Lifetime Sunburn Trajectories and Risk of Cutaneous Melanoma and Squamous Cell Carcinoma

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Question: What are the lifetime trajectories of sunburns among Norwegian women, and how do these relate to subsequent risk of cutaneous melanoma and squamous cell carcinoma?

Findings: In this prospective cohort study, we identified five classes of lifetime sunburn trajectories, in line with health behaviors generally observed in people. We found that trajectories with high sunburn frequencies in childhood and throughout life increased both melanoma and cSCC risks in Norwegian women.

Meaning: Lifetime trajectories of sunburns were identified for the first time, and the findings provide supporting evidence that avoiding sunburns throughout life, in particular in childhood, is crucial.

ABSTRACT (345/350 words)

Importance: No study has prospectively investigated sunburn patterns over age periods from childhood to adulthood, and their associations with skin cancer risk.

Objective: To identify lifetime trajectories of sunburns, and compare the association between these trajectories and subsequent risk of cutaneous melanoma and squamous cell carcinoma (cSCC).

Design: Norwegian Women and Cancer Study, established in 1991, with follow-up through 2018.

Setting: Population-based cohort study

Participants: We included 168,553 women born 1927-1963. Baseline questionnaires were issued 1991-2007, and follow-up questionnaires every 5-7 years.

Exposures: Participants reported pigmentation factors, sunbathing vacations and indoor tanning. Annual frequencies of sunburns were reported for childhood, adolescence and adulthood.

Main Outcomes and Measures: Information on cancer diagnoses, emigration and death were obtained through linkage to the Cancer Registry of Norway, using the unique personal identification number of Norwegian citizens.

Results: We identified five classes («stable low», «low-moderate-low», «low to high», «high to low», and «stable high») of individual lifetime sunburn trajectories with similar shapes when estimated in three samples aged up to 39 (*n*=159,773), up to 49 (*n*=153,297) and up to 59 years (*n*=119,170). Mean follow-up ranged 14.3-19.5 years in the three samples, during which 1,252-1,774 women were diagnosed with incident primary melanoma and 739-871 with incident primary cSCC. With hazard ratios (HRs) and 95% confidence intervals (CIs) estimated using Cox proportional hazards model, the «stable high» and «high to low» trajectories showed significant increased melanoma and cSCC risks compared to the «stable

low» trajectory across all samples (HRs for trajectories up to 39 years for «stable high» and «high to low»: melanoma, HR=1.50, 95%CI 1.28-1.75 and HR=1.44 95%CI 1.20-1.73; cSCC, HR=1.51, 95%CI 1.22-1.87 and HR=1.47 95%CI 1.14-1.91). Other trajectories showed increased risk, although generally weaker and mainly non-significant estimates. We found no significant heterogeneity between melanoma and cSCC estimates.

Conclusion and Relevance: By studying for the first time lifetime trajectories of sunburns, we found that high sunburn frequency throughout life increases melanoma and cSCC risk. Furthermore, sunburns in childhood are especially important for subsequent risk of these skin cancers. Avoiding sunburns throughout life, in particular in childhood, is therefore crucial.

INTRODUCTION

Cutaneous melanoma (hereafter melanoma) and cutaneous squamous cell carcinoma (cSCC) continue to increase in fair-skinned populations worldwide,[1-3] and represent a substantial burden for individuals, societies and health care systems.[4-8]

While sun exposure is the main environmental cause of melanoma and cSCC, the relationships between sun exposure and these two cancers are complex and likely different. Cutaneous SCC is mainly related to cumulative (chronic, lifetime) sun exposure,[1,9] while both cumulative and intermittent sun exposure play a role in melanoma development depending on anatomic site.[10,11]

Sunburn is an inflammatory response of the skin to acute sun exposure. Studies comparing people migrating to low latitudes at different ages, found that childhood may be a susceptible phase for the harmful effects of overexposure to the sun.[12-14] During childhood, melanocytes may be more susceptible to initiation of ultraviolet radiation (UVR)-induced carcinogenesis through sunburns, thus increasing melanoma risk.[14-18] In their meta-analysis, Gandini et al[19] found higher melanoma risk for people with sunburns in childhood than for people with sunburns in adulthood, although differences between the estimates of the two groups were not significant. Later, in the meta-analysis by Dennis et al,[20] the effect estimate was highest for people with sunburns in adulthood but increased melanoma risks were also found for people with sunburns in childhood and adolescence. For cSCC, increased risk has been found after sunburns in childhood,[21-24] but not after sunburns in adulthood.[21,22] Lifetime number of sunburns is associated with both increased risk of melanoma[19,20] and cSCC[25-28]. Only one cohort study has investigated the association between sunburns and both melanoma and cSCC risks, but timing of sunburns was not assessed.[27] No study has investigated sunburn patterns over age periods from childhood to adulthood, and their associations with melanoma and cSCC, likely because of the challenges involved.[19] An individual's behavior in

relation to sunburn frequency in early life may affect future behavior,[29] including future sunburn frequency, making it difficult to relate sunburns at different ages to skin cancer risk.

To overcome these challenges, we used latent class mixed models in the large population-based Norwegian Women and Cancer (NOWAC) cohort study[30] to (i) identify lifetime sunburn trajectories, and (ii) compare the associations between these trajectories and melanoma and cSCC occurrence.

METHODS

The NOWAC cohort

In the NOWAC cohort, women were selected randomly from the Norwegian Population Register, and issued a questionnaire at study inclusion in 1991-2007.[30,31] In total, 172,472 women aged 31-70 years participated (response, 54%). First and second follow-up questionnaires were issued approximately every five years (response 80% and 79%, respectively). All women provided informed consent, and data were handled in accordance with the relevant ethical regulations. The STROBE reporting guidelines were used.[32] The study has been approved by the Regional Committees for Medical and Health Research Ethics of North Norway (2021/252094/REK Nord) and the Norwegian Centre for Research Data (2021/147992).

Annual number of sunburns

Annual number of sunburns that resulted in pain, blistering and subsequent peeling (never, 1, 2-3, 4-5, ≥6), were recorded at study inclusion for childhood (0-9 years), adolescence (10-19 years), and adulthood (≥20 years). In follow-up questionnaires, information was updated with number of sunburns since last questionnaire. Depending on the questionnaire (inclusion or follow-ups) and age at inclusion, sunburn frequencies in adulthood were recorded for age

periods of varying lengths (range, 1-26 years), and converted into 10-year periods (20-29, 30-39, 40-49 [if applicable] and 50-59 [if applicable] years).

