Original investigation

Both Cardiovascular and Cerebrovascular Events are Decreased Following Long-term NB-UVB Phototherapy in Patients with Vitiligo: A Propensity-score Matching Analysis

Jung Min Bae, MD, PhD,[1*] Yoon-Seob Kim, MD,[2*] Eun Ho Choo, MD,[3] Mi-Yeon Kim MD,[4] Jun Young Lee, MD, PhD,[5] Hyung-Ok Kim, MD, PhD,[6] and Young Min Park, MD, PhD.[5]

[1]Department of Dermatology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; [2]Department of Microbiology, College of Medicine, The Catholic University of Korea, Seoul, Korea; [3]Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; [4]CNP Skin Clinic, Seoul, Korea; [5]Department of Dermatology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; [6]Line Dermatology Clinic, Seoul, Korea

*Drs. Bae and Kim contributed equally to this work.

Running head: Cardiovascular Events and NB-UVB Phototherapy

Orcids:

Jung Min Bae, https://orcid.org/0000-0001-5975-8519

Yoon Seob Kim, https://orcid.org/0000-0003-1660-010X

Eun Ho Choo, https://orcid.org/0000-0003-3166-3176

Mi-Yeon Kim, https://orcid.org/0000-0002-3162-6650

Jun Young Lee, https://orcid.org/0000-0002-8650-1759

Hyung-Ok Kim, https://orcid.org/0000-0003-1243-0094

Young Min Park, https://orcid.org/0000-0002-3631-0807

Manuscript word count: 2336

Number of references: 44

Table count: 3

Figure count: 2

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.16830

Correspondence: Young Min Park, MD, PhD.
Department of Dermatology, Seoul St. Mary's Hospital,
222 Banpo-daero, Seocho-gu, Seoul, 06591, Korea
E-mail: 96015367@cmcnu.or.kr
Tel: + 82-2-2258-6223; Fax: + 82-2-599-9950

IRB status statement: The study was approved by the Institutional Review Board of St. Vincent's Hospital (VC17ZESI0090).

Funding sources: This study was funded by the Ministry of Science, ICT & Future Planning (grant number: NRF- 2017R1E1A1A01076780).

Conflict of interest: The authors declare no conflict of interest.
Dr. Bae has nothing to disclose.
Dr. Kim has nothing to disclose.
Dr. Choo has nothing to disclose.
Dr. Kim has nothing to disclose.
Dr. Lee has nothing to disclose.
Dr. Kim has nothing to disclose.
Dr. Park has nothing to disclose.

Role of the Funder/Sponsor: The funding source had no role in designing the study, the collection, management, analysis, and interpretation of the data, the preparation, review or approval of the manuscript, or the decision to submit the manuscript for publication.

Abstract

Background: Systemic effects of long-term narrowband ultraviolet B (NB-UVB) phototherapy have not been well studied in vitiligo patients. An 11-year nationwide population-based retrospective cohort study was conducted using the Korean National Health Insurance claims database (2007–2017).

Objectives: To investigate the effects of long-term NB-UVB phototherapy on the risk of cardiovascular and cerebrovascular events in vitiligo patients.

Methods: This study included vitiligo patients with ≥100 phototherapy sessions (phototherapy group, n = 3,229) and <3 phototherapy sessions (no phototherapy group, n = 9,687), in which covariables with age, sex, insurance type, and comorbidities such as diabetes, hypertension, and hyperlipidemia were matched by 1:3 propensity score matching. The outcomes of interest were cardiovascular (ischemic heart disease and myocardial infarction) and cerebrovascular events (cerebrovascular infraction and hemorrhage). Cox proportional hazards models were used to assess the associations between NB-UVB phototherapy and each event.

Results: The risk of cardiovascular or cerebrovascular events was significantly decreased in the phototherapy group compared with the no phototherapy group (hazard ratio [HR] 0.637, 95% confidence interval [CI] 0.523–0.776). Subgroup analysis revealed that the risk of cardiovascular (HR 0.682, 95% CI 0.495–0.940) and cerebrovascular events (HR 0.601, 95% CI 0.470–0.769) were significantly lower in the phototherapy group than the no phototherapy group, respectively.

Conclusions: Our findings suggest that long-term NB-UVB phototherapy could decrease the risk of cardiovascular and cerebrovascular events in patients with vitiligo.

Keywords: Cardiovascular; Epidemiology; Photobiology; Phototherapy; Vitiligo

Abbreviations list

NB-UVB: Narrowband ultraviolet B

NHI: National Health Insurance

ICD-10-CM: International Classification of Disease, Tenth Revision, Clinical Modification

IHD: ischemic heart disease

MI: myocardial infarction

CIF: cerebral infarction

CH: cerebral hemorrhage

HR: hazard ratio

CI: confidence interval

Introduction

Vitiligo is a chronic depigmentation skin disorder characterized by white macules and patches that affects 1% of the population worldwide.[1,2] Narrowband ultraviolet B (NB-UVB) phototherapy using a peak wavelength of 311 nm has been the mainstay of vitiligo treatment for decades.[3] The mechanism of action of NB-UVB phototherapy involves suppression of autoreactive T cells in the skin and the induction of repigmentation via melanocyte differentiation, proliferation, and migration from the hair follicles or surrounding healthy skin.[4,5] In patients with vitiligo, NB-UVB phototherapy is administered two to three times per week for several months to years to achieve marked repigmentation.[3,6] Therefore, the long-term UV exposure associated with phototherapy has been a major concern for patients with vitiligo.

