-Yeup Kim). This research was also supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT).

Author contributions. J.K., D.K., and H.H. designed and conducted the study. H.H. produced the manuscript. S.K. and J.K. carried out calculations and statistics. All authors read and approved the final manuscript.

H.H. and S.K contributed equally.

D.K. and J.K. contributed equally.

Competing interests. The authors declare no competing interests.

Data availability. The datasets presented in the current study are available from the corresponding authors upon request.

References

1. Thompson TL, Amedee R. Vertigo: a review of common peripheral and central vestibular disorders. Ochsner J. 2009 Spring;9(1):20-6.
2. von Brevern M, Radtke A, Lezius F, *et al*. Epidemiology of benign paroxysmal positional vertigo: a population based study. J Neurol Neurosurg Psychiatry. 2007;78(7): 710.
3. Anagnostou E, Kararizou E, Evdokimidis I. Treatment Maneuvers for Benign Paroxysmal Positional Vertigo in the Very Old. Eur Neurol 2017;77:23–24
4. Wang J, Chi FL, Jia XH, *et al*. Does benign paroxysmal positional vertigo explain age and gender variation in patients with vertigo by mechanical assistance maneuvers? Neurol Sci. 2014 Nov;35(11):1731-6.
5. Hall SF, Ruby RR, McClure JA. The mechanics of benign paroxysmal vertigo. J Otolaryngol 1979; 8:151.
6. Møller M.N., Kirkeby S., Vikeså J. *et al*. Gene expression demonstrates an immunological capacity of the human endolymphatic sac. Laryngoscope. Aug;125(8):E269-75 (2015).
7. Egami N., Kakigi A., Takeda T *et al*. Type 1 allergy-induced endolymphatic hydrops and the suppressive effect of H1-receptor antagonist (olopatadine hydrochloride). Otol Neurotol. Mar;35(3):e104-9 (2014).

8. Yoo T.J. Etiopathogenesis of Ménière's disease: a hypothesis. Ann Otol Rhinol Laryngol 113:6–12 (1984).
9. Møller M.N., Kirkeby S., Cayé-Thomasen P. Innate immune defense in the inner ear - mucines are expressed by the human endolymphatic sac. J Anat Feb;230(2):297-302 (2017).
10. Chiarella G, Russo D, Monzani F, *et al*. HASHIMOTO THYROIDITIS AND VESTIBULAR DYSFUNCTION. Endocr Pract. 2017 Jul;23(7):863-868.
11. Modugno GC, Pirodda A, Ferri GG, *et al*. A relationship between autoimmune thyroiditis and benign paroxysmal positional vertigo? Medical Hypotheses (2000) 54(4), 614–615.
12. Papi G, Corsello SM, Milite MT, *et al*. Association between benign paroxysmal positional vertigo and autoimmune chronic thyroiditis. Clinical Endocrinol (2009) 70, 169-171.
13. Pedullá M, Fierro V, Papacciuolo V, *et al*. Atopy as a risk factor for thyroid autoimmunity in children affected with atopic dermatitis. J Eur Acad Dermatol Venereol. 2014 Aug;28(8):1057-60.
14. Pedullà M, Fierro V, Marzuillo P, *et al*. Skin disease and thyroid autoimmunity in atopic South Italian children. World J Clin Pediatr. 2016 Aug 8;5(3):288-92.
15. Parnes LS, Agrawal SK, Atlas J. Diagnosis and management of benign paroxysmal positional vertigo (BPPV). CMAJ. 2003 Sep 30; 169(7): 681–693.
16. Amor-Dorado JC, Llorca J, Costa-Ribas C, *et al*. Giant cell arteritis: a new association with benign paroxysmal positional vertigo. Laryngoscope 2004; 114:1420.
17. Villiger PM, Adler S, Kuchen S, *et al*. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016 May 7;387(10031):1921-7.
18. Ungar B, Garcet S, Gonzalez J *et al*. An Integrated Model of Atopic Dermatitis Biomarkers Highlights the Systemic Nature of the Disease. J Invest Dermatol. 2017 Mar;137(3):603-613.
19. Khattri S, Shemer A, Rozenblit M, *et al*. Cyclosporine in patients with atopic dermatitis modulates activated inflammatory pathways and reverses epidermal pathology. J Allergy Clin Immunol. 2014 Jun;133(6):1626-34.
20. Yen YC, Lin YS, Weng SF, *et al*. Risk of sudden sensorineural hearing loss in patients with psoriasis: a retrospective cohort study. Am J Clin Dermatol. 2015 Jun;16(3):213-20.
21. Vir D, Sharma P, Mahajan R, *et al*. Investigation of high-frequency hearing loss and outer hair cell function of the cochlea in patients with psoriasis: a case-control study. Clin Exp Dermatol. 2018 Oct 2.
22. Ottas A, Fishman D, Okas TL, *et al*. Blood serum metabolome of atopic dermatitis: Altered energy cycle and