Covariates

Annual number of weeks spent on sunbathing vacations in high and/or lower latitudes (never, 1, 2-3, 4-6, ≥7), and history of use of indoor tanning devices (never, rarely, 1, 2, 3-4 times/month, >1 time/week) were recorded for the same age periods as sunburns. We calculated the cumulative number of weeks spent on sunbathing vacations[33,34] and categorized it as none, lowest, middle, or highest tertile. Use of indoor tanning devices was categorized as never/ever. Residential ambient UVR exposure was categorized based on mean ambient UVR hours of the region of residence[35] (latitudes 70°-58°) as low (northern Norway), medium-low (central Norway), medium (south-western Norway), and highest (south-eastern Norway).[31,33] Participants reported the number of years of education (categorized as ≤10, 11-13, ≥14 years), smoking status (never, former, current), hair color (black/dark brown, brown, blond/yellow, red), untanned skin color (color scale from 1 [very fair] to 10 [very dark]; categorized as light [1-3], medium [4-5], dark [6-8], very dark [9-10]), freckling when sunbathing (no, yes), and number of asymmetrical nevi >5mm in diameter on the legs (0, 1, 2-3, 4-6, 7-12, 13-24, ≥25; categorized as 0, 1, >1). Skin reactions to acute sun exposure (brown without being red first, red, red with burning, red with burning and blistering) and chronic sun exposure (deep brown, brown, light brown, never brown) were recorded for a subsample of the cohort.

Follow-up

The cohort was linked to the Cancer Registry of Norway using the unique personal identification number of Norwegian residents ensuring complete information on cancer diagnoses and vital status (alive, emigrated, dead; before and after receiving the questionnaires), with dates of diagnosis, emigration or death, until December 31, 2018.

Melanoma and cSCC cases were identified by the *International Classification of Diseases, Seventh Revision* (ICD-7), codes 190.0-190.9 for melanoma and 191.0-191.9 for cSCC (including the ICD-O-3 morphology codes 80703, 80713, 80763, 80953, 80513, 80723, and 80743). We excluded cases with code 190.5/191.4 (perineum, perianal) because they are unrelated to UVR exposure. The Cancer Registry of Norway does not routinely record information on basal cell carcinoma.

Study sample

Of the 172,472 women who returned questionnaires, 169,768 received questions about sunburns at study inclusion (Figure 1). We excluded women with very dark skin (grades 9-10) (*n*=290), prevalent melanoma (*n*=803) or cSCC (*n*=86), and women that emigrated or died before date of questionnaire return (*n*=36), resulting in 168,553 women, born 1927-1965. Due to the wide age range at inclusion (31-71 years), and in order to use the maximum number of women with sunburn information available for four, five, and six age decades, three samples were created: sample <40, sample <50 and sample <60. For sample <40 (used for analyses of sunburn trajectories 0-39 years), we excluded women with missing sunburn information in all age decades <40 years (*n*=8,780), resulting in 159,773 women. For sample <50 (used for analyses of sunburn trajectories 0-49 years), we further excluded women with missing sunburn information in all age decades <50 years (*n*=6,476), resulting in 153,297 women. For sample <60 (used for analyses of sunburn trajectories 0-59 years), we further excluded women with missing sunburn information in all age decades <60 years (*n*=34,127), resulting in 119,170 women.

STATISTICAL ANALYSIS

We calculated the average number of annual sunburns in each age decade by converting the recorded numbers into 0, 1, 2.5, 4.5 or 7 sunburns/year, and averaging over each decade.

Classes of individual lifetime sunburn trajectories were then identified in each sample, using a latent class mixed model (LCMM).[36-38] The model assumes that the population consists of k latent classes (underlying, unobserved groups of subjects) that follow class-specific sunburn trajectories. The average lifetime sunburn trajectory in each class was modeled using a class-specific mixed model, with median age in each decade as time scale, and average annual number of sunburns in each decade as longitudinal outcome. Median age in each decade was included as a second order polynomial, and a random intercept was included allowing observations to be correlated in time (Supplementary Material 1).

The optimal number of classes of sunburn trajectories was identified based on quality of model fit (Akaike/Bayesian Information Criterion, residual plots), classification power (model entropy, posterior probabilities), and relevance of the trajectories (Supplementary Material 1). Sankey diagrams illustrate similarities of participants' classifications across the three samples (Supplementary eFigures 1-3). The association between class-membership and melanoma/cSCC risk was estimated separately for melanoma and cSCC in each of the three samples with hazard ratios (HRs) and 95% confidence intervals (CIs; robust variances) using Cox proportional hazards models. We used age as time scale and stratified by year at inclusion. We used proportional assignment to account for the classification uncertainty, allowing each participant to contribute to each class weighted according to its posterior probability of belonging to each class[39-41] (Supplementary Material 2). Adjustments were chosen based on a directed acyclic graph[42,43] (Supplementary eFigure 4) and included residential ambient UVR exposure, hair color, freckling when sunbathing and cumulative number of sunbathing vacations.

Start of follow-up (hereafter baseline) was age at reception of the last questionnaire used to create sunburn trajectories. All trajectories were estimated before baseline, and all exposure and covariate information was collected prior to cancer diagnosis. Participants

contributed with person-years of follow-up from baseline to first primary melanoma diagnosis, cSCC diagnosis, emigration, death, or end of follow-up, whichever occurred first. We censored incident cSCCs and incident melanomas in analyses of melanoma risk and cSCC risk, respectively. Two pathways have been proposed for melanoma: melanomas that arise primarily on intermittently or chronically sun exposed anatomic sites.[10] Thus, we analyzed the association between class-membership and site-specific risk of melanoma: head/neck/upper limbs (ICD-7 codes 190.0, 190.2) and trunk/lower limbs (ICD-7 codes 190.1, 190.3, 190.4, 190.7).[44] We censored incident trunk/lower limbs melanomas in analyses of head/neck/upper limbs melanoma risk, and vice versa. Heterogeneity of the HRs between melanoma and cSCC, and between melanoma sites were tested using the contrast test statistic.[45]

The LCMM handles missing sunburn information when estimating trajectories.[37] When combining the other covariates, we had up to 27% missing data (up to 17% for individual covariates, Table 1), and used multiple imputation with chained equations[46] to impute 40 data sets.

We conducted several complete-case sensitivity analyses. To investigate potential selection bias, we conducted analyses including prevalent melanomas and cSCCs. We used alternative methods for class-allocation to account for class-membership uncertainty[39,40,47] (Supplementary Material 2). Finally, we also conducted all analyses based on an alternative LCMM. For further details, and additional sensitivity analyses, see Supplementary Material 3. All tests were 2-sided and deemed to be significant at $P<0.05$. Statistical analyses were conducted using R version 3.6.1, and the lcmm package version 1.9.2.