The cutaneous effects of NB-UVB phototherapy are widely recognized and include short-term events such as transient erythema, blistering and hyperpigmentation, and long-term events such as premature photoaging.[7,8] However, the systemic effects of NB-UVB phototherapy on aspects of internal health have not been fully investigated. On the other hand, the prevalence of cardiovascular disease has been known to be associated with latitude or seasonal variation.[9-15] Furthermore, previous epidemiological studies have demonstrated that reduced exposure to sunlight leads to decrease in high-density lipoprotein levels,[16] and increase in blood pressure,[15] all-cause mortality[17] and incidence of stroke.[18] Thus, the effects of long-term UV exposure on cardiovascular system need to be clarified.

In the present study, we investigated the effects of long-term NB-UVB phototherapy on the risk of cardiovascular and cerebrovascular events in patients with vitiligo using the Korean National Health Insurance (NHI) claims database covering an 11-year period.

Materials and methods

Data source

Data were obtained from the Korean NHI claims database, which contains all NHI claims, and the records of the Korean Medical Aid program for the period 2007–2017. The Korean NHI system is a mandatory health insurance program that covers nearly 50 million Korean residents.[19] The database uses the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes. The study was approved by the Institutional Review Board of St. Vincent's Hospital (VC17ZESI0090).

Study population

All patients aged ≥40 years who were diagnosed with vitiligo (ICD-10-CM code L80) and visited physicians at least four times for that condition between 2007 and 2017 were included in the study to minimize misdiagnosis. The patients were classified into two groups according to the number of NB-UVB phototherapy treatment sessions they had undergone: <3, and ≥100. The no phototherapy group was defined as patients who had <3 phototherapy sessions, given that a few exposures would be expected to have a minimal effect on general health. Patients diagnosed with chronic obstructive pulmonary disease (J44), chronic kidney disease (N18), liver cirrhosis (K4, K703), and/or heart failure (I50) were excluded to ensure that only generally healthy patients were included in the study. Furthermore, to ensure that only new events associated with phototherapy were assessed, patients diagnosed with outcome of interest of any cardiovascular or cerebrovascular event prior to the diagnosis of vitiligo were also excluded from the enrollment.

Propensity score matching

Propensity score matching with confounding variables including age, sex, socioeconomic status (indicated by insurance type), and the presence of diabetes, hypertension and hyperlipidemia, was done in 1:3 ratio between the phototherapy group and the no phototherapy group. Comorbidities included diabetes (E10, E11, E12, E13, and E14), hypertension (I10), and hyperlipidemia (E78) were defined as at least ten visits to physicians for that condition during the study period.

Outcomes of interest

The outcomes of interest were cardiovascular and cerebrovascular events that occurred after

enrollment in the study: both types of event result from atherosclerosis, a chronic inflammatory condition of the cardiovascular system. Cardiovascular events included ischemic heart disease (IHD) (I24) and myocardial infarction (MI) (I21), and cerebrovascular events included cerebral infarction (CIF) (I63) and cerebral hemorrhage (CH) (I60, I61, and I62). Validation studies regarding the accuracy of diagnosis codes of MI and cerebrovascular disease in Korea showed high degree of agreement with clinical hospital records, in which positive predictive value for MI and CIF/CH were found to be more than 70% and 90%, respectively.[20,21] The diagnoses were defined by at least one visit to a physician for the corresponding diagnostic code during the study period. The index date was defined as the date on which patient was first diagnosed with vitiligo during the study period. The overall risk of such events was compared between the two groups. End point of follow-up in this study was the date on which cardiovascular or cerebrovascular events occurred, or the end date of the study period. Because data source included all NHI claims, all patients were followed up until the end of study period except for death, which was excluded from the analysis.

Subgroup analysis

To investigate the risk of cardiovascular or cerebrovascular events in subgroups of patients by sex and age, we did subgroup analysis in subpopulation of male and female, and age of 40-59 years and ≥60 years.

Statistical analysis

Chi-square test was used to compare the proportion of the demographic characteristics of the two groups. Stratified Cox proportional hazards models were used to assess the associations between NB-UVB phototherapy and each event. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study population

This study included patients with ≥100 phototherapy sessions (phototherapy group, n = 3,229) and <3 phototherapy sessions (no phototherapy group, n = 9,687), in which covariables with age, sex, insurance type, comorbidities such as diabetes, hypertension, and hyperlipidemia were matched by 1:3 propensity score matching. Given that psoralen was not available in Korea during the study period, NB-UVB was the only type of phototherapy represented in the sample. The mean age of the patients was 52.9 ± 8.6 years, and 37.9% of patients were male in the two groups, respectively (Table 1). The inclusion and exclusion criteria and propensity score matching procedure of the study population were summarized in the flow diagram (Figure 1).

Overall risk of cardiovascular or cerebrovascular events

The overall incidence rates of cardiovascular or cerebrovascular events were 95.6 and 60.0 per 10,000 person-years in the no phototherapy and phototherapy groups, respectively. The risk of all events was significantly decreased in the phototherapy group compared with the no phototherapy group (hazard ratio [HR] 0.637, 95% confidence interval [CI] 0.523 – 0.776). (Table 2)

Risk of each cardiovascular event

The risk of cardiovascular events in the phototherapy group was significantly lower than that in the no phototherapy group (HR 0.682, 95% CI 0.495 – 0.940). Furthermore, the phototherapy group showed lower risk of IHD (HR 0.700, 95% CI 0.498 – 0.984) and MI (HR 0.508, 95% CI 0.239 – 1.081) than the no phototherapy group; however, the decreased risk of MI did not reach statistical significance, possibly due to the small number of events (Figure 2).