the markers of systemic inflammation. PLOS One. 2017 Nov 27;12(11):e0188580.

23. Jagger A. *et al*. Regulatory T cells and the immune aging process: a mini-review. Gerontology. 60(2):130-7 (2014)

24. Hughes CA, Proctor L. Benign paroxysmal positional vertigo. Laryngoscope 1997; 107:607.

25. Dispenza F, De Stefano A, Mathur N, *et al*. Benign paroxysmal positional vertigo following whiplash injury: a myth or a reality? Am J Otolaryngol 2011; 32:376.

Tables

Variable		*n*	%
Total patients		1,113,656	100.0
Sex	Male	558,186	50.12
	Female	555,470	49.88
Age distribution (years)	0	108,614	9.75
	1~4	52,082	4.68
	5~9	74,637	6.70
	10~14	70,962	6.37
	15~19	70,135	6.30
	20~24	84128	7.55
	25~29	85,303	7.66
	30~34	97,177	8.73
	35~39	88,505	7.95
	40~44	93,776	8.42
	45~49	72,811	6.54
	50~54	53,333	4.79
	55~59	43,015	3.86
	60~64	42,753	3.84
	65~69	31,891	2.86
	70~74	20,939	1.88
	75~79	12,850	1.15
	80~84	7,063	0.63
	85+	3682	0.33

Age group (years)	≤65	1,037,231	93.14
	>65	76,425	6.86
Income deciles	0	28,332	2.54
	1	63,625	5.71
	2	65,585	5.89
	3	77,713	6.98
	4	91,386	8.21
	5	105,376	9.46
	6	119,392	10.72
	7	131,489	11.81
	8	142,484	12.79
	9	145,778	13.09
	10	142496	12.80
Income Ranges	0~4	326,641	29.33
	5~7	356,257	31.99
	8~10	430,758	38.68
Disability Grade	Normal (Grade 0)	1,087,242	97.63
	Moderate (Grade 1~2)	8,943	0.80
	Severe (Grade 3~6)	17,471	1.57
BPPV	No	1,105,918	99.31
	Yes	7,738	0.69
AD	No	1,105,616	99.28
	Yes	8,040	0.72
Vitiligo	No	1,112,385	99.89
	Yes	1,271	0.11

TABLE 1. Baseline characteristics. *Abbreviations*: *AD*, atopic dermatitis; *BPPV*, benign paroxysmal positional vertigo.

Variable		BPPV, *n* (%)		*p*-value
		No	Yes	
AD	No	1,097,917 (99.28)	7,699 (99.50)	0.023*
	Yes	8,001 (0.72)	39 (0.50)	

Vitiligo	No	1,104,658 (99.89)	7,727 (99.86)	0.464
	Yes	1,260 (0.11)	11 (0.14)	

TABLE 2. Relationship between BPPV and atopic and vitiligo. *Abbreviations*: *AD*, atopic dermatitis; *BPPV*, benign paroxysmal positional vertigo. *statistically significant for $p<0.05$.