RESULTS

Mean (SD) age at baseline was 49 (8.4) years for the 159,773 women in sample <40, 51 (6.1) years for the 153,297 women in sample <50 and 56 (3.9) years for the 119,170 women in sample <60 (Table 1). Respectively, in sample <40, sample <50 and sample <60, 1,774, 1,678 and 1,252 women were diagnosed with incident primary melanoma and 871, 854 and 739 with incident primary cSCC during a mean (SD) follow-up of 19.5 (6.5) years, 17.5 (5.5) years, and 14.3 (4.2) years. Participants in sample <60 were recruited later and less likely to never have been on sunbathing vacations; all other characteristics were similar in the three samples.

Lifetime sunburn trajectories

The best model identified five classes of sunburn trajectories from 0-39 years (sample <40): «stable low» (16.6%), «low-moderate-low» (8.3%), «low to high» (16.6%), «high to low» (13.8%), and «stable high» (44.7%) (Figure 2). Women in the «stable low» trajectory were more likely to be from northern Norway, less educated and current smokers, have darker hair and skin color, no freckles, and sunbathe less (Supplementary eTable 1). In contrast, women in the «stable high» trajectory were more likely to have lighter hair color, and more severe skin reactions to acute sun exposure.

The best model identified five classes of sunburn trajectories from 0-49 years (sample <50; Supplementary eFigure 5) and 0-59 years (sample <60; Figure 3), labelled as in sample <40 (Figure 2). Trajectories in sample <60 were somewhat different from those in samples <40 and <50, in particular the «low-moderate-low» trajectory, which started at a higher level and included a higher proportion of participants. Participant characteristics in samples <50 and <60 were distributed similarly as in sample <40 (Supplementary eTables 2 and 3).

The Sankey diagrams (Supplementary eFigures 1-3) showed that «low-moderate-low» trajectory was the class with the most dissimilarities across the samples. Posterior

probabilities of belonging to this class were in general lower than for the other classes (Supplementary Material 1).

Sunburn trajectories and skin cancer risk

Complete-case and multiple imputation analyses showed similar results, we therefore present results from multiple imputation analyses. Compared to «stable low», we found significant increased melanoma and cSCC risks for «stable high» and «high to low» trajectories. HRs were similar across samples, but strongest for sample <40 («stable high» versus «stable low» melanoma: HR=1.50, 95%CI 1.28-1.75; cSCC: HR=1.51, 95%CI 1.22-1.87; «high to low» versus «stable low» melanoma: HR=1.44, 95%CI 1.20-1.73; cSCC: HR=1.47, 95%CI 1.14-1.91). In general, compared to «stable low», no significant increased skin cancer risk was found for «low to high» or «low-moderate-low» trajectories, except for «low-moderate-low» in sample <60 (melanoma: HR=1.29, 95%CI 1.07-154, cSCC: HR=1.46, 95%CI 1.17-1.83). In all samples, and for all trajectories, effect estimates did not differ significantly between melanoma and cSCC ($0.39 \leq P_{heterogeneity} \leq 0.95$, Table 2).

Melanoma site specific analyses gave similar results as the overall analysis, and effect estimates did not differ significantly between sites ($0.13 \leq P_{heterogeneity} \leq 0.99$, Supplementary eTable 4).

Sensitivity analyses including prevalent melanomas and cSCCs, and analyses using alternative methods for class allocation (Supplementary eTables 5-7) gave similar results. Analyses using the alternative LCMM identified somewhat different trajectories, but with similar results for the associations between these trajectories and skin cancer risk (Supplementary eFigure 6 and eTable 8).

DISCUSSION

In this large, prospective cohort study of Norwegian women, we identified five classes of lifetime sunburn trajectories, with similar shapes when estimated over four (0-39 years), five (0-49 years) or six (0-59 years) decades. Women with high number of sunburns throughout life («stable high» trajectory) and high numbers in childhood but low in adulthood («high to low» trajectory) showed significant increased melanoma and cSCC risks compared to women with low numbers throughout life («stable low» trajectory). Low number of sunburns in childhood and high in adulthood («low to high» trajectory) increased melanoma and cSCC risk, although non-significantly. Finally, women with «low-moderate-low» sunburn-trajectory showed non-significant increased melanoma and cSCC risk when estimated over four and five decades and significantly increased risk when estimated over six decades.

Lifetime sunburn trajectories

To our knowledge, no previous study has yet described lifetime sunburn trajectories. The identified trajectories are in line with latent clusters of health behaviors expected in a population.[48-51] There are people who live consistently healthy or unhealthy lifestyles, represented in the «stable low» and «stable high» trajectories. However, in our study, sunburn frequencies not only depend on people's behavior but also on their phenotype and place of living.[52] This was confirmed by a larger proportion of women with fair complexion and sun-sensitive skin in the «stable high» trajectory and with women of darker complexion and from northern Norway in the «stable low» trajectory. Women with many sunburns in childhood might learn from their painful experience and protect themselves more in adulthood, resulting in «high to low» trajectories. Conversely, parents might protect their children from sunburns in childhood but not in adolescence, a phase with lower health-seeking behaviors.[53] People then become more health-conscious with age, leading to the «low-moderate-low» trajectories,[54] and the decreasing trajectories observed when estimated over six decades.

Sunburn trajectories and skin cancer risk

Similar to other studies, we found no differences in the estimates between melanoma and cSCC,[24,26,27] nor between melanoma occurring on chronically sun-exposed sites (head/neck/upper limbs) and intermittently sun-exposed sites (trunk/lower limbs).[27] Lifetime number of sunburns is associated with both skin cancers and previous studies reported effect estimates similar to ours for «stable high» trajectories (range melanoma: 1.52-2.27, cSCC: 1.40-2.40)[19,20,25-28]. Interestingly, women with «high to low» and «stable high» trajectories had similar risks of developing these skin cancers, despite a higher cumulative number of sunburns in the «stable high» trajectory. These two trajectories combined correspond to higher number of sunburns in childhood, and studies investigating childhood sunburns also found increased skin cancer risks with similar effect estimates (range melanoma: 1.63-3.20, cSCC: 1.55-2.32)[19,20,22-24] though less precision. Women with «low to high» trajectories had no significantly increased risk compared to «stable low» trajectories even though the cumulative number of sunburns was more or less the same than for «high to low» trajectories. Those findings support that childhood is a susceptible phase for harms from overexposure to the sun[12-18] and may be a driving factor for melanoma and cSCC risk in our analysis.

