Br J Dermatol 2024; **190**:680–688
https://doi.org/10.1093/bjd/ljad472
Advance access publication date: 28 November 2023

BJD
British Journal of Dermatology
Epidemiology

The association between serum 25-hydroxyvitamin D levels and psoriasis in a large population-based cohort: a cross-sectional analysis of The Tromsø Study 2015–16

Marita Jenssen,[1,2] Anne-Sofie Furberg,[3,4] Rolf Jorde,[5] Tom Wilsgaard[2] and Kjersti Danielsen[1,2]

[1]Department of Dermatology; and [3]Department of Microbiology and Infection Control University Hospital of North Norway, Tromsø, Norway
[2]Department of Community Medicine; and [5]Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway
[4]Faculty of Health Sciences and Social Care, Molde University College, Molde, Norway
Correspondence: Marita Jenssen. E-mail: marita.jenssen@unn.no

Linked Article: Näslund-Koch and Skov *Br J Dermatol* 2024; **190**:611–612.

Abstract

Background Case–control studies indicate an association between lower serum 25-hydroxyvitamin D [25(OH)D] levels and psoriasis. Data from larger population-based cohorts including mild cases are sparse.

Objectives To investigate the association between 25(OH)D and psoriasis in a large population-based cohort, and assess possible effect modification by overweight.

Methods Data from the Tromsø Study 2015–16 (Tromsø7), which included 19 520 participants from the general population aged 40–79 years, were subjected to a cross-sectional analysis. We assessed the shapes of the relationships between 25(OH)D and psoriasis using fractional polynomials. Odds ratios (ORs) for lifetime and active psoriasis were estimated using logistic regression. Adjusted models included month of blood sampling, body mass index (BMI), age and sex. Two-way and additive interaction between BMI and 25(OH)D were explored.

Results From a total of 19 520 participants [10 203 women (52.3%); mean age 56.3 years (SD 10.4); mean 25[OH]D, 63.4 nmol L^{-1} (SD 21.9)], 2088 (10.7%) reported lifetime psoriasis and 1179 (6.0%) reported active psoriasis the past 12 months. There was no association between 25(OH)D and lifetime psoriasis [OR per 10 nmol L^{-1} increase in 25(OH)D 1.02, 95% confidence interval (CI) 0.99–1.04]. The relationship between 25(OH)D and active psoriasis was suggested to be nonlinear, but the model was not significant ($P = 0.098$). There was evidence for a superadditive effect (i.e. larger than the sum of the factors) of BMI > 27.5 kg m^{-2} and 25(OH)D < 25 nmol L^{-1} on the odds for active psoriasis (OR 1.92, 95% CI 1.18–3.12), but not for lifetime psoriasis (OR 1.41, 95% CI 0.93–2.15). There was no evidence for two-way interaction between BMI and 25(OH)D.

Conclusions This large population-based study found no significant relationship between 25(OH)D and psoriasis. The analysis may have been underpowered to detect a threshold effect in the lower 25(OH)D spectrum. Interaction analysis indicates that high BMI and vitamin D deficiency combined increase the odds of active psoriasis more than the sum of these factors, with an estimated 92% higher odds for active psoriasis in participants with BMI > 27.5 kg m^{-2} and 25(OH)D < 25 nmol L^{-1}. Providing advice to prevent vitamin D deficiency may be considered in the follow-up of overweight patients with psoriasis.

What is already known about this topic?

- Association between lower 25-hydroxyvitamin D [25(OH)D] levels and psoriasis has been found in case–control studies in hospital settings.
- Evidence from larger population-based cohorts including the whole spectrum of psoriasis cases are sparse.

What does this study add?

- This large population-based study found no significant relationship between 25(OH)D levels and psoriasis. The analysis may have been underpowered to detect a threshold effect in the lower 25(OH)D spectrum.
- Having the combination of body mass index > 27.5 kg m^{-2} and 25(OH)D < 25 nmol L^{-1} increased the odds of active psoriasis more than the sum of these factors, yielding 92% higher odds for active psoriasis.

Accepted: 20 November 2023

Psoriasis is a chronic relapsing immune-mediated inflammatory skin disease.[1] It is estimated to affect 2–4% of adults in Western countries, but prevalence varies between populations and geographical locations.[2] Lifetime prevalence as high as 11% has been reported in Northern Norway.[3] Differences in lifestyle and environmental exposures, such as sunlight, may contribute to the variation in psoriasis prevalence.[2,3]

Vitamin D (vitD) is produced in the skin when exposed to sunlight,[4] and has several effects of importance to skin physiology.[5] Its regulatory effects on the immune system, and on keratinocyte proliferation and maturation, are of particular relevance to psoriasis.[5–7] We utilize these effects in psoriasis treatment when prescribing topical vitD analogues.[1]

Serum 25-hydroxyvitamin D [25(OH)D] is used to evaluate an individual's vitD status.[4] Overweight is associated with both low 25(OH)D levels[4] and higher odds for psoriasis.[8] Association between lower 25(OH)D levels and psoriasis has been reported in small case–control studies from highly selected populations, and after adjustment for body mass index (BMI).[6,7] Data from population-based cohorts are sparse; one North American population-based study found no association between psoriasis and 25(OH)D.[9] Recently, two studies have suggested a nonlinear relationship between 25(OH)D and psoriasis, in addition to effect modification by body composition (central obesity and BMI).[10,11] A favourable response of oral vitD in patients with psoriasis has been described in open trials and case reports,[12–15] but results from randomized clinical trials are inconsistent.[16–21]

Most psoriasis cases are mild and treated by general practitioners. To provide more informed advice regarding follow-up on vitD status in this large patient group, there is a need for more data that includes the whole spectrum of patients with psoriasis. In the present study, we aimed to investigate the association between 25(OH)D and psoriasis in the population-based Tromsø Study, and explore possible effect modification by body composition/overweight, sex and age. We hypothesized that lower 25(OH)D levels are associated with psoriasis, also after adjustment for body composition. We further hypothesized that the association is modified by body composition; specifically, that being overweight will strengthen the association.