Risk of each cerebrovascular event

The risk of cerebrovascular events was significantly lower in the phototherapy group than that in the no phototherapy group (HR 0.601, 95% CI 0.470 – 0.769). The phototherapy group also showed lower risk of CIF (HR 0.581, 95% CI 0.448 – 0.754) and CH (HR 0.955, 95% CI 0.493 – 1.853) than the no phototherapy group (Figure 2).

Subgroup analysis by sex and age

Subgroup analysis by sex revealed decreased risk of overall risk of cardiovascular or cerebrovascular events in male (HR 0.748, 95% CI 0.548 – 1.021) and female (HR 0.574, 95% CI 0.444 – 0.743), respectively (Table 3). Subgroup analysis by age revealed decreased risk of overall risk of cardiovascular or cerebrovascular events in both patients with age of 40-59 years (HR 0.730, 95% CI 0.560 – 0.953) and patients with age of ≥60 years (HR 0.599, 95% CI 0.445 – 0.807) as well.

Discussion

In the present study, we found the significantly decreased risk of cardiovascular or cerebrovascular events (HR 0.637) in patients who underwent ≥100 NB-UVB phototherapy sessions (n = 3,229) compared with the propensity score matched no phototherapy group (n = 9,687). The phototherapy group was also associated with lower risk of cardiovascular (HR 0.682) and cerebrovascular events (HR 0.601) than the no phototherapy group, respectively. Those findings were consistent in the subgroups according to sex (male and female) or age (40-59 years and ≥60 years).

The short-term effects of UV radiation on the cardiovascular system have been investigated in a few clinical studies. One study showed that whole-body broadband UVB irradiation at suberythematous doses three times per week significantly lowered ambulatory daytime and nighttime blood pressure for 6 weeks in nine patients with mild essential hypertension.[22] In clinical studies on healthy volunteers, whole-body UVA irradiation has been shown to rapidly vasodilate the arterial vasculature and subsequently lower blood pressure via the release of nitric oxide.[23,24] In a 12-week, randomized, double-blind clinical trial of adalimumab, phototherapy, and placebo for patients with psoriasis, phototherapy decreased serum CRP, and interleukin-6, whereas it increased high-density lipoprotein-p, but not decreased metabolic markers (insulin, adiponectin, and leptin) and radiologically measured vascular inflammation.[25] However, the long-term effects of UV radiation have not been investigated. In the present study, we assumed that ≥100 phototherapy sessions represent long-term phototherapy because it usually takes more than one or two year and found that long-term phototherapy would decrease the risk of cardiovascular and cerebrovascular events in patients with vitiligo. Taken together, these findings suggest that long-term NB-UVB phototherapy could influence systemically on the cardiovascular system beyond the cutaneous effects.

Several experimental studies have investigated the mechanism of action underlying the effect of phototherapy on the cardiovascular system. An *in vitro* study showed a marked increase in nitric oxide release from human foreskin keratinocytes and microvascular endothelial cells following UVA phototherapy.[26] NB-UVB phototherapy reduced the degree of intimal hyperplasia in a carotid balloon injury rat model,[27] and UVB exposure inhibited the development of atherosclerosis via regulation of the proatherogenic T cell response in atherosclerosis-prone mice.[28] Furthermore, phototherapy has been shown to suppress the inflammatory Th1/Th17 axis[29] and decrease inflammatory markers in patients with psoriasis.[30,31] Taken together, it could be

suggested that long-term NB-UVB phototherapy influences the cardiovascular system not only reducing blood pressure via nitric oxide release from the skin, but also by inhibiting the progression of atherosclerosis via regulating the proatherogenic T cell response. However, more studies are needed to identify the mechanism of action mediating the systemic effects of UV radiation on the cardiovascular system.

Previous studies on psoriasis have shown that the use of systemic anti-inflammatory drugs decreased the risk of cardiovascular event in patients with psoriasis, and these findings were presumed to be due to alleviation of increased systemic inflammation in psoriasis.[32-35] Because most studies focused on the effects of systemic anti-inflammatory drugs, the effect of phototherapy itself on cardiovascular system was not investigated even in psoriasis, and one study revealed that patients with psoriasis who were treated with TNF inhibitors exhibited a lower risk of cardiovascular event, compared to patients with psoriasis treated with phototherapy.[36] Vitiligo patients represent a medically healthy population without increased cardiovascular or cerebrovascular risk, because the melanocyte-specific autoimmunity is hardly associated with systemic inflammation. Therefore, our study implies incidental benefits of NB-UVB phototherapy for cardiovascular disease in a general healthy population.

Another potential mechanism of the protective phototherapy on cardiovascular system includes vitamin D. Phototherapy is known to increase serum concentration of 25(OH)D3.[37-39] Vitamin D deficiency may result in enhanced susceptibility of cardiovascular diseases via pro-oxidant and pro-inflammatory mechanisms, and have an influence on endothelial function and arterial thrombogenesis.[40,41] However, there are controversies of the association between vitamin D and cardiovascular diseases. Observational studies suggest the association between low vitamin D levels and cardiovascular diseases.[42,43] Recent meta-analysis of 21 randomized clinical trials suggested that vitamin D supplementation cannot reduce cardiovascular diseases.[41]

Unexpectedly, in this study, vitiligo patients who received phototherapy were much less than those who did not, although phototherapy is the main treatment of vitiligo. Probably this is because excimer laser is preferred rather than phototherapy especially in private clinic (excimer is not regarded as phototherapy), and quite a few patients still have oriental medicine or no treatment, all of which show a real-world practice environment in Korea.