Previous studies could not confirm whether early-life sunburns increased melanoma risk more than later-life sunburns.[19,20] This might be because unlike the present study, melanoma risk was compared with exposure in different periods of life separately. Early-life behavior may affect later behavior, making it difficult to disentangle the direct effects on disease risk of exposure in different age periods.[29]

For cSCC, the literature suggests increased risk associated with sunburns in childhood[21-24] but not in adulthood[21,22], in line with our findings for trajectories estimated over four and five decades. However, when estimated over six decades, almost all trajectories had higher cSCC risk compared to the «stable low» trajectory indicating that repeated

sunburns over a long period of life, represent high amounts of cumulative exposure, an important cSCC risk factor.[1,9]

Limitations

We have a well-characterized cohort with no major selection bias,[55] complete follow-up and >99% of melanomas and cSCCs were morphologically verified.[56] Nonetheless, this study has limitations. Measuring sunburn is challenging, and reproducibility studies found generally lower reliability coefficients for sunburn than for other skin cancer risk factors.[57] Poor measurement can result in exposure misclassification, especially for younger age decades. All exposure information was collected before cancer diagnosis, thus misclassification is likely non-differential, limiting the potential for recall bias. Residual confounding is inevitable in observational studies. Using all information available in NOWAC, we identified potential confounders based on a directed acyclic graph, and sensitivity analyses using alternative adjustments yielded similar results.

Conclusion

We identified five latent classes of sunburn trajectories, in line with health behaviors generally observed in people. By studying for the first time lifetime sunburn trajectories, we found that high sunburn frequencies throughout life increased both melanoma and cSCC risks in Norwegian women. Importantly, the results suggest that childhood is a more susceptible phase with regard to sunburns and subsequent risk of these skin cancers. It is therefore crucial to emphasize the importance of avoiding sunburns throughout life, and in particular in childhood.

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The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Access to data and data analysis

Simon Lergenmuller had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

363

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FIGURE LEGENDS

Figure 1 Selection of participants from enrolment into the study sample, Norwegian Women and Cancer Study, 1991-2018; cSCC, cutaneous squamous cell carcinoma.

Figure 2 Estimated average lifetime trajectories of sunburns up to 39 years (sample <40, *n*=159,773). The left panel shows the estimated average trajectories of sunburn up to 39 years in the five latent classes. The right panel shows the estimated average trajectory for each class separately (bold line), with a sample of 500 observed individual trajectories displayed in the background, picked at random among participants with highest probabilities of belonging to each class. A random jitter was added to the observed trajectories in order to distinguish common trajectories; no, number.

Figure 3 Estimated average lifetime trajectories of sunburns up to 59 years (sample <60, *n*=119,170). The left panel shows the estimated average trajectories of sunburn up to 59 years in the five latent classes. The right panel shows the estimated average trajectory for each class separately (bold line), with a sample of 500 observed individual trajectories displayed in the background, picked at random among participants with highest probabilities of belonging to each class. A random jitter was added to the observed trajectories in order to distinguish common trajectories; no, number.

521 **Table 1.** Participant Characteristics in the Three Samples Used to Estimate Classes of
522 Individual Lifetime Sunburn Trajectories

523

	Samples used to estimate the sunburn trajectories		
	Sample <40[a]	**Sample <50**[b]	**Sample <60**[c]
No. of women	159,773	153,297	119,170
Mean (SD) age at baseline, years	49.0 (8.4)	51.3 (6.1)	56.1 (3.9)
Total person-years of follow-up	3,112,435	2,689,943	1,698,739
Mean (SD) person-years of follow-up	19.5 (6.5)	17.5 (5.5)	14.3 (4.2)
Incident melanoma cases	1,774	1,678	1,252
Mean (SD) age at melanoma diagnosis, years	61.9 (9.0)	62.7 (8.3)	65.4 (7.0)
Incident cSCC cases	871	854	739
Mean (SD) age at cSCC diagnosis, years	68.0 (9.1)	68.2 (9.0)	69.7 (8.2)
	No. (%)[d]	No. (%)[d]	No. (%)[d]
Recruitment year to the NOWAC study			
1991-1994	55,633 (34.8)	50,835 (33.2)	32,157 (27.0)
1995-1999	38,000 (23.8)	36,322 (23.7)	30,129 (25.3)
2000-2008	66,140 (41.4)	66,140 (43.1)	56,884 (47.7)
Residential ambient UVR exposure			
Low (northern Norway)	17,862 (11.2)	16,921 (11.0)	12,469 (10.5)
Medium-low (central Norway)	33,981 (21.3)	33,296 (21.7)	27,554 (23.1)
Medium (south-western Norway)	78,085 (48.9)	74,495 (48.6)	56,925 (47.8)
Highest (south-eastern Norway)	29,845 (18.7)	28,585 (18.6)	22,222 (18.6)
Education, years			
≤10	51,927 (34.2)	49,760 (34.2)	39,536 (35.1)
11-13	45,512 (29.9)	43,457 (29.8)	32,889 (29.2)
≥14	54,571 (35.9)	52,428 (36.0)	40,099 (35.6)
Missing	7,763	7,652	6,646
Smoking status at baseline			
Never	53,929 (34.2)	52,162 (34.4)	42,085 (35.7)
Former	54,959 (34.8)	53,351 (35.2)	42,647 (36.2)
Current	48,915 (31.0)	45,949 (30.3)	33,088 (28.1)
Missing	1,970	1,835	1,350
Hair color			
Black/dark brown	25,611 (17.1)	24,723 (17.0)	19,852 (17.1)
Brown	60,411 (40.3)	58,638 (40.3)	46,795 (40.2)
Blond/yellow/red	64,065 (42.7)	62,123 (42.7)	49,703 (42.7)
Missing	9,686	7,813	2,820
Untanned skin color			
Dark	27,842 (21.6)	27,834 (21.6)	22,304 (20.8)
Medium	48,814 (37.9)	48,805 (37.9)	40,554 (37.8)
Light	52,072 (40.5)	52,054 (40.4)	44,350 (41.4)
Missing	31,045	24,604	11,962
Freckling when sunbathing			
No	85,697 (64.8)	85,680 (64.8)	72,367 (65.8)
Yes	46,556 (35.2)	46,535 (35.2)	37,673 (34.2)
Missing	27,520	21,082	9,130

Table 1. Participant Characteristics in the Three Samples Used to Estimate Classes of Individual Lifetime Sunburn Trajectories (continued)