Materials and methods

Participants and setting

The Tromsø Study is a single-centre, multipurpose, population-based study with repeated high-quality health surveys of inhabitants of the municipality of Tromsø, Norway. The design and cohort profile have been previously described in detail.[22,23] In this cross-sectional study, we used data from the seventh survey (Tromsø7), conducted from March 2015 to October 2016. Everyone in the municipality aged $\geq$40 years (a total of 32 591 individuals) was invited, of whom 21 083 attended (65%).[23] Data on health, disease and lifestyle were collected using two general questionnaires, and trained personnel performed blood sampling and clinical measurements using standardized procedures.[22]

We excluded participants aged $>$79 years (n=761), those with missing data on self-reported psoriasis (n=578), missing 25(OH)D (n=142) or BMI measurements (n=46), and pregnant women (n=36). This left 19 520 participants (10 203 women, 9317 men) who were included in the present study (Figure S1; see Supporting Information).

Ethics and reporting

Our study was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (REC North 2016/1790). All participants gave written informed consent. We report our findings in accordance with the STROBE guideline.[24]

Psoriasis case definition

Lifetime psoriasis was defined by answering 'Yes' to the question, 'Do you have, or have you ever had psoriasis?' The question has been acceptably validated in the Norwegian population.[25] Active psoriasis was defined by answering 'Yes' to the question, 'If you have, or have had psoriasis, have you had a psoriasis rash within the last 12 months?'

25-hydroxyvitamin D measurements

Nonfasting blood samples were analysed consecutively by the Department of Laboratory Medicine, University Hospital of North Norway. For serum 25(OH)D an in-house liquid chromatography–tandem mass spectrometry method was used, which detects both 25(OH)D_3 and 25(OH)D_2.[26] The sum of these measurements is presented as 25(OH)D in the Results section. The laboratory takes part in the external Vitamin D External Quality Assessment Scheme (DEQAS) programme.

Strata of 25(OH)D levels were made based on the current guideline from the Institutes of Medicine and the Endocrine Society;[27] 25(OH)D $<$ 25 nmol L^{-1} was defined as 'deficient', 25–50 nmol L^{-1} was defined as 'insufficient', and $>$ 50 nmol L^{-1} was defined as 'sufficient'. Grouped data are presented using five 25(OH)D groups ($<$ 25, 25–49, 50–74, 75–99 and $\geq$ 100).

Other measurements

Age is reported in years, as recorded on 31 December 2015. We defined four age groups (40–49, 50–59, 60–69 and 70–79 years).

Weight and height were measured with participants wearing light clothing and no shoes.[23] BMI was calculated as weight in kilograms divided by height in metres squared. Grouped data are presented according to current World Health Organization (WHO) thresholds,[28] and dichotomized based on the WHO proposed threshold for public health action (BMI $>$ 27.5).[29] Hip and waist circumference were measured using a measuring tape at the level of the umbilicus and greater trochanters, respectively.[23]

Body composition was assessed using whole-body dual-energy X-ray absorptiometry (DEXA) (GE Lunar Prodigy, GE Healthcare, Oslo, Norway) in a subsample of 3670 participants (Appendix S2.5; see Supporting Information).[23]

Smoking and solar exposure were assessed using the following questions: 'Do you/did you smoke daily? – Yes,

currently/Yes, previously/No'; 'Do you use a solarium? – Yes, weekly/Yes, sometimes/Never'; 'Have you been on holiday in the sun during the last two months? – Yes/No'.

VitD supplements use was assessed with the following three questions: (i) 'Do you use cod liver oil or cod liver oil capsules?'; (ii) 'Do you use omega 3 capsules (fish oil, seal oil)?' and (iii) 'Do you use vitamin supplement with vitD? – Daily/Daily during winter/Sometimes/Never'. A participant was defined as a 'Supplement user' if they answered 'Daily' or 'Daily during winter' to one or more of the vitD supplement questions.

Statistical analysis

Basic characteristics are presented as mean and standard deviation (SD) for continuous variables, and as number and percentages for categorical variables. Logistic regression analysis was applied to assess the association between 25(OH)D and psoriasis. The outcome was lifetime or active psoriasis (binary). The predictor was measured 25(OH)D (continuous). To adjust for seasonal variation in 25(OH)D, all models included month of blood sampling as indicator variables for each month, with January as reference. As a sensitivity analysis, we used 25(OH)D *z*-scores as an alternative approach to seasonal adjustment. The *z*-scores were calculated separately for each month [*z*-score = measured 25(OH)D − month mean 25(OH)D/SD of the month mean].

We used fractional polynomials (FP) to find the model which best described the shape of the 25(OH)D–psoriasis relationship. FPs assess 44 models using 8 powers in 1 term or combined in 2 terms. We evaluated model fit using Akaike information criteria. 25(OH)D was transformed in accordance with the powers from the best-fitted model, and thereafter used in a standard logit model. The association between 25(OH)D and psoriasis in this best-fitted model was tested with a standard Wald test with one or two degrees of freedom. In models that included transformed 25(OH)D, odds ratio (OR) estimates were calculated using a 25(OH)D level of 50 nmol L^{-1} as reference.

Before selecting variables to include in adjusted models, we developed Direct Acyclic Graphs (DAGs)[30] (Figure S2; see Supporting Information). BMI (continuous), age (continuous) and sex were considered to be possible confounders, and included as covariates. Recent sunny holiday, solarium use and use of vitD supplements are obvious 'parents' of 25(OH)D in the DAG, but their relationship with psoriasis is more complex. As the outcome might affect vitD supplement use/sun habits, we found it unreasonable to include these as covariates. To evaluate their influence on the 25(OH)D–psoriasis relationship, we repeated the main analyses in the subgroup of participants who neither used supplements nor solarium nor reported recent sunny holiday (hereafter referred to as the nonsupplement subgroup) as a sensitivity analysis.

We explored two-way interactions between 25(OH)D and BMI, age and sex by assessing the significance of cross-product terms in the logit models. We assessed additive interaction between 25(OH)D and BMI using four groups based on dichotomized 25(OH)D ($\geq$ or $<$ 25 nmol L^{-1}) and BMI ($>$ or $\leq$ 27.5), and estimated OR for psoriasis using 25(OH)D $\geq$ 25 + BMI $\leq$ 27.5 as reference group.

We performed the analyses using SPSS version 28.0, and Stata version 17.0 for the FP models. All analyses were done two-sided and were reported using a 95% confidence interval (CI).