Our study has several limitations. First, the identification of diagnoses based on disease codes may have involved error. To minimize the misdiagnosis, we defined vitiligo as the recording

of four or more documented physician contacts for the condition.[44] Second, we were unable to obtain detailed disease-related information, including the subtype, extent, onset, duration of vitiligo, and dosage of phototherapy. Third, the study may have involved selection bias, as patients who underwent ≥100 phototherapy sessions could have had better general health than those who received no phototherapy, although covariables were matched between the two groups through propensity score matching. To minimize the risk of confounding, we excluded patients with organ failures including heart failure, chronic obstructive pulmonary disease, chronic kidney disease, and liver cirrhosis, and patients with cardiovascular or cerebrovascular events prior to the enrollment. However, other potential confounding factors, such as body mass index, family history, smoking, and lifestyle may have influenced our findings. Fourth, we did not assess mortality because the data was not available in the database. Finally, our results in Koreans, the known lower risk group of skin cancer, may not be generalizable to patients of other ethnicities. Potential pros and cons of long-term phototherapy can be different between ethnicities, such as risk of skin cancer, therefore necessitate further investigation. Nevertheless, our study has strengths in that all eligible patients with vitiligo in one country were included and followed up for 11 years without attrition of patient numbers.

In conclusion, long-term NB-UVB phototherapy was found to be associated with the decreased risk of cardiovascular or cerebrovascular event in patients with vitiligo in a nationwide population-based cohort study. Our findings provide clinicians and researchers with insights into the beneficial effects of UV radiation on the cardiovascular system. Furthermore, our findings may be useful for patients with vitiligo who are concerned about the systemic adverse effects of long-term NB-UVB phototherapy. Further studies in other ethnic groups are needed to confirm our findings. Further studies are needed to measure the effect of phototherapy on the atherosclerosis, by means of intima-media thickness and/or coronary artery imaging.

ACKNOWLEDGMENTS

This study was funded by the Ministry of Science, ICT & Future Planning 1`grant number: NRF-2017R1E1A1A01076780).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author Y.M.P.. The database used in this study, the Korean NIH claims database, can be assessed by permission.

AUTHOR CONTRIBUTIONS

Drs J.M.B. and Y.M.P had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Conceptualization and design: J.M.B, Y.M.P.;

Acquisition: J.M.B.

Analysis and interpretation of data: All authors;

Drafting of the manuscript: J.M.B., Y.S.K., Y.M.P.

Critical revision of the manuscript of important intellectual content: All authors

Statistical anlaysis: J.M.B.

Obtained funding: J.M.B.

Administrative, technical or material support: J.M.B., Y.M.P.

Supervision: J.M.B., Y.M.P.

References

1. Ezzedine K, Eleftheriadou V, Whitton M, et al. Vitiligo. Lancet 2015;386:74-84.
2. Lee H, Lee MH, Lee DY, et al. Prevalence of vitiligo and associated comorbidities in Korea. Yonsei Med J 2015;56:719-25.
3. Bae JM, Jung HM, Hong BY, et al. Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. JAMA Dermatol 2017;153:666-74.
4. Goldstein NB, Koster MI, Hoaglin LG, et al. Narrow Band Ultraviolet B Treatment for Human Vitiligo Is Associated with Proliferation, Migration, and Differentiation of Melanocyte Precursors. J Invest Dermatol 2015;135:2068-76.
5. Lee CH, Wu SB, Hong CH, et al. Molecular Mechanisms of UV-Induced Apoptosis and Its Effects on Skin Residential Cells: The Implication in UV-Based Phototherapy. Int J Mol Sci 2013;14:6414-35.
6. Rodrigues M, Ezzedine K, Hamzavi I, et al. Current and emerging treatments for vitiligo. J Am Acad Dermatol 2017;77:17-29.
7. Felsten LM, Alikhan A, Petronic-Rosic V. Vitiligo: a comprehensive overview Part II: treatment options and approach to treatment. J Am Acad Dermatol 2011;65:493-514.
8. Zhang P, Wu MX. A clinical review of phototherapy for psoriasis. Lasers Med Sci 2018;33:173-80.
9. Feelisch M, Kolb-Bachofen V, Liu D, et al. Is sunlight good for our heart? Eur Heart J 2010;31:1041-5.
10. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension 1997;30:150-6.
11. Kloner RA, Poole WK, Perritt RL. When throughout the year is coronary death most likely to occur? A 12-year population-based analysis of more than 220 000 cases. Circulation 1999;100:1630-4.
12. Brennan PJ, Greenberg G, Miall WE, et al. Seasonal variation in arterial blood pressure. Br Med J (Clin Res Ed) 1982;285:919-23.
13. Baldassarre D, Nyyssonen K, Rauramaa R, et al. Cross-sectional analysis of baseline data to identify the major determinants of carotid intima-media thickness in a European population: the IMPROVE study. Eur Heart J 2010;31:614-22.
14. Scragg R. Seasonality of cardiovascular disease mortality and the possible protective effect