	Samples used to estimate the sunburn trajectories		
	Sample <40[a]	**Sample <50**[b]	**Sample <60**[c]
	No. (%)[d]	No. (%)[d]	No. (%)[d]
No. of asymmetric nevi >5mm on legs			
0	127,893 (88.2)	122,491 (88.2)	94,252 (88.1)
1	9,825 (6.8)	9,403 (6.8)	7,279 (6.8)
>1	7,230 (5.0)	6,940 (5.0)	5,430 (5.1)
Missing	14,825	14,463	12,209
Skin reaction to acute sun exposure[e]			
Brown without being red first	25,456 (27.7)	23,795 (27.8)	17,320 (28.4)
Red	46,027 (50.0)	42,926 (50.2)	30,985 (50.8)
Red with burning	16,296 (17.7)	14,977 (17.5)	10,062 (16.5)
Red with burning and blistering	4,195 (4.6)	3,861 (4.5)	2,588 (4.2)
Missing	67,799	67,738	58,215
Skin reaction to chronic sun exposure[e]			
Deep brown	12,410 (15.0)	11,621 (14.9)	8,373 (14.3)
Brown	47,390 (57.3)	44,757 (57.3)	33,647 (57.5)
Light brown	21,403 (25.9)	20,305 (26.0)	15,432 (26.4)
Never brown	1,500 (1.8)	1,420 (1.8)	1,086 (1.9)
Missing	77,070	75,194	60,632
Cumulative no. of weeks on sunbathing vacations			
None	16,976 (12.3)	12,145 (9.3)	6,656 (6.4)
Lowest tertile	40,659 (29.4)	40,401 (30.9)	32,283 (31.1)
Middle tertile	40,198 (29.1)	38,687 (29.6)	32,470 (31.3)
Highest tertile	40,407 (29.2)	39,674 (30.3)	32,494 (31.3)
Missing	21,533	22,390	15,267
Indoor tanning			
Never	46,258 (33.4)	41,968 (32.0)	32,864 (31.7)
Ever	92,392 (66.6)	89,044 (68.0)	70,755 (68.3)
Missing	21,123	22,285	15,551

Abbreviations: cSCC, cutaneous squamous cell carcinoma; no., number; NOWAC, Norwegian Women and Cancer; SD, standard deviation; UVR, ultraviolet radiation

[a] Sample <40: Sample used to estimate classes of individual lifetime trajectories up to 39 years. Including all women with information on sunburns in at least one age decade <40 years.

[b] Sample <50: Sample used to estimate classes of individual lifetime trajectories up to 49 years. Including all women from sample <40 that had information on sunburns in at least one age decade <50 years.

[c] Sample <60: Sample used to estimate classes of individual lifetime trajectories up to 59 years. Including all women from sample <50 that had information on sunburns in at least one age decade <60 years.

[d] Because of rounding, percentages may not sum up to 100%

[e] Recorded in subsamples of the cohort

Table 2: HRs (95% CI) for Classes of Lifetime Sunburn Trajectories and Risk of Melanoma and Cutaneous Squamous Cell Carcinoma

			Complete-case analyses[a]					Multiple imputation analyses[b]		
			Melanoma		cSCC		P for heterogeneity[d]	Melanoma	cSCC	P for heterogeneity[d]
	No. of women	%[c]	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)		HR (95% CI)	HR (95% CI)	
Class of lifetime sunburn trajectory[e]										
Sample <40: trajectories up to 39 years[f]	**117,352**		**1,293**		**613**					
Stable low	18,191	15.5	134	1.00 [Reference]	68	1.00 [Reference]		1.00 [Reference]	1.00 [Reference]	
Low-moderate-low	10,509	9.0	76	0.98 (0.75-1.28)	32	1.06 (0.72-1.57)	0.74	1.09 (0.87-1.36)	1.21 (0.89-1.66)	0.58
Low to high	20,104	17.1	192	1.15 (0.93-1.42)	100	1.29 (0.96-1.73)	0.52	1.20 1.00-1.43)	1.24 (0.98-1.58)	0.80
High to low	17,108	14.6	206	1.39 (1.12-1.72)	82	1.36 (0.99-1.87)	0.91	1.44 (1.20-1.73)	1.47 (1.14-1.91)	0.88
Stable high	51,440	43.8	685	1.44 (1.20-1.73)	331	1.55 (1.19-2.02)	0.66	1.50 (1.28-1.75)	1.51 (1.22-1.87)	0.95
Sample <50: trajectories up to 49 years[g]	**117,101**		**1,260**		**610**					
Stable low	22,583	19.3	166	1.00 [Reference]	88	1.00 [Reference]		1.00 [Reference]	1.00 [Reference]	
Low-moderate-low	12,116	10.3	112	1.13 (0.90-1.41)	61	1.14 (0.84-1.55)	0.95	1.12 (0.92-1.36)	1.15 (0.89-1.49)	0.85
Low to high	15,601	13.2	135	1.07 (0.86-1.33)	70	1.19 (0.89-1.60)	0.56	1.11 (0.92-1.33)	1.14 (0.90-1.46)	0.84
High to low	24,924	21.3	304	1.39 (1.15-1.67)	150	1.45 (1.12-1.88)	0.78	1.40 (1.19-1.64)	1.48 (1.19-1.83)	0.70
Stable high	41,877	35.8	543	1.41 (1.19-1.68)	241	1.36 (1.06-1.74)	0.80	1.44 (1.24-1.67)	1.37 (1.12-1.69)	0.73
Sample <60: trajectories up to 59 years[h]	**96,407**		**992**		**551**					
Stable low	18,735	19.4	135	1.00 [Reference]	73	1.00 [Reference]		1.00 [Reference]	1.00 [Reference]	
Low-moderate-low	19,601	20.3	198	1.21 (0.98-1.49)	136	1.60 (1.22-2.08)	0.11	1.29 (1.07-1.54)	1.46 (1.17-1.83)	0.39
Low to high	12,721	13.2	102	1.06 (0.84-1.34)	67	1.24 (0.92-1.68)	0.42	1.12 (0.91-1.37)	1.17 (0.91-1.51)	0.77
High to low	13,837	14.4	150	1.32 (1.07-1.64)	80	1.44 (1.08-1.91)	0.65	1.34 (1.10-1.62)	1.43 (1.13-1.82)	0.66
Stable high	31,513	32.7	407	1.48 (1.22-1.79)	195	1.34 (1.04-1.74)	0.55	1.50 (1.27-1.78)	1.35 (1.09-1.68)	0.46

Abbreviations: cSCC, cutaneous squamous cell carcinoma; CI, confidence interval; HR, hazard ratio; no., number

[a] Cox proportional hazards model with age as the time scale, stratified by calendar year at study inclusion and adjusted for residential ambient ultraviolet radiation exposure, hair color, freckling when sunbathing, and cumulative number of sunbathing vacations. Participants were assigned to classes using proportional assignment.

[b] Analyses with multiple imputation of missing data conducted using chained equations and a total of 40 imputed data sets, using the same models as in the complete-case analyses (sample <40: *n*=159,773 [1,774 melanoma cases, 871 cSCC cases]; sample <50: *n*=153,297 [1,678 melanoma cases, 854 cSCC cases]; sample <60: *n*=119,179 [1,252 melanoma cases, 739 cSCC cases]).