Results

Self-reported psoriasis prevalence and basic characteristics

Among 19 520 participants (52.3% of whom were women) with mean age 56.3 years (SD 10.4), 2088 (10.7%) reported lifetime psoriasis and 1179 (6.0%) reported active psoriasis in the past 12 months (Table 1). Participants with psoriasis had higher average age, BMI, hip and waist circumference, total body fat percentage, and reported more sedentary activity during leisure time compared with participants without psoriasis (Table 1). Participants with psoriasis also reported smoking, solarium use and taking omega-3 capsules and oral vitD supplements daily or daily during winter more often than those without psoriasis (Table 1).

25-hydroxyvitamin D levels

Overall mean 25(OH)D was 63.4 nmol L^{-1} (SD 21.9). There was no difference in mean 25(OH)D between participants with or without psoriasis. Mean 25(OH)D was lower in current smokers, younger age groups, higher BMI groups, men and in those with completed college/university degree. Higher average 25(OH)D levels were observed when participants reported sunny holidays in the last 2 months, use of solarium and vitD supplements, and in samples taken during summer and autumn (Table S1; see Supporting Information). These observations did not differ between participants with or without psoriasis.

The prevalence of vitD deficiency [25(OH)D $<$ 25 nmol L^{-1}] and insufficiency ($<$ 50 nmol L^{-1}) was equal between participants with and without psoriasis (Table 1).

Association between 25-hydroxyvitamin D and psoriasis

When assessing the relationship between 25(OH)D and lifetime psoriasis using FPs, the best-fitted model included 25(OH)D as a linear term. We found no association between measured 25(OH)D and lifetime psoriasis in either unadjusted or adjusted models (Table 2).

When assessing the relationship between 25(OH)D and active psoriasis, the two-term model including 25(OH)D raised to the power of −1 and 1 had the best fit. The model suggests a U-shaped relationship between 25(OH)D levels and active psoriasis, with increasing OR for active psoriasis when 25(OH)D is $<$ 25 nmol L^{-1} or $>$ 150 nmol L^{-1} ($P = 0.008$) (Figure 1a, Table 3). This first FP model was largely affected by the participants with highest 25(OH)D levels, where reverse causation is a likely explanation for the observed association (e.g. caused by phototherapy or large supplement doses). Therefore, we refitted the model after excluding participants with 25(OH)D $>$ 150 nmol L^{-1} (21 nonpsoriasis participants, 4 participants with active psoriasis). This changed the best-fitting model to the one-term model including 25(OH)D raised to the power of −2; however, this model did not show a

Table 1 Characteristics of the participants ($n = 19\,520$). The Tromsø Study 2015–16

	No psoriasis	Lifetime psoriasis[a]	Active psoriasis[b]
Number of participants	17 432 (89.3)	2088 (10.7)	1179 (6.0)
Age (years), mean (SD)	56.2 (10.4)	57.3 (10.2)	57.1 (10.3)
Age groups (years)			
40–49	5618 (32.2)	575 (27.5)	331 (28.1)
50–59	5202 (29.8)	602 (28.8)	348 (29.5)
60–69	4356 (25.0)	625 (29.9)	333 (28.2)
70–79	2256 (12.9)	286 (13.7)	167 (14.2)
Sex			
Female	9129 (52.4)	1074 (51.4)	598 (50.7)
Male	8303 (47.6)	1014 (48.6)	581 (49.3)
College/university education	8789 (50.4)	939 (45.0)	504 (42.7)
25(OH)D (nmol L^{-1}), mean (SD)	63.3 (21.9)	63.8 (22.4)	63.9 (23.2)
25(OH)D groups (nmol L^{-1})			
< 25	361 (2.1)	41 (2.0)	28 (2.4)
25–49	4603 (26.4)	564 (27.0)	321 (27.2)
50–74	7691 (44.1)	881 (42.2)	490 (41.6)
75–99	3811 (21.9)	488 (23.4)	269 (22.8)
≥ 100	966 (5.5)	114 (5.5)	71 (6.0)
BMI (kg m^{-2}), mean (SD)	27.3 (4.5)	28.0 (4.8)	28.3 (5.0)
BMI groups (kg m^{-2})			
≤ 24.9	5730 (32.9)	557 (26.7)	291 (24.7)
25–29.9	7592 (43.6)	931 (44.6)	523 (44.4)
30–34.9	3098 (17.8)	432 (20.7)	262 (22.2)
35–39.9	773 (4.4)	133 (6.4)	79 (6.7)
≥ 40	2439 (1.4)	35 (1.7)	24 (2.0)
Hip circumference (cm), mean (SD)	103.9 (8.5)	104.7 (8.9)	105.0 (9.2)
Waist circumference (cm), mean (SD)	94.9 (13.0)	97.2 (13.2)	98.1 (13.5)
Total body fat percentage,[c] mean (SD)	34.9 (9.1)	36.0 (8.6)	36.6 (8.2)
Use cod liver oil or cod liver oil capsules[d]	4160 (24.9)	468 (23.5)	257 (22.8)
Use omega 3 capsules[e]	4168 (24.9)	551 (27.4)	327 (28.6)
Use vitD supplements[f]	3610 (21.5)	478 (23.8)	271 (23.9)
Sunny vacation during the past 2 months	3188 (18.4)	383 (18.5)	207 (17.6)
Use solarium			
Yes, weekly	42 (0.2)	9 (0.4)	5 (0.4)
Yes, sometimes	3356 (19.3)	451 (21.7)	262 (22.3)
Never	13983 (80.4)	1623 (77.9)	909 (77.3)
Physical activity leisure time			
Reading, watching TV/screen or other sedentary activity?	2319 (13.7)	323 (16.0)	212 (18.6)
Walking, cycling or other forms of exercise at least 4 h a week?	9881 (58.2)	1176 (58.3)	658 (57.8)
Participation in recreational sports, heavy gardening, snow shovelling, etc. at least 4 h a week?	4223 (24.9)	462 (22.9)	241 (21.2)
Participation in hard training or sports competitions, regularly several times a week?	542 (3.2)	57 (2.8)	28 (2.5)
Smoking			
Current	2376 (13.7)	357 (17.2)	219 (18.7)
Former	7474 (43.2)	1083 (52.3)	615 (52.6)
Never	7441 (43.0)	632 (30.5)	336 (28.7)

25(OH)D, serum 25-hydroxyvitamin D; BMI, body mass index. [a]Lifetime psoriasis was defined by answering 'Yes' to the question 'Do you have, or have you ever had, the skin disease psoriasis?' [b]Active psoriasis was defined by answering 'Yes' to the question 'Do you have, or have you had, psoriasis rash the last 12 months?' Missing value = 12 participants. [c]In total, 3347 participants in our cohort attended a Dual-energy X-ray absorptiometry scan (3159 nonactive psoriasis, 187 active psoriasis). [d]Reported use of cod liver oil daily or daily during winter season. [e]Reported use of omega 3 capsules daily or daily during winter season. [f]Reported use of vitamin D supplements daily or daily during winter season. Continuous variables are provided as mean (SD) and categorical variables are provided as *n* (%). Number of participants may vary owing to missing values.

