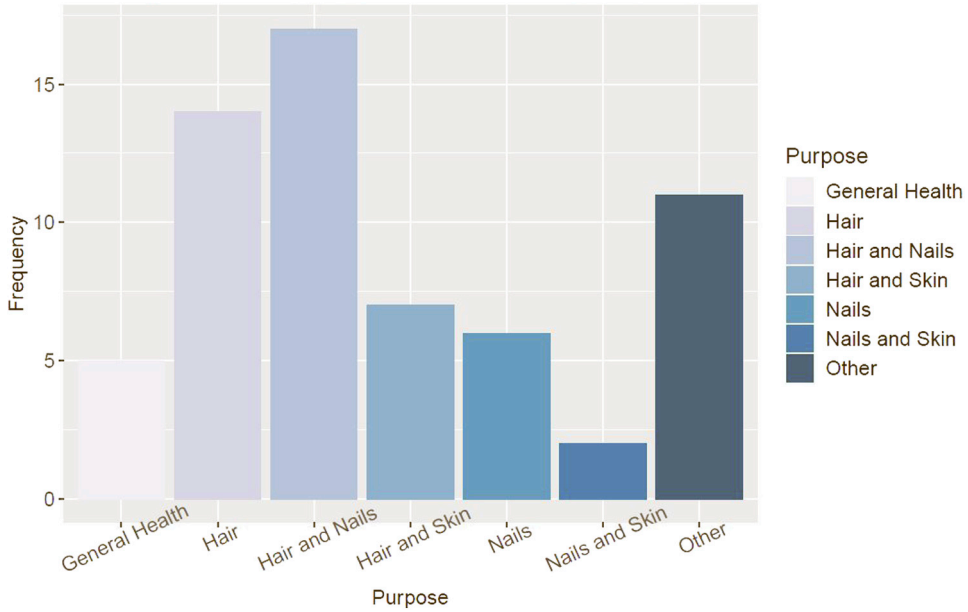

Fig 1. Frequency of biotin use, by purpose, for subjects who reported an improvement in any condition (n = 62).

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Risk for neurodegenerative disorders in Korean patients with vitiligo: A nationwide retrospective cohort study

To the Editor: Vitiligo is an acquired depigmenting disorder with an autoimmune nature.[1] In line with its autoimmune-based pathogenesis, previous studies have indicated a significant association of vitiligo with several autoimmune diseases.[2] Neurodegenerative disorders, such as Parkinson disease (PD) and Alzheimer disease (AD), are caused by progressive degeneration of neuronal cells. Emerging evidence has demonstrated that autoimmunity is one of the etiologies for PD and AD.[3,4] However, whether vitiligo is associated with an increased risk for neurodegenerative disorders has not been investigated. We conducted a nationwide, retrospective cohort study to examine the risk for neurodegenerative disorders in patients with vitiligo using the Korean National Health Insurance Service health screening cohort.

Among the initial cohort (N = 514,866), a total of 1500 patients aged 40-79 years who had visited clinics >3 times during 2002-2003 with a principal diagnosis of vitiligo (L80, N480, N880, N894, and N904 according to the International Classification of Diseases, 10th Revision diagnostic codes) were defined as the vitiligo group. Members of the nonvitiligo group were matched at a 1:9 ratio (N = 13,500) on the basis of age (by 5-year age

Table I. Frequency of neurodegenerative disorders in the nonvitiligo and vitiligo groups

	Parkinson disease			Alzheimer disease		
Group	No. cases/total	%	*P* value	No. cases/total	%	*P* value
Nonvitiligo	193/13,500	1.4	.255	474/13,500	3.5	.304
Vitiligo	16/1500	1.1		45/1500	3.0	
Total	209/15,000	1.4		519/15,000	3.5	

Table II. aHR for neurodegenerative disorders by extent of vitiligo

	Parkinson disease			Alzheimer disease		
Variable	No. cases/total	aHR*	95% CI	No. cases/total	aHR*	95% CI
Nonvitiligo	193/13,500	Reference		474/13,500	Reference	
Vitiligo	16/1500	0.828	0.408-1.677	45/1500	0.860	0.593-1.247
No UV therapy	12/806	1.311	0.567-3.031	21/806	0.742	0.404-1.363
Less extensive UV therapy, <36%	2/538	0.381	0.094-1.548	20/538	1.082	0.641-1.826
Extensive UV therapy, ≥37%	2/156	1.335	0.326-5.471	4/156	0.973	0.395-2.397

Nonvitiligo and vitiligo groups were matched on sex, age, and smoking history.
aHR, Adjusted hazard ratio; *CI*, confidence interval; *UV*, ultraviolet.
*HRs were additionally adjusted for socioeconomic status and medical conditions including hypertension, dyslipidemia, atrial fibrillation, myocardial infarction, congestive heart failure, peripheral aortic diseases, cardiovascular diseases, dementia, pulmonary diseases, connective tissue diseases, peptic ulcer, liver diseases, diabetes, diabetes with complications, paralysis, renal diseases, malignancies, metastasis, severe liver diseases, HIV infection, ischemic stroke, hemorrhagic stroke, osteoporosis, hyperthyroidism, hypothyroidism, hyperparathyroidism, and hypoparathyroidism.