[c] Because of rounding, percentages may not sum up to 100%

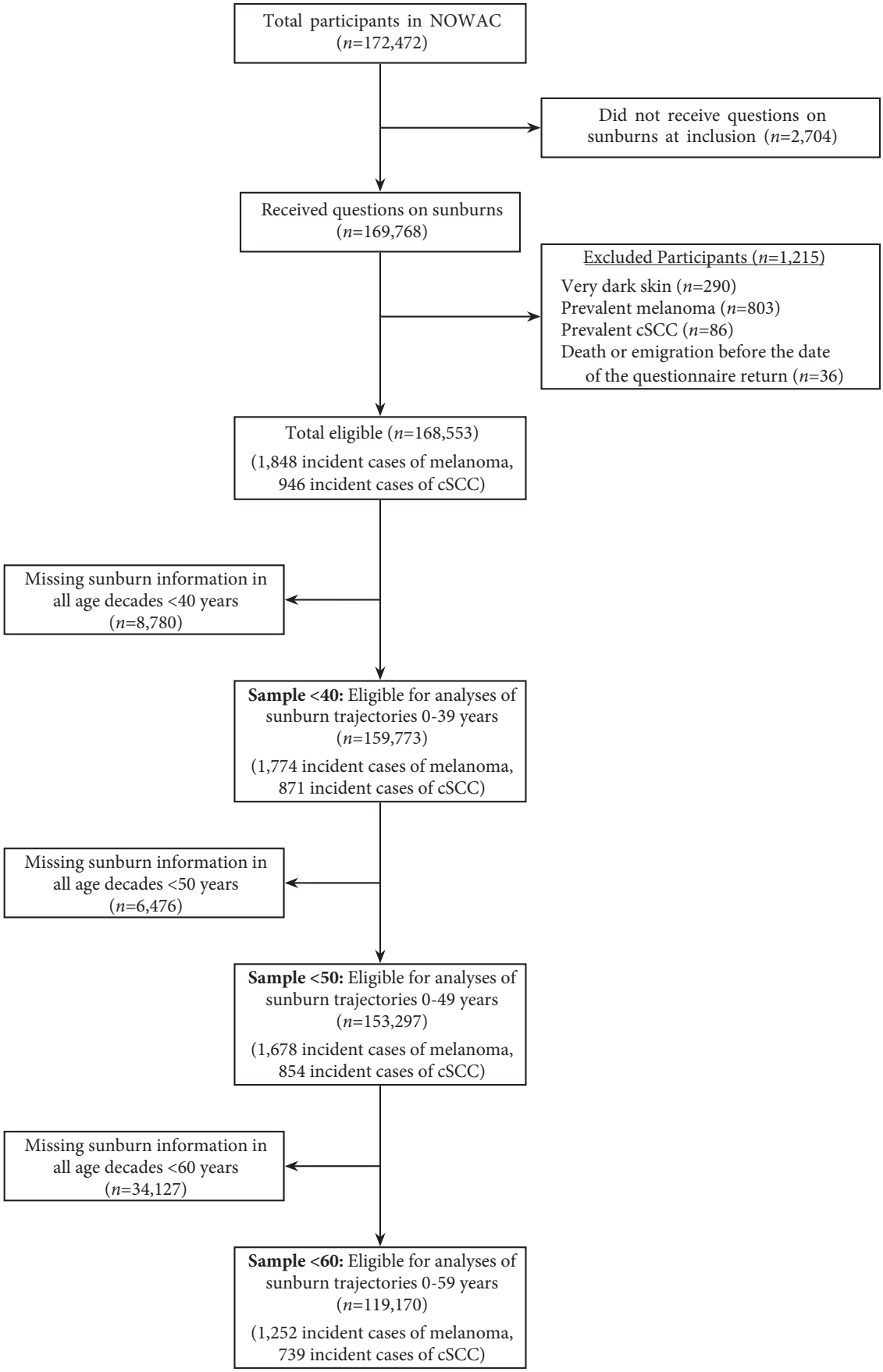
[d] Heterogeneity test conducted using the contrast test statistic.

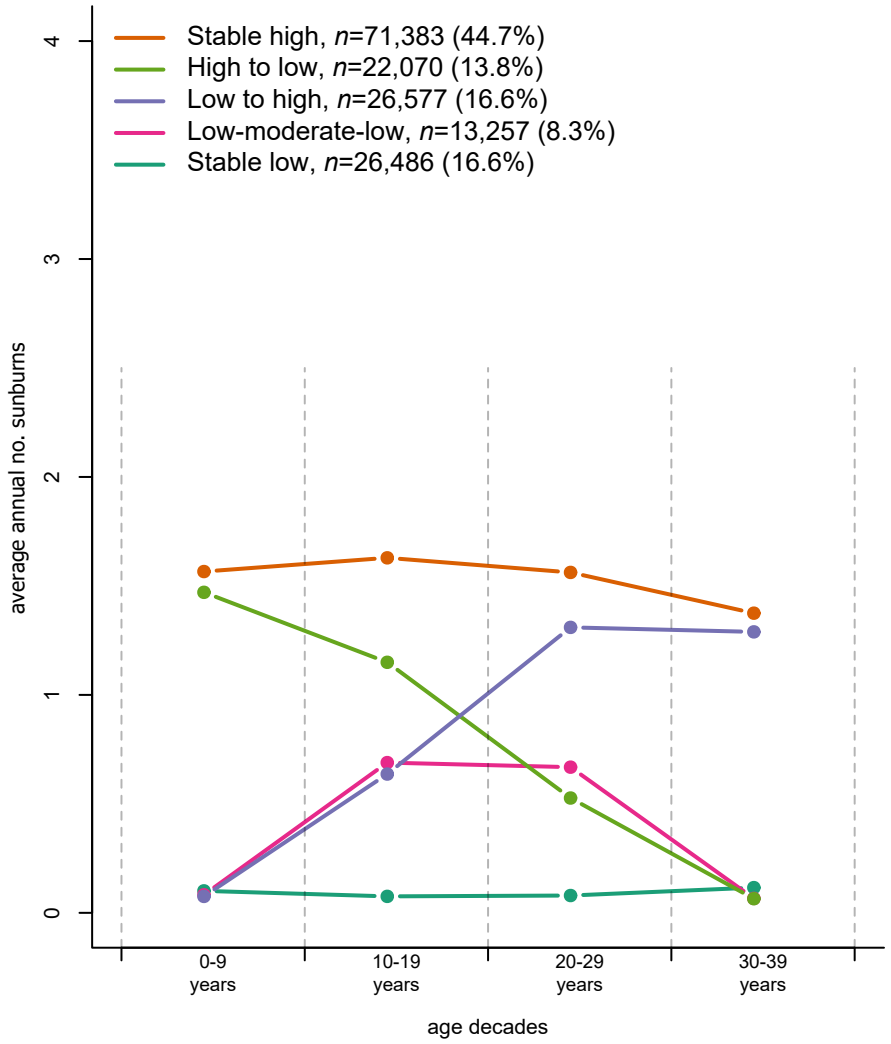
[e] Classes of individual lifetime trajectories estimated from a latent class mixed model. Mean annual number of sunburns was modelled using I-splines with 4 equidistant knots. Mixed model with random intercept only.