Table 2 Odds ratios (ORs) for reporting lifetime psoriasis per 10 nmol L^{-1} increase in serum 25(OH)D level (2088 participants with psoriasis, 17 432 nonpsoriasis participants). The Tromsø Study 2015–16

Predictor	OR (95% CI) (unadjusted)[a]	*P*-values	OR (95% CI) (adjusted)[b]	*P*-values	OR (95% CI) (adjusted)[c]	*P*-values
25(OH)D, per 10 nmol L^{-1} increase	1.01 (0.99–1.04)	0.17	1.00 (0.98–1.03)	0.80	1.02 (0.99–1.04)	0.18
Age, per 10 years increase			1.10 (1.05–1.15)	< 0.001	1.09 (1.05–1.15)	< 0.001
Sex (male)			1.04 (0.95–1.14)	0.43	1.01 (0.92–1.11)	0.76
BMI, per 5 kg m^{-2} increase					1.19 (1.13–1.25)	< 0.001

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval. [a]Logistic regression model. All models included month of blood sampling. [b]Adjusted for age and sex. [c]Adjusted for age, sex and BMI.

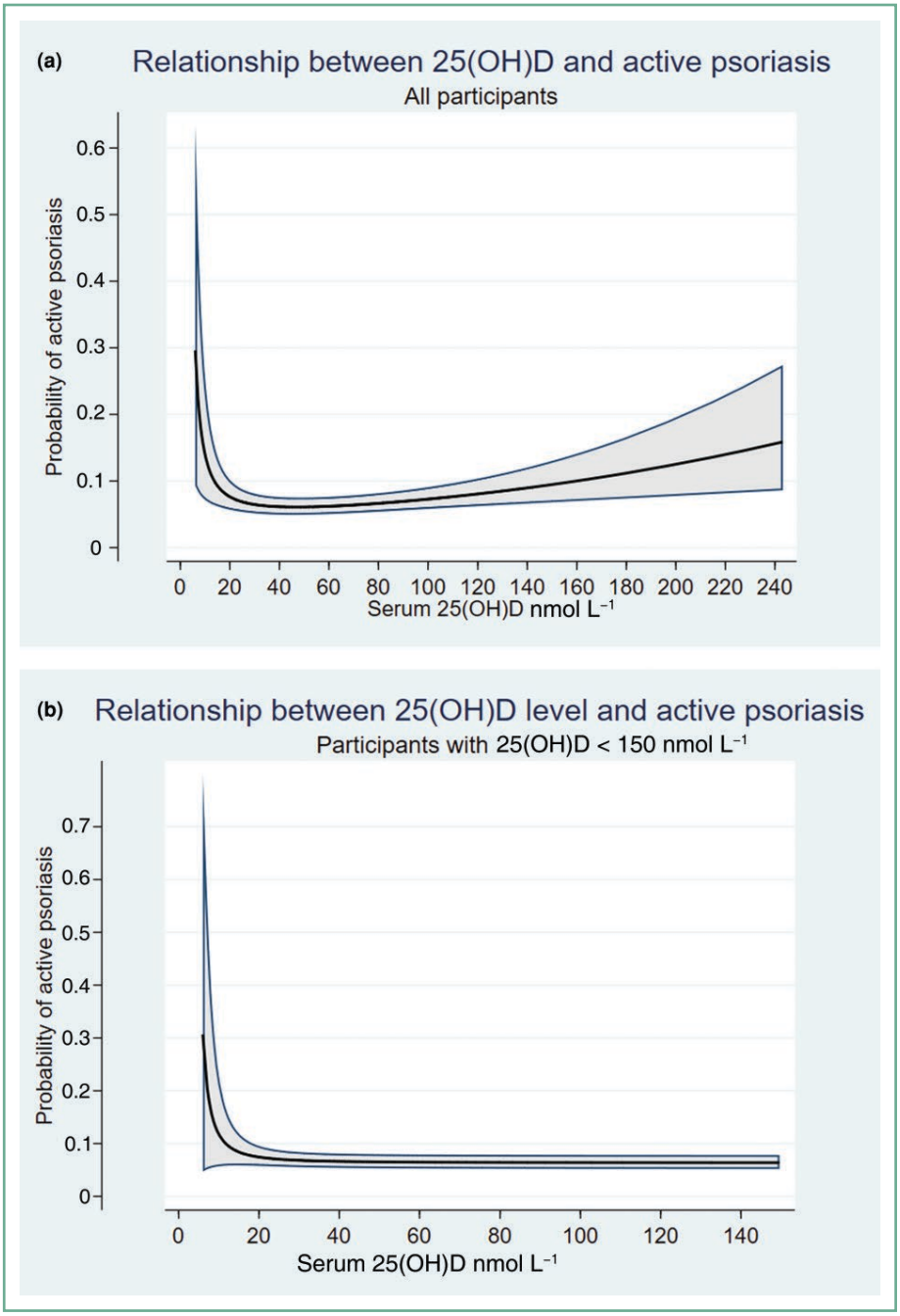

Figure 1 Nonlinear relationship between 25-hydroxyvitamin D [25(OH)D] levels and active psoriasis. Both models are adjusted for month of blood sampling, body mass index (BMI), age and sex. The Tromsø Study 2015–16.(a) Two-term model including 25(OH)D raised to the power of −1 and 1 (1179 participants with active psoriasis, 17 432 nonpsoriasis participants) ($P=0.008$). (b) One-term model including 25(OH)D raised to the power of −2 (1175 participants with active psoriasis, 17 411 nonpsoriasis participants) ($P=0.098$). Participants with 25(OH)D > 150 nmol L^{-1} excluded.

statistically significant result ($P=0.098$) (Figure 1b, Table 3). Using different thresholds for 25(OH)D (e.g. 120 nmol L^{-1} or 140 nmol L^{-1}) gave the same finding.