of ultra-violet radiation. Int J Epidemiol 1981;10:337-41.
15. Scragg R, Rahman J, Thornley S. Association of sun and UV exposure with blood pressure and cardiovascular disease: A systematic review. J Steroid Biochem Mol Biol 2019;187:68-75.
16. Kent ST, Cushman M, Howard G, et al. Sunlight exposure and cardiovascular risk factors in the REGARDS study: a cross-sectional split-sample analysis. BMC Neurol 2014;14:133.
17. Lindqvist PG, Epstein E, Landin-Olsson M, et al. Avoidance of sun exposure is a risk factor for all-cause mortality: results from the Melanoma in Southern Sweden cohort. J Intern Med 2014;276:77-86.
18. Kent ST, McClure LA, Judd SE, et al. Short- and long-term sunlight radiation and stroke incidence. Ann Neurol 2013;73:32-7.
19. Lee YH, Han K, Ko SH, et al. Data Analytic Process of a Nationwide Population-Based Study Using National Health Information Database Established by National Health Insurance Service. Diabetes Metab J 2016;40:79-82.
20. Park TH, Choi JC. Validation of Stroke and Thrombolytic Therapy in Korean National Health Insurance Claim Data. J Clin Neurol 2016;12:42-8.
21. Kimm H, Yun JE, Lee SH, et al. Validity of the diagnosis of acute myocardial infarction in korean national medical health insurance claims data: the korean heart study (1). Korean Circ J 2012;42:10-5.
22. Krause R, Buhring M, Hopfenmuller W, et al. Ultraviolet B and blood pressure. Lancet 1998;352:709-10.
23. Oplander C, Volkmar CM, Paunel-Gorgulu A, et al. Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from intracutaneous photolabile nitric oxide derivates. Circ Res 2009;105:1031-40.
24. Liu D, Fernandez BO, Hamilton A, et al. UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. J Invest Dermatol 2014;134:1839-46.
25. Mehta NN, Shin DB, Joshi AA, et al. Effect of 2 Psoriasis Treatments on Vascular Inflammation and Novel Inflammatory Cardiovascular Biomarkers: A Randomized Placebo-Controlled Trial. Circ Cardiovasc Imaging 2018;11:e007394.
26. Holliman G, Lowe D, Cohen H, et al. Ultraviolet Radiation-Induced Production of Nitric

Oxide:A multi-cell and multi-donor analysis. Sci Rep 2017;7:11105.
27. Kohyama S, Morimoto Y, Nakai K, et al. Effectiveness of narrow-band ultraviolet-B phototherapy for prevention of intimal hyperplasia in a rat carotid balloon injury model. Lasers Surg Med 2007;39:659-66.
28. Sasaki N, Yamashita T, Kasahara K, et al. UVB Exposure Prevents Atherosclerosis by Regulating Immunoinflammatory Responses. Arterioscler Thromb Vasc Biol 2017;37:66-74.
29. Buhl T, Schon MP. Peeking into immunoregulatory effects of phototherapy. Exp Dermatol 2016;25:511-2.
30. Kawashima K, Torii K, Furuhashi T, et al. Phototherapy reduces serum resistin levels in psoriasis patients. Photodermatol Photoimmunol Photomed 2011;27:152-5.
31. Romani J, Caixas A, Carrascosa JM, et al. Effect of narrowband ultraviolet B therapy on inflammatory markers and body fat composition in moderate to severe psoriasis. Br J Dermatol 2012;166:1237-44.
32. Ahlehoff O, Skov L, Gislason G, et al. Cardiovascular outcomes and systemic anti-inflammatory drugs in patients with severe psoriasis: 5-year follow-up of a Danish nationwide cohort. J Eur Acad Dermatol Venereol 2015;29:1128-34.
33. Hjuler KF, Bottcher M, Vestergaard C, et al. Association Between Changes in Coronary Artery Disease Progression and Treatment With Biologic Agents for Severe Psoriasis. JAMA Dermatol 2016;152:1114-21.
34. Wu JJ, Joshi AA, Reddy SP, et al. Anti-inflammatory therapy with tumour necrosis factor inhibitors is associated with reduced risk of major adverse cardiovascular events in psoriasis. J Eur Acad Dermatol Venereol 2018;32:1320-6.
35. Fernandez-Armenteros JM, Gomez-Arbones X, Buti-Soler M, et al. Psoriasis, metabolic syndrome and cardiovascular risk factors. A population-based study. J Eur Acad Dermatol Venereol 2019;33:128-35.
36. Wu JJ, Sundaram M, Cloutier M, et al. The risk of cardiovascular events in psoriasis patients treated with tumor necrosis factor-α inhibitors versus phototherapy: An observational cohort study. J Am Acad Dermatol 2018;79:60-8.
37. Feldmeyer L, Shojaati G, Spanaus KS, et al. Phototherapy with UVB narrowband, UVA/UVBnb, and UVA1 differentially impacts serum 25-hydroxyvitamin-D3. J Am Acad