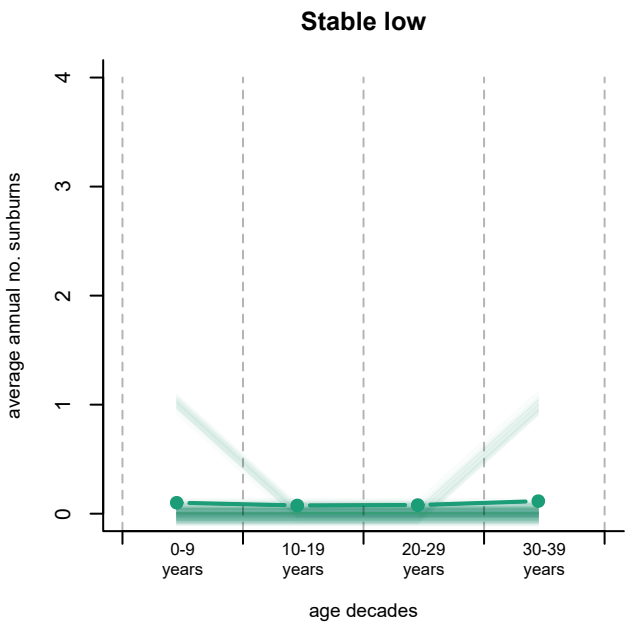
[f] Trajectories estimated using sunburn information up to 39 years.

[g] Trajectories estimated using sunburn information up to 49 years.

[h] Trajectories estimated using sunburn information up to 59 years.


Total participants in NOWAC (n=172,472)
Did not receive questions on sunburns at inclusion (n=2,704)
Received questions on sunburns (n=169,768)
Excluded Participants (n=1,215)
Very dark skin (n=290)
Prevalent melanoma (n=803)
Prevalent cSCC (n=86)
Death or emigration before the date of the questionnaire return (n=36)
Total eligible (n=168,553)
(1,848 incident cases of melanoma, 946 incident cases of cSCC)
Missing sunburn information in all age decades <40 years (n=8,780)
Sample <40: Eligible for analyses of sunburn trajectories 0-39 years (n=159,773)
(1,774 incident cases of melanoma, 871 incident cases of cSCC)
Missing sunburn information in all age decades <50 years (n=6,476)
Sample <50: Eligible for analyses of sunburn trajectories 0-49 years (n=153,297)
(1,678 incident cases of melanoma, 854 incident cases of cSCC)
Missing sunburn information in all age decades <60 years (n=34,127)
Sample <60: Eligible for analyses of sunburn trajectories 0-59 years (n=119,170)
(1,252 incident cases of melanoma, 739 incident cases of cSCC)


Sample <40 (n=159,773)
Stable high, n=71,383 (44.7%)
High to low, n=22,070 (13.8%)
Low to high, n=26,577 (16.6%)
Low-moderate-low, n=13,257 (8.3%)
Stable low, n=26,486 (16.6%)
average annual no. sunburns
0
1
2
3
4
0-9 years
10-19 years
20-29 years
30-39 years
age decades


Stable low
average annual no. sunburns
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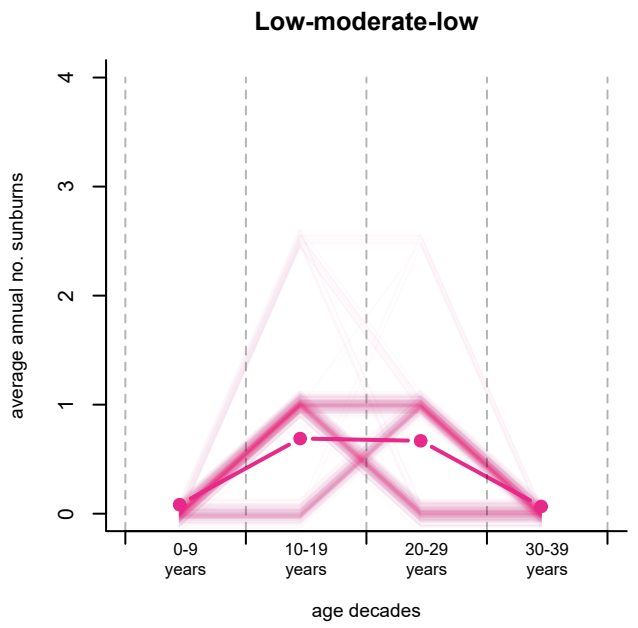
Low-moderate-low
average annual no. sunburns
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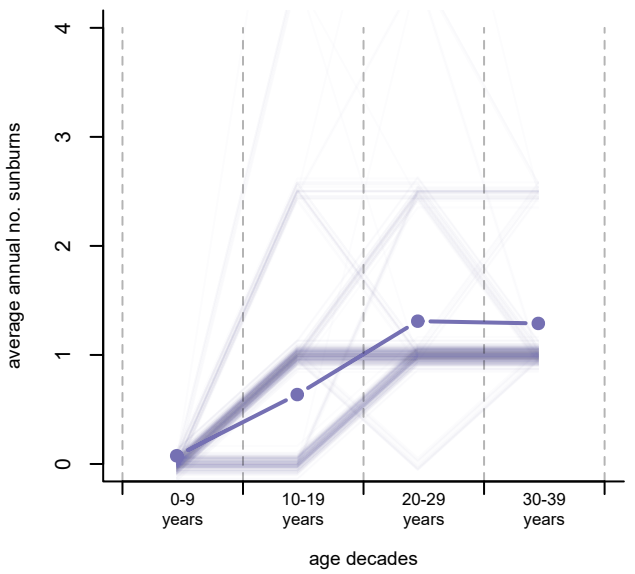
0-9 years
10-19 years
20-29 years
30-39 years
age decades