Effect modification

We found no evidence for two-way interaction between 25(OH)D and BMI, 25(OH)D and age or 25(OH)D and sex, in either the model for lifetime psoriasis or active psoriasis. We found evidence for a superadditive effect (i.e. larger than the sum of the factors) of BMI > 27.5 and 25(OH)D < 25 nmol L^{-1} on the odds for active psoriasis (OR 1.92, 95% CI 1.18–3.12), but not for lifetime psoriasis (OR 1.41, 95% CI 0.93–2.15) (Figure 2, Table 4). Relative excess risk owing to interaction and synergy index are not estimated, as these are unsuitable when ORs are < 1 in any of the groups.[31]

Sensitivity analyses

Recoding missing psoriasis to nonpsoriasis did not alter the result from the regression analyses (data not shown). It had minimal effect on the prevalence estimate, which

Table 3 Odds ratios (ORs) for active psoriasis as a function of serum 25(OH)D.[a] The Tromsø Study 2015–16

25(OH)D level (nmol L^{-1})		Number of participants[b]		Two-term model (FP −1, 1)[c]		One-term model (FP −2)[d]	
				Unadjusted	Adjusted[e]	Unadjusted	Adjusted[e]
Point value	Interval	Nonpsoriasis	Active psoriasis	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]
10	6.0–15.0	29	6	2.74 (1.34–5.58)	2.48 (1.20–5.15)	2.09 (0.97–4.49)	1.91 (0.88–4.11)
20	15.1–25.0	341	23	1.33 (1.06–1.68)	1.27 (1.00–1.61)	1.17 (0.99–1.39)	1.15 (0.97–1.36)
30	25.1–40.0	2097	135	1.09 (1.00–1.19)	1.06 (0.97–1.17)	1.06 (1.00–1.12)	1.05 (0.99–1.11)
50	40.1–62.5	6465	420	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
75	62.6–87.5	6228	429	1.05 (0.98–1.12)	1.07 (1.00–1.15)	0.98 (0.97–1.00)	0.99 (0.97–1.00)
100	87.6–125.0	2125	150	1.15 (1.00–1.33)	1.20 (1.04–1.40)	0.98 (0.95–1.00)	0.98 (0.96–1.00)
150	125.1–175.0	143	15	1.47 (1.07–2.04)	1.61 (1.15–2.25)	NA	NA
200	175.1–243.2	4	1	1.94 (1.16–3.25)	2.20 (1.29–3.75)	NA	NA

25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; FP, fractional polynomials; NA, not applicable. [a]Calculated at the given point value. [b]Number of participants in each 25(OH)D level interval. [c]Two-term model including 25(OH)D raised to the power of −1 and 1 (1179 participants with active psoriasis, 17 432 nonpsoriasis participants). [d]One-term model including 25(OH)D raised to the power of −2 (1175 participants with active psoriasis, 17 411 nonpsoriasis participants). Participants with 25(OH)D > 150 nmol L^{-1} were excluded. [e]Adjusted for body mass index, age and sex. All models include month of blood sampling.

was reduced from 10.6% to 10.3% (Appendix S2.1; see Supporting Information).

Repeating the main analyses in the nonsupplement subgroup (n = 6517, 685 of whom reported lifetime psoriasis and 381 reported active psoriasis) had minimal effect on the results (Appendix S2.3, Tables S2, S3, Figure S3; see Supporting Information).

Seasonal adjustment using 25(OH)D z-scores had minimal impact on the findings (Appendix S2.4, Table S4, Figure S4; see Supporting Information).

In participants with an available DEXA scan (n = 3670), we compared models including total body fat percentage or BMI as adjustment for body composition. The OR estimates for the association between 25(OH)D and psoriasis were unchanged between the models, indicating that BMI gives a valid adjustment for body composition in the main analyses (Appendix S2.5, Tables S5, S6, Figure S5; see Supporting Information).

Discussion

In this large population-based sample, we could not find a significant relationship between 25(OH)D and psoriasis. The limited number of participants in the lower 25(OH)D spectrum may have prevented us from detecting a potential threshold effect. We did observe a superadditive effect of vitD deficiency and high BMI on the odds for active

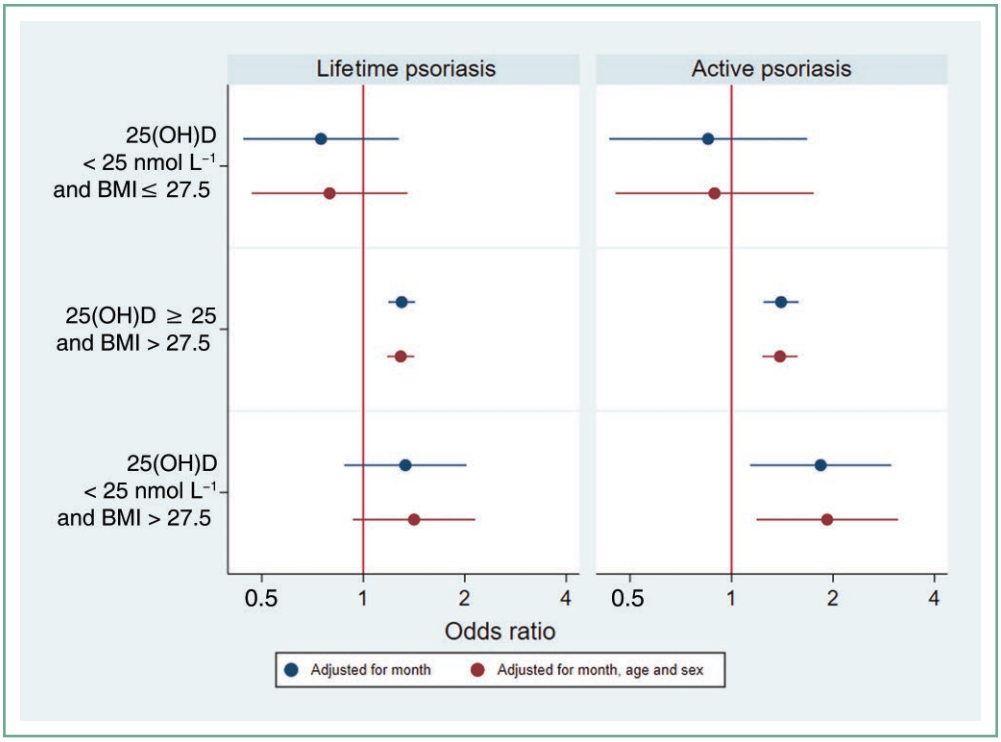

Figure 2 Odds ratio estimates for psoriasis in groups based on dichotomized body mass index (BMI) and 25-hydroxyvitamin D [25(OH)D] levels. Reference group BMI < 27.5 kg m^{-2} and 25(OH)D > 25 nmol L^{-1}. The Tromsø Study 2015–16.

