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Capsule summary

- UV exposure may differentially impact risk of melanoma by sex and age group.
- The female sex plays a significant and independent role in early onset melanoma.
- More effective preventive strategies can be developed based on the understanding of sex- and age-specific melanoma causes.

An age-dependent interaction between sex and geographical UV index in melanoma risk

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Abstract

Background: UV exposure may not equally impact melanoma development in different sexes and ages. Whether and how these factors interact with each other in melanoma risk is unknown.

Objective: This study attempts to estimate interactions among UVI, sex and age in melanoma risk.

Methods: Melanoma incidence data was collected from 42 cancer registries. Geographical UV index (UVI) was collected from local satellite stations. Negative binomial regression models were used to estimate the impact of each risk factor and their interactions.

Results: Sex, UVI and age, as well as interactions between any two of these factors were significantly associated with melanoma risk. In younger age groups, the female sex is an independent risk factor for melanoma that is not impacted by ambient UV exposure. In older age groups, however, the female sex interacts with UV exposure as a risk factor, exhibiting a protective effect. The switching age category is 45-49, which correlates with dramatic hormonal changes.

Limitations: the interaction between sex and UVI is measured at an ecological level.

Conclusion: The interaction between sex and UVI is age-dependent. The female sex is an independent risk factor for early onset melanoma, but the female sex also protects against UV-associated melanoma in older age groups.

Key words: melanoma, UV, UVI, latitude, gender, sex, epidemiology

Abbreviations and acronyms: UVI, ultraviolet index; ASR, age-standardized rate