Low to high
average annual no. sunburns
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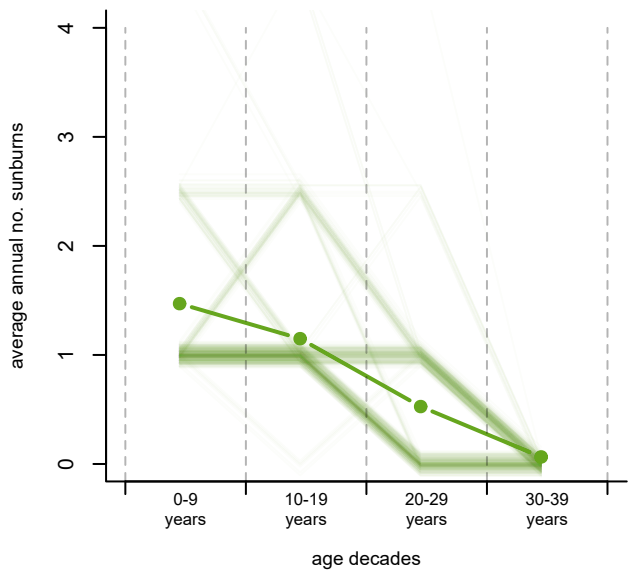
30-39 years
age decades


High to low
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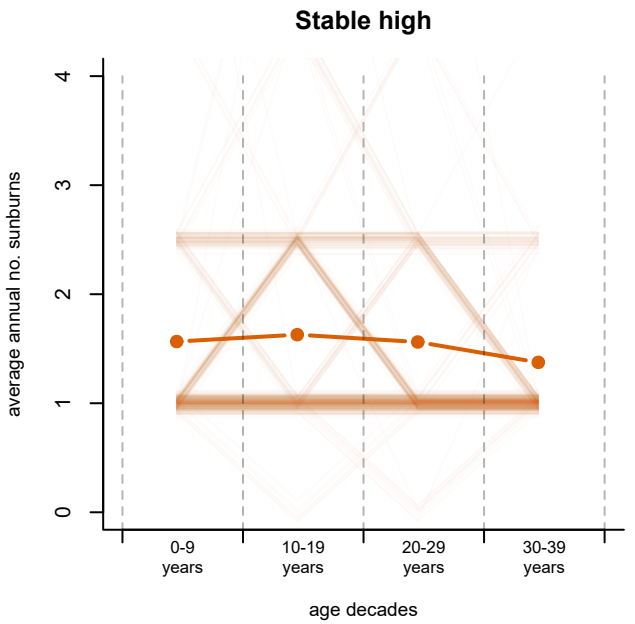
Stable high
average annual no. sunburns
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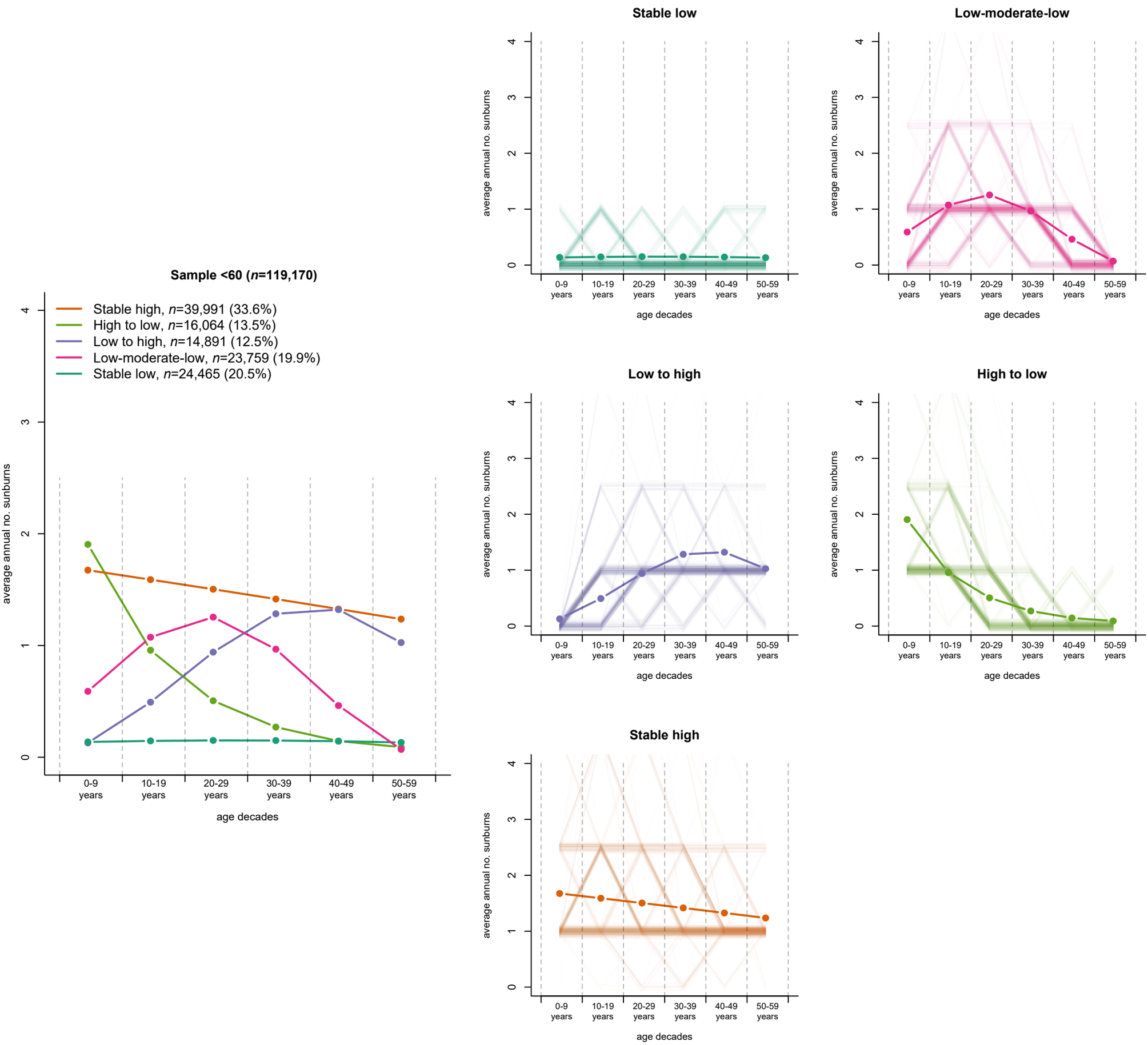
age decades


Sample <60 (n=119,170)
Stable high, n=39,991 (33.6%)
High to low, n=16,064 (13.5%)
Low to high, n=14,891 (12.5%)
Low-moderate-low, n=23,759 (19.9%)
Stable low, n=24,465 (20.5%)
average annual no. sunburns
0
1
2
3
4
0-9 years
10-19 years
20-29 years
30-39 years
40-49 years
50-59 years
age decades
Stable low
Low-moderate-low
Low to high
High to low
Stable high