Sex	Variable		BPPV, *n* (%)		*p*-value
			No	Yes	
Male	AD	No	552,247 (99.34)	2,284 (99.61)	0.119
		Yes	3,646 (0.66)	9 (0.39)	
	vitiligo	No	555,361 (99.90)	2,291 (99.91)	0.896
		Yes	532(0.10)	2(0.09)	
Female	AD	No	545,670 (99.21)	5,415 (99.45)	0.045*
		Yes	4,355 (0.79)	30 (0.55)	
	Vitiligo	No	549,297 (99.87)	5,436 (99.83)	0.507
		Yes	728 (0.13)	9 (0.17)	

TABLE 3. Relationship between BPPV and AD and vitiligo by sex. *Abbreviations*: *AD*, atopic dermatitis; *BPPV*, benign paroxysmal positional vertigo. *statistically significant for $p<0.05$.

Age group	Variable		BPPV, *n* (%)		*p*-value
			No	Yes	
≤65	AD	No	1,022,463 (99.23)	6,848 (99.49)	0.015*
		Yes	7,885 (0.77)	35 (0.51)	
	Vitiligo	No	1,029,167 (99.89)	6,873 (99.85)	0.454
		Yes	1,181 (0.11)	10 (0.15)	
>65	AD	No	75,454 (99.85)	851 (99.53)	0.021*
		Yes	116 (0.15)	4 (0.47)	
	Vitiligo	No	75,491 (99.90)	854 (99.88)	0.911

		Yes	79 (0.10)	1 (0.12)	

TABLE 4. Relationship between BPPV and atopic and vitiligo by age (≤65 & >65). *Abbreviations*: *AD*, atopic dermatitis; *BPPV*, benign paroxysmal positional vertigo. *statistically significant for $p<0.05$.

Income Brackets	Variable		BPPV, *n* (%)		*p*-value
			No	Yes	
0~4 [Lower]	AD	No	322,809 (99.48)	2,116 (99.39)	0.585
		Yes	1,703 (0.52)	13 (0.61)	
	Vitiligo	No	324,223 (99.91)	2,123 (99.72)	0.003*
		Yes	289 (0.09)	6 (0.28)	
5~7 [Middle]	AD	No	351,513 (99.26)	2,130 (99.58)	0.089
		Yes	2,605 (0.74)	9 (0.42)	
	Vitiligo	No	353,754 (99.90)	2,138 (99.95)	0.419
		Yes	364 (0.10)	1 (0.05)	
8~10 [Upper]	AD	No	423,595 (99.14)	3,453 (99.51)	0.017*
		Yes	3,693 (0.86)	17 (0.49)	
	Vitiligo	No	426,681 (99.86)	3,466 (99.88)	0.676
		Yes	607 (0.14)	4 (0.12)	

TABLE 5. Relationship between BPPV and atopic and vitiligo by income tiers. *Abbreviations*: *AD*, atopic dermatitis; *BPPV*, benign paroxysmal positional vertigo. *statistically significant for $p<0.05$.

Grade	Variable		BPPV, *n* (%)		*p*-value
			No	Yes	
Normal	AD	No	1,071,769 (99.27)	7,503 (99.48)	0.027*
		Yes	7,931 (0.73)	39 (0.52)	
	Vitiligo	No	1,078,459 (99.89)	7,531 (99.85)	0.430
		Yes	1,241 (0.11)	11 (0.15)	

Moderate	AD	No	8,876 (99.74)	44 (100.0)	0.736
		Yes	23 (0.26)	0 (0.0)	
	Vitiligo	No	8,897 (99.98)	44 (100.0)	0.921
		Yes	2 (0.02)	0 (0.0)	
Severe	AD	No	17,272 (99.73)	152 (100.0)	0.521
		Yes	47 (0.27)	0 (0.0)	
	Vitiligo	No	17,302 (99.90)	152 (100.0)	0.699
		Yes	17 (0.10)	0 (0.0)	

TABLE 6. Relationship between BPPV and atopic dermatitis/vitiligo by disability. *Abbreviations*: *AD*, atopic dermatitis; *BPPV*, benign paroxysmal positional vertigo. *statistically significant for $p<0.05$.