Dermatol 2013;69:530-6.
38. Weinhold A, Obeid R, Vogt T, et al. Prospective Investigation of 25(OH)D3 Serum Concentration Following UVB Narrow Band Phototherapy in Patients with Psoriasis and Atopic Dermatitis. Anticancer Res 2016;36:1439-44.
39. Simonsen S, Bonefeld CM, Thyssen JP, et al. Increase in Vitamin D but not Regulatory T Cells following Ultraviolet B Phototherapy of Patients with Atopic Dermatitis. Acta Derm Venereol 2019;99:139-45.
40. Kim HA, Perrelli A, Ragni A, et al. Vitamin D Deficiency and the Risk of Cerebrovascular Disease. Antioxidants (Basel) 2020;9.
41. Barbarawi M, Kheiri B, Zayed Y, et al. Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83 000 Individuals in 21 Randomized Clinical Trials: A Meta-analysis. JAMA Cardiol 2019;4:765-76.
42. Kim DH, Sabour S, Sagar UN, et al. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). Am J Cardiol 2008;102:1540-4.
43. Pekkanen MP, Ukkola O, Hedberg P, et al. Serum 25-hydroxyvitamin D is associated with major cardiovascular risk factors and cardiac structure and function in patients with coronary artery disease. Nutr Metab Cardiovasc Dis 2015;25:471-8.
44. Bae JM, Lee JH, Yun JS, et al. Vitiligo and overt thyroid diseases: A nationwide population-based study in Korea. J Am Acad Dermatol 2017;76:871-8.

Figure legends

Figure 1. Flow diagram of inclusion and exclusion criteria of study population and 1:3 propensity score matching. Heart failure (HF); chronic obstructive pulmonary disease (COPD); chronic kidney disease (CKD); and liver cirrhosis (LC); ischemic heart disease (IHD); myocardial infarction (MI); cerebral infarction (CIF); cerebral hemorrhage (CH).

Figure 2. Incidence rates (per 10,000 person-years) with 95% confidence interval (CI) of the cardiovascular or cerebrovascular events in the narrowband ultraviolet B phototherapy groups (≥100) and no phototherapy groups, and forest plots of hazard ratios with 95% CI between them.

Table 1. Characteristics of the study population

	No phototherapy group, N (%)	Phototherapy group, N (%)	*P*-Value
Total	9,687 (100%)	3,229 (100.0%)	
Age (Mean ± SD)	52.9 ±8.6	52.9 ±8.6	1.0000
(Median [IQR])	51.0 (46.0-59.0)	51.0 (46.0-59.0)	
40-49	4,023 (41.5%)	1,341 (41.5%)	
50-59	3,405 (35.2%)	1,135 (35.2%)	
60-69	1,902 (19.6%)	634 (19.6%)	
70-79	351 (3.6%)	117 (3.6%)	
80-	6 (0.1%)	2 (0.1%)	
Sex			1.0000
Male	3,672 (37.9%)	1,224 (37.9%)	
Female	6,015 (62.1%)	2,005 (62.1%)	
NB-UVB sessions[1]			
100-199		2,001 (62.0%)	
200-399		943 (29.2%)	
400-599		220 (6.8%)	
600-799		50 (1.5%)	
800-		15 (0.5%)	
Insurance type			1.0000
Health insurance	9,258 (95.6%)	3,086 (95.6%)	
Medical aid	429 (4.4%)	143 (4.4%)	
Comorbidity			
Diabetes mellitus	1,227 (12.7%)	409 (12.7%)	1.0000
Hypertension	3,504 (36.2%)	1,168 (36.2%)	1.0000
Hyperlipidemia	2,697 (27.8%)	899 (27.8%)	1.0000

NB-UVB, narrowband ultraviolet B; SD, standard deviation

Table 2. Risk of cardiovascular or cerebrovascular events in vitiligo patients with no phototherapy and ≥100 sessions of narrowband ultraviolet B phototherapy

	Incidence rate[1] (95% CI)	Events (n)	Patients (n)	Person-years	Hazard ratio (95% CI)	*P*-value
All events						
No phototherapy	95.6 (87.4-104.2)	507	9,687	53,059	Reference	
Phototherapy (≥100)	60 (49.8-71.7)	122	3,229	20,329	0.637 (0.523–0.776)	< 0.0001
Cardiovascular events						
No phototherapy	33.8 (29.1-39.0)	184	9,687	54,458	Reference	
Phototherapy (≥100)	22.7 (16.7-30.2)	47	3,229	20,705	0.682 (0.495–0.940)	0.0192
Cerebrovascular events						
No phototherapy	64.2 (57.6-71.3)	345	9,687	53,754	Reference	
Phototherapy (≥100)	38.0 (30.0–47.4)	78	3,229	20,526	0.601 (0.470–0.769)	< 0.0001
Ischemic heart disease						
No phototherapy	29.3 (25.0-34.2)	160	9,687	54,572	Reference	
Phototherapy (≥100)	20.3 (14.6-27.4)	42	3,229	20,729	0.700 (0.498-0.984)	0.0399
Myocardial infarction						
No phototherapy	7.8 (5.7-10.5)	43	9,687	55,035	Reference	
Phototherapy (≥100)	3.8 (1.7-7.6)	8	3,229	20,876	0.508 (0.239-1.081)	0.0787
Cerebrovascular infarction						
No phototherapy	58.7 (52.4-65.5)	316	9,687	53,876	Reference	
Phototherapy (≥100)	33.6 (26.1-42.5)	69	3,229	20,565	0.581 (0.448-0.754)	< 0.0001
Cerebrovascular hemorrhage						
No phototherapy	6.0 (4.1-8.4)	33	9,687	55,086	Reference	