Table 4 ORs for psoriasis in groups based on dichotomized BMI and 25(OH)D levels. The Tromsø Study 2015–16

						OR estimates for lifetime psoriasis ($n = 19\,520$)		OR estimates for active psoriasis ($n = 18\,611$)	
	BMI > 27.5	25(OH)D < 25	Nonpsoriasis ($n = 17\,432$)	Lifetime psoriasis ($n = 2088$)	Active psoriasis ($n = 1179$)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Single effects	–	No	17071	2047	1151	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	–	Yes	361	41	28	0.92 (0.66–1.28)	0.98 (0.70–1.36)	1.14 (0.77–1.69)	1.20 (0.81–1.78)
	No	–	10090	1069	580	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	Yes	–	7342	1019	599	1.30 (1.19–1.43)	1.30 (1.18–1.42)	1.42 (1.26–1.59)	1.41 (1.25–1.58)
Combined effects	No	No	9907	1054	571	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	No	Yes	183	15	9	0.75 (0.44–1.27)	0.79 (0.47–1.35)	0.85 (0.43–1.68)	0.89 (0.45–1.75)
	Yes	No	7164	993	580	1.30 (1.19–1.42)	1.29 (1.18–1.42)	1.40 (1.25–1.58)	1.39 (1.23–1.57)
	Yes	Yes	178	26	19	1.33 (0.88–2.02)	1.41 (0.93–2.15)	1.84 (1.14–2.98)	1.92 (1.18–3.12)

BMI, body mass index; CI, confidence interval; OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D. [a]Adjusted for age and sex. All models include month of blood sampling.

psoriasis, yielding an estimated 92% higher odds in those who had 25(OH)D < 25 nmol L^{-1} and BMI > 27.5 compared with those who had 25(OH)D > 25 nmol L^{-1} and BMI < 27.5. The result was statistically significant, but should be interpreted with caution, as we had few cases in this subgroup.

So far, only a few studies have investigated the possible nonlinear relationship between 25(OH)D and psoriasis (i.e. possible threshold effects). A recent study using data from the UK Biobank (UKB) suggests such a nonlinear relationship.[10] However, the findings were not supported by a Mendelian randomization (MR) study from the same cohort.[32] A recently published Danish population-based study found no evidence of a nonlinear relationship between 25(OH)D and moderate-to-severe psoriasis.[33] However, like our study, they also had few cases with 25(OH)D levels < 25 nmol L^{-1}. Methodological differences, including different psoriasis outcome classifications, may explain the contradictory findings. Further research is needed to clarify a potential dose–response relationship between 25(OH)D and psoriasis.

Psoriasis was strongly associated with BMI and body fat percentage in our sample, in agreement with previous literature.[34] The evidence regarding a possible interaction between 25(OH)D and overweight in relation to psoriasis is limited. Two recent studies give some support to an effect modification by body composition (central obesity and BMI);[10,11] however, the mechanisms that could bring about this effect are not known. Obesity associated low-grade inflammation has been linked to psoriasis,[8,34,35] and vitD deficiency may contribute to the proinflammatory state in obesity.[35] Thus, we consider it plausible that the two factors may act synergistically in driving inflammation. Our findings suggest that vitD deficiency may be linked to active psoriasis. Overweight individuals have increased odds for both psoriasis and vitD deficiency,[4,8] and our findings indicate that the two factors combined increase the odds of active psoriasis more than the sum of these factors.

The prevalence of vitD deficiency and insufficiency was low in our sample overall, and was not increased among participants with psoriasis. This finding is in line with two other population-based studies,[9,33] but is in contrast with most data from hospital-based case–control studies.[7] Hospital-based studies may be affected by selection bias, as they generally include participants with more extensive disease and possibly more comorbidities.

Some limitations to our study warrant discussion. We found no association between lifetime psoriasis and 25(OH)D, neither overall nor in interaction analysis. It is more plausible that current 25(OH)D is associated with psoriasis activity rather than past or inactive disease, considering the effects of vitD on the immune system and keratinocytes.[6,7] Our active psoriasis question has a 12-month recall period, which is not ideal. However, a high correlation between 25(OH)D measurements taken a year apart has been demonstrated.[36] Therefore, we consider it reasonable to use a point measurement to infer relationship with disease activity over the past year. That said, we would have preferred a more precise measurement of current disease activity/severity, which also would have enabled us to evaluate possible effect modification by severity. Based on a previous study from the sixth Tromsø Study, also utilizing prescription data,[37] and the results from the validation study discussed below,[25] we can assume that most participants with psoriasis in our sample have mild disease.[37]

Self-reported lifetime psoriasis, using the same question as in Tromsø7, has been acceptably validated in the Norwegian population (sensitivity 54%, specificity 99%).[25] The low sensitivity was mainly explained by unrecognized scalp psoriasis.[25] In light of this, a considerable amount of psoriasis cases may be misclassified as nonpsoriasis in our sample, but the number of false-positive cases can be assumed to be low. Therefore, the prevalence of lifetime psoriasis in our sample is probably an underestimation of the true prevalence in the population. The active psoriasis question has not been formally validated, but is only answered by those who confirm lifetime psoriasis. However, we cannot exclude that some misclassification of other dermatological conditions (i.e. false-positive active psoriasis) can occur in participants who had coexisting skin diseases. The expected misclassification of both lifetime and active psoriasis cases can be assumed to be unaffected by 25(OH)D levels (i.e. nondifferential in relation to the exposure), and may possibly bias the estimated ORs in our study towards the null.[38]

Cohort studies tend to recruit the healthiest in the population.[22,39] Consequently, underestimation of average BMI/body fat percentage and overestimation of average 25(OH)D are likely to be present in our study. If this affects participants with and without psoriasis equally, relative differences will not be affected. However, physical impairment caused by comorbid diseases (which are more prevalent among patients with psoriasis),[40] and hesitation to expose skin lesions, may affect attendance and cause

underrepresentation of individuals with psoriasis, which can further attenuate the association.