groups), sex, and smoking history to get proper controls in the stratum. The outcome, the occurrence of PD (G20 and F023) and AD (F00 and G30), was measured between the vitiligo and nonvitiligo groups through the follow-up period (2004-2013). Subgroup analyses were performed according to the extent of vitiligo determined by the ultraviolet therapy codes denoting exposed body surface area (less extensive <36% and extensive ≥37%). Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were estimated by applying a Cox proportional hazard regression model.

The total disease rate was 1.1% for PD and 3.0% for AD in vitiligo group and 1.4% for PD and 3.5% for AD in nonvitiligo group, which was not statistically significant (χ^2 test; Table I). In the multivariate Cox proportional hazard model, the overall risks for PD and AD were not significantly increased in the vitiligo group compared with nonvitiligo controls (aHR 0.828, 95% CI 0.408-1.677 for PD; aHR 0.860, 95% CI 0.593-1.247 for AD; Table II). Subgroup analyses also showed that the risks for PD and AD were not increased according to the extent of vitiligo (Table II).

The pathogenesis of vitiligo encompasses both melanocyte vulnerability and autoimmunity by interferon γ–producing, melanocyte-specific $CD8^+$ T cells.[1] Because vitiligo involves melanocyte destruction caused by an autoimmune mechanism and neuromelanin, which has a similar structure to epidermal melanin and is known to be involved in the pathogenesis of PD,[5] we aimed in our study to determine whether vitiligo patients had a higher risk for neurodegenerative disorders. However, our 10-year nationwide cohort study showed that vitiligo was not significantly associated with an overall risk for neurodegenerative disorders. Although our study has limitations, such as possible incorrect diagnoses and a lack of clinical information of vitiligo in the National Health Insurance Service database, we were the first to use this large nationwide cohort to explore whether an association between vitiligo and neurodegenerative disorders could be detected over 10 years of follow-up. Further investigations are needed to validate our results from other larger and longer cohorts.

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Rosacea: Relative risk versus absolute risk of malignant comorbidities

To the Editor: Rosacea is associated with an increased risk of malignancies such as thyroid cancer, basal cell carcinoma, glioma, hepatic cancer, breast cancer, and nonmelanoma skin cancer.[1-3] Relative risk (RR) is used to report the associations, but attributable risk or number needed to harm provides a clearer, absolute picture regarding the association between rosacea and malignant comorbidities. We did a PubMed search using the terms *rosacea*, *comorbidities*, and *study* and analyzed cohort studies in which the entity precedes the malignancy, linking rosacea malignant comorbidities and calculating attributable risk per 10,000 person-years and number needed to harm (Table I). The cohort studies analyzed were conducted between June 1, 2008, and June 1, 2018.

The RRs of thyroid cancer, glioma, and hepatic cancer were 1.60, 1.43, and 1.42, respectively. The attributable risks of these comorbidities were 1.41, 1.44, and 0.46 per 10,000 patient-years, respectively.[1-3] The numbers of patients needed to be seen in 1 year to attribute 1 case of these conditions to rosacea were 7080, 6963, and 21,645, respectively. The higher number of patients who need to be seen in 1 year to attribute a case of hepatic cancer to rosacea despite an RR similar to that of the other malignant comorbidities is due to the lower baseline incidence rate of hepatic cancer (Table I).

These findings raise questions about whether recommendations for screening for these malignant comorbidities are appropriate.[4] Physicians often use relative terms rather than absolute terms in evaluating risk and presenting risks to patients.[5] In a questionnaire study, 28 of 88 physicians agreed with the invalid statement "being diagnosed with rosacea increases the chance of developing hepatocellular carcinoma by 42%. This means that for every 10 people who developed rosacea, about 4 people will get hepatocellular carcinoma."[6] However, more than 20,000 patients would need to be seen in 1 year before 1 case of hepatocellular carcinoma could be attributed to rosacea.

Cancer screenings can provide great benefit in the proper context; however, they are not without consequences. For example, 0.7 % of liver biopsies result in severe intraperitoneal hematoma.[7] The risk of development of hepatic cancer attributed to rosacea is about 0.005%. Unfortunately, screening recommendations provided in studies linking rosacea and its comorbidities rely solely on relative association, which is an incomplete and potentially misleading way to depict associations. Exclusively portraying associations in relative terms and physicians' limited ability to delineate statistical significance may result in overestimation of the clinical importance of exposures.

Knowing absolute and relative risks provides physicians with a clearer understanding and more transparent discussions with patients. The absolute terms present a better understanding regarding rosacea's impact on public health and clinical settings.

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