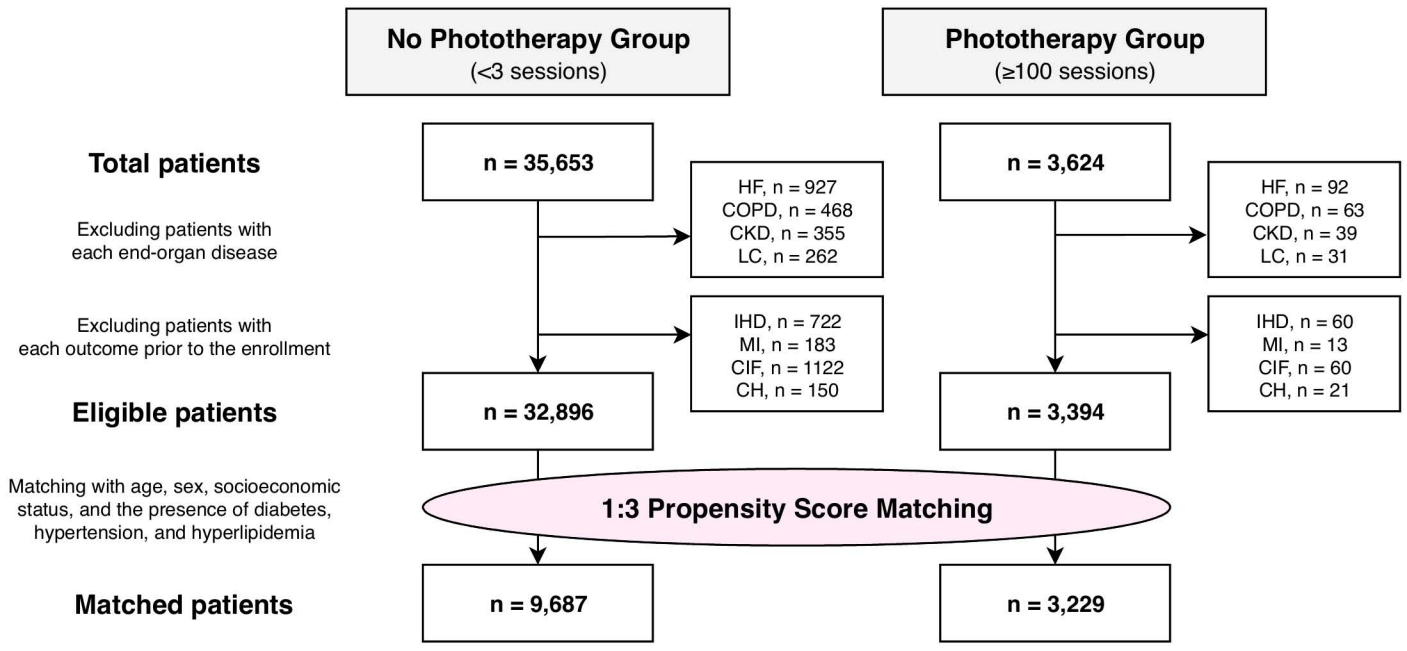
Phototherapy (≥100)	5.8 (3.0-10.0)	12	3,229	20,858	0.955 (0.493-1.853)	0.8923

[1]Incidence rate per 10,000 person-years. CI, confidence level; HR, hazard ratio.

Table 3. Subgroup analysis according to the sex and age

	Male		Female		40-59 years		60- years	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
All events								
No phototherapy	Reference		Reference		Reference		Reference	
Phototherapy (≥100)	0.748 (0.548-1.021)	0.0672	0.574 (0.444-0.743)	<0.0001	0.730 (0.560-0.953)	0.0206	0.599 (0.445-0.807)	0.0007
Cardiovascular events								
No phototherapy	Reference		Reference		Reference		Reference	
Phototherapy (≥100)	0.780 (0.495-1.228)	0.2829	0.603 (0.384-0.949)	0.0289	0.675 (0.445-1.024)	0.0645	0.758 (0.459-1.251)	0.2779
Cerebrovascular events								
No phototherapy	Reference		Reference		Reference		Reference	
Phototherapy (≥100)	0.691 (0.456-1.047)	0.0811	0.560 (0.412-0.759)	0.0002	0.764 (0.545-1.070)	0.1174	0.523 (0.363-0.753)	0.0005
Ischemic heart disease								
No phototherapy	Reference		Reference		Reference		Reference	
Phototherapy (≥100)	0.799 (0.491-1.300)	0.3660	0.624 (0.387-1.004)	0.0517	0.659 (0.420-1.033)	0.0688	0.831 (0.494-1.398)	0.4853
Myocardial infarction								
No phototherapy	Reference		Reference		Reference		Reference	
Phototherapy (≥100)	0.571 (0.218-1.498)	0.2552	0.430 (0.127-1.454)	0.1746	0.728 (0.315-1.684)	0.4586	0.182 (0.024-1.363)	0.0972
Cerebrovascular infarction								
No phototherapy	Reference		Reference		Reference		Reference	
Phototherapy (≥100)	0.624 (0.396-0.983)	0.0421	0.560 (0.407-0.770)	0.0004	0.720 (0.499-1.037)	0.0776	0.529 (0.364-0.771)	0.0009
Cerebrovascular hemorrhage								
No phototherapy	Reference		Reference		Reference		Reference	
Phototherapy (≥100)	1.563 (0.615-3.973)	0.3477	0.617 (0.232-1.641)	0.3335	1.040 (0.453-2.385)	0.9265	0.879 (0.289-2.677)	0.8209

CI, confidence level; HR, hazard ratio.