Our first model for active psoriasis suggests higher odds for active psoriasis in those with 25(OH)D > 150 nmol L^{-1}. We do not believe that 25(OH)D levels in the high normal range (150–200 nmol L^{-1}), increase risk for active psoriasis. Rather, reverse causality because of recent phototherapy [which typically results in 25(OH)D at the high normal range][41] or high vitD supplement doses, may be a more likely explanation for this finding. As only 25 participants had 25(OH)D > 150 (4 active psoriasis, 21 nonpsoriasis), and they had a large effect on the model overall, we decided to model the relationship after excluding these outliers. The second model suggests a threshold with higher odds for active psoriasis at very low 25(OH)D levels (< 20 nmol L^{-1}); however, this finding was not statistically significant.

When using a cross-sectional design we cannot exclude the possibility that reverse causality could have an effect on our findings. However, some evidence of the temporal relationship can be found in previous studies, supporting the view that that 25(OH)D may be of importance for psoriasis development. One prospective study, using data from UKB, found an increased hazard for incident psoriasis in participants who were vitD deficient (25[OH]D < 25 nmol L^{-1}) compared with those whose vitD levels were sufficient (> 50 nmol L^{-1}).[10] Two recently published MR studies have demonstrated a causal relationship between genetically predicted lower 25(OH)D and psoriasis.[10,42] However, a third MR study did not find such a relationship.[43] Another MR study, which investigated the effect of genetically predicted psoriasis on 25(OH)D levels, found that reversed causality is unlikely.[44] A recent American randomized clinical trial suggested a preventive effect of vitD supplements on autoimmune disease in general.[45] The study included few psoriasis cases, and no clear evidence for prevention of psoriasis was demonstrated. We have recently found that vitD supplements did not affect psoriasis severity through winter in mild cases with low 25(OH)D.[21]

Our study has several strengths. It compiles a large, population-based sample, where the invitation of whole birth cohort minimizes the risk of selection bias. An attendance proportion of 65% is acceptable to assume good representativeness of the general population aged 40–79 years. Seasonal variation in 25(OH)D was accounted for using two different approaches, yielding approximately the same results. 25(OH)D measurement error was minimized using a validated liquid chromatography–mass spectrometry method. Our data also included thorough measures of relevant confounders. We used a flexible FP model to evaluate the shape of the 25(OH)D–psoriasis relationship, and assessed relevant effect modification by overweight. Sensitivity analyses, including restricting analysis to the nonsupplement subgroup, did not alter our findings.

In this population-based study we could not find a significant relationship between 25(OH)D and psoriasis. The analysis may have been underpowered to detect a threshold effect in the lower 25(OH)D spectrum. Interaction analysis indicates that high BMI and vitD deficiency combined increase the odds of active psoriasis more than the sum of these factors, with an estimated 92% increased odds for active psoriasis in participants with BMI > 27.5 and 25(OH)D < 25 nmol L^{-1}. Providing advice to prevent vitD deficiency may be considered in the follow-up of overweight patients with psoriasis.

Acknowledgements

We want to thank the participants and staff of the seventh survey of the Tromsø Study. The authors acknowledge support from the Northern Norway Regional Health Authority for providing grants for this research (grant number HNF1361-17).

Funding sources

M.J., K.D. and A.-S. F. have received research grants from Northern Norway Regional Health Authority [grant number HNF1361-17 (M.J.) and SFP1167-14 (K.D., A.-S.F.] and the Odd Berg Medical Research Foundation (M.J., K.D.). The funders were not involved in the design or conduct of the study; nor in the collection, management, analysis and interpretation of the data; nor in the preparation, review or approval of the manuscript; nor in the decision to submit the manuscript for publication.

Conflicts of interest

K.D. reports having served as a consultant, lecturer and participating in sponsored events/meetings by Novartis, AbbVie, LEO Pharma, UCB Pharma, Almirall, Meda Pharma, Bristol Myers Squibb, Galderma and Celgene. The other authors declare no conflicts of interest.

Data availability

Data may be obtained from a third party and are not publicly available. The legal restrictions on data availability are set by the Tromsø Study Data and Publication Committee in order to control for data sharing, including publication of datasets with the potential of reverse identification of deidentified sensitive participant information. However, the data can be obtained from the Tromsø Study upon application to the Tromsø Study Data and Publication Committee.

Ethics statement

All participants gave written informed consent prior to study participation. The study was approved by the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics, North Norway.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

References

1 Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA* 2020; **323**:1945–60.
2 Parisi R, Iskandar IYK, Kontopantelis E *et al.* National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. *BMJ* 2020; **369**:m1590.