No Phototherapy Group
(<3 sessions)
Phototherapy Group
(≥100 sessions)
Total patients
n = 35,653
n = 3,624
HF, n = 927
COPD, n = 468
CKD, n = 355
LC, n = 262
HF, n = 92
COPD, n = 63
CKD, n = 39
LC, n = 31
Excluding patients with each end-organ disease
Excluding patients with each outcome prior to the enrollment
IHD, n = 722
MI, n = 183
CIF, n = 1122
CH, n = 150
IHD, n = 60
MI, n = 13
CIF, n = 60
CH, n = 21
Eligible patients
n = 32,896
n = 3,394
Matching with age, sex, socioeconomic status, and the presence of diabetes, hypertension, and hyperlipidemia
1:3 Propensity Score Matching
Matched patients
n = 9,687
n = 3,229

All events	No phototherapy	Phototherapy (≥100)	Hazard ratio (95% CI)
Male	88.4 (76.1–102.2)	65.4 (48.7–86)	0.748 (0.548–1.021)
Female	100.1 (89.5–111.6)	56.6 (44.2–71.4)	0.574 (0.444–0.743)
40–59 yrs	61.1 (53.6–69.2)	43.9 (34.3–55.5)	0.730 (0.560–0.953)
≥60 yrs	199.1 (175.8–224.6)	118.2 (88.3–155)	0.599 (0.445–0.807)
Total	**95.6 (87.4–104.2)**	**60.0 (49.8–71.7)**	**0.637 (0.523–0.776)**

Cardiovascular events	No phototherapy	Phototherapy (≥100)	Hazard ratio (95% CI)
Male	39.3 (31.3–48.7)	30.2 (19.4–45)	0.780 (0.495–1.228)
Female	30.3 (24.7–36.8)	18.0 (11.4–27)	0.603 (0.384–0.949)
40–59 yrs	26.0 (21.3–31.5)	17.4 (11.5–25.1)	0.675 (0.445–1.024)
≥60 yrs	56.0 (44.4–69.8)	41.6 (25–64.9)	0.758 (0.459–1.251)
Total	**33.8 (29.1–39)**	**22.7 (16.7–30.2)**	**0.682 (0.495–0.940)**

Cerebrovascular events	No phototherapy	Phototherapy (≥100)	Hazard ratio (95% CI)
Male	51.9 (42.6–62.6)	35.4 (23.6–51.2)	0.691 (0.456–1.047)
Female	72.1 (63.2–81.9)	39.6 (29.4–52.2)	0.560 (0.412–0.759)
40–59 yrs	36.6 (30.9–43)	27.4 (19.9–36.8)	0.764 (0.545–1.070)
≥60 yrs	146.2 (126.6–168.1)	76.0 (52.6–106.2)	0.523 (0.363–0.753)
Total	**64.2 (57.6–71.3)**	**38.0 (30–47.4)**	**0.601 (0.470–0.769)**

Ischemic heart disease	No phototherapy	Phototherapy (≥100)	Hazard ratio (95% CI)
Male	33.6 (26.2–42.3)	26.4 (16.3–40.4)	0.799 (0.491–1.300)
Female	26.6 (21.4–32.8)	16.4 (10.2–25.1)	0.624 (0.387–1.004)
40–59 yrs	22.8 (18.3–27.9)	14.9 (9.5–22.1)	0.659 (0.420–1.033)
≥60 yrs	48.1 (37.3–60.9)	39.3 (23.3–62.2)	0.831 (0.494–1.398)
Total	**29.3 (25–34.2)**	**20.3 (14.6–27.4)**	**0.700 (0.498–0.984)**

Myocardial infarction	No phototherapy	Phototherapy (≥100)	Hazard ratio (95% CI)
Male	11.2 (7.2–16.7)	6.2 (2–14.6)	0.571 (0.218–1.498)
Female	5.6 (3.4–8.8)	2.3 (0.5–6.8)	0.430 (0.127–1.454)
40–59 yrs	6.1 (4–9.1)	4.3 (1.7–8.9)	0.728 (0.315–1.684)
≥60 yrs	12.6 (7.4–19.8)	2.2 (0.1–12)	0.182 (0.024–1.363)
Total	**7.8 (5.7–10.5)**	**3.8 (1.7–7.6)**	**0.508 (0.239–1.081)**

Cerebrovascular infarction	No phototherapy	Phototherapy (≥100)	Hazard ratio (95% CI)
Male	47.0 (38.2–57.2)	29.0 (18.4–43.6)	0.624 (0.396–0.983)
Female	66.1 (57.6–75.5)	36.4 (26.6–48.5)	0.560 (0.407–0.770)
40–59 yrs	32.5 (27.2–38.6)	23.0 (16.2–31.7)	0.720 (0.499–1.037)
≥60 yrs	136.0 (117.1–157.1)	71.4 (48.8–100.8)	0.529 (0.364–0.771)
Total	**58.7 (52.4–65.5)**	**33.6 (26.1–42.5)**	**0.581 (0.448–0.754)**

Cerebrovascular hemorrhage	No phototherapy	Phototherapy (≥100)	Hazard ratio (95% CI)
Male	5.6 (2.9–9.8)	8.7 (3.5–18)	1.563 (0.615–3.973)
Female	6.2 (3.9–9.5)	3.9 (1.3–9.1)	0.617 (0.232–1.641)
40–59 yrs	4.7 (2.8–7.3)	4.9 (2.1–9.7)	1.040 (0.453–2.385)
≥60 yrs	9.8 (5.3–16.4)	8.6 (2.4–22.1)	0.879 (0.289–2.677)
Total	**6.0 (4.1–8.4)**	**5.8 (3–10)**	**0.955 (0.493–1.853)**