3 Danielsen K, Olsen A, Wilsgaard T, Furberg AS. Is the prevalence of psoriasis increasing? A 30-year follow-up of a population-based cohort. *Br J Dermatol* 2013; **168**:1303–10.
4 Holick MF, Binkley NC, Bischoff-Ferrari HA *et al.* Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**:1911–30.
5 Umar M, Sastry KS, Al Ali F *et al.* Vitamin D and the pathophysiology of inflammatory skin diseases. *Skin Pharmacol Physiol* 2018; **31**:74–86.
6 Barrea L, Savanelli MC, Di Somma C *et al.* Vitamin D and its role in psoriasis: an overview of the dermatologist and nutritionist. *Rev Endocr Metab Disord* 2017; **18**:195–205.
7 Hambly R, Kirby B. The relevance of serum vitamin D in psoriasis: a review. *Arch Dermatol Res* 2017; **309**:499–517.
8 Paroutoglou K, Papadavid E, Christodoulatos GS, Dalamaga M. Deciphering the association between psoriasis and obesity: current evidence and treatment considerations. *Current Obes Rep* 2020; **9**:165–78.
9 Wilson PB. Serum 25-hydroxyvitamin D status in individuals with psoriasis in the general population. *Endocrine* 2013; **44**:537–9.
10 Zhang Y, Jing D, Zhou G *et al.* Evidence of a causal relationship between vitamin D status and risk of psoriasis from the UK Biobank study. *Front Nutr* 2022; **9**:807344.
11 Kuang Y, Xiao Y, Fang Z *et al.* Association of serum vitamin D with psoriasis and effect modification by central obesity. *Front Med (Lausanne)* 2020; **7**:236.
12 Finamor DC, Sinigaglia-Coimbra R, Neves LCM *et al.* A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis. *Dermatoendocrinol* 2013; **5**:222–34.
13 Mahtani R, Nair PM. Daily oral vitamin D3 without concomitant therapy in the management of psoriasis: a case series. *Clin Immunol Commun* 2022; **2**:17–22.
14 Morimoto S, Kumahara Y. A patient with psoriasis cured by 1 alpha-hydroxyvitamin D3. *Med J Osaka Univ* 1985; **35**:51–4.
15 Morimoto S, Yoshikawa K, Kozuka T *et al.* Treatment of psoriasis vulgaris by oral administration of 1α-hydroxyvitamin D3—open-design study. *Calcif Tissue Int* 1986; **39**:209–12.
16 Theodoridis X, Grammatikopoulou MG, Stamouli E-M *et al.* Effectiveness of oral vitamin D supplementation in lessening disease severity among patients with psoriasis: a systematic review and meta-analysis of randomized controlled trials. *Nutrition* 2021; **82**:111024.
17 Charoenngam N, Holick MF. Immunologic effects of vitamin D on human health and disease. *Nutrients* 2020; **12**:2097.
18 Jarrett P, Camargo CA, Coomarasamy C, Scragg R. A randomized, double-blind, placebo-controlled trial of the effect of monthly vitamin D supplementation in mild psoriasis. *J Dermatolog Treat* 2018; **29**:324–8.
19 Ingram MA, Jones MB, Stonehouse W *et al.* Oral vitamin D3 supplementation for chronic plaque psoriasis: a randomized, double-blind, placebo-controlled trial. *J Dermatolog Treat* 2018; **29**:648–57.
20 Disphanurat W, Viarasilpa W, Chakkavittumrong P, Pongcharoen P. The clinical effect of oral vitamin D2 supplementation on psoriasis: a double-blind, randomized, placebo-controlled study. *Dermatol Res Pract* 2019; 2019:**5237642**.
21 Jenssen M, Furberg A-S, Jorde R *et al.* Effect of vitamin D supplementation on psoriasis severity in patients with lower-range serum 25-hydroxyvitamin d levels: a randomized clinical trial. *JAMA Dermatol* 2023; **159**:518–25.
22 Jacobsen BK, Eggen AE, Mathiesen EB *et al.* Cohort profile: the Tromsø Study. *Int J Epidemiol* 2011; **41**:961–7.
23 Hopstock LA, Grimsgaard S, Johansen H *et al.* The seventh survey of the Tromsø Study (Tromsø7) 2015–2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. *Scand J Public Health* 2022; **50**:919–29.
24 von Elm E, Altman DG, Egger M *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007; **335**:806–8.
25 Modalsli EH, Snekvik I, Åsvold BO *et al.* Validity of self-reported psoriasis in a general population: The HUNT Study, Norway. *J Invest Dermatol* 2016; **136**:323–5.
26 Grimnes G, Almaas B, Eggen AE *et al.* Effect of smoking on the serum levels of 25-hydroxyvitamin D depends on the assay employed. *Eur J Endocrinol* 2010; **163**:339–48.
27 Pludowski P, Holick MF, Grant WB *et al.* Vitamin D supplementation guidelines. *J Steroid Biochem* 2018; **175**:125–35.
28 World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000: **894**:i–xii, 1–253.
29 WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; **363**:157–63.
30 Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008; **8**:70.
31 Knol MJ, VanderWeele TJ, Groenwold RH *et al.* Estimating measures of interaction on an additive scale for preventive exposures. *Eur J Epidemiol* 2011; **26**:433–8.
32 Zhao SS, Mason A, Gjekmarkaj E *et al.* Associations between vitamin D and autoimmune diseases: Mendelian randomization analysis. *Semin Arthritis Rheum* 2023; https://doi.org/10.1016/j.semarthrit.2023.152238
33 Näslund-Koch C, Vedel-Krogh S, Bojesen SE, Skov L. Plasma vitamin D is not associated with moderate-to-severe psoriasis: results from Danish general population studies. *J Invest Dermatol* 2023; **143**:2068–71.
34 Jensen P, Skov L. Psoriasis and obesity. *Dermatology* 2016; **232**:633–9.
35 Todosenko N, Vulf M, Yurova K *et al.* Causal links between hypovitaminosis D and dysregulation of the T cell connection of immunity associated with obesity and concomitant pathologies. *Biomedicines* 2021; **9**:1750.
36 Jorde R, Sneve M, Hutchinson M *et al.* Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population-based study and during 12 months in an intervention study. *Am J Epidemiol* 2010; **171**:903–8.
37 Danielsen K, Wilsgaard T, Olsen AO *et al.* Elevated odds of metabolic syndrome in psoriasis: a population-based study of age and sex differences. *Br J Dermatol* 2015; **172**:419–27.
38 Rothman KJ, Lash TL, VanderWeele TJ, Haneuse S. *Modern Epidemiology*, 4th edn. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins, 2021.
39 Langhammer A, Krokstad S, Romundstad P *et al.* The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med Res Methodol* 2012; **12**:143.
40 Takeshita J, Grewal S, Langan SM *et al.* Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol* 2017; **76**:377–90.
41 Ryan C, Moran B, McKenna MJ *et al.* The effect of narrowband UV-B treatment for psoriasis on vitamin D status during wintertime in Ireland. *Arch Dermatol* 2010; **146**:836–42.
42 Zhao SS, Mason A, Gjekmarkaj E *et al.* Associations between vitamin D and autoimmune diseases: Mendelian randomization analysis. *Semin Arthritis Rheum* 2023; **62**:152238.
43 Bohmann P, Stein MJ, Konzok J *et al.* Relationship between genetically proxied vitamin D and psoriasis risk: a Mendelian randomization study. *Clin Exp Dermatol* 2023; **48**:642–7.
44 Drodge DR, Budu-Aggrey A, Paternoster L. Causal analysis shows evidence of atopic dermatitis leading to an increase in vitamin D levels. *J Invest Dermatol* 2021; **141**:1339–41.
45 Hahn J, Cook NR, Alexander EK *et al.* Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ* 2022; **376**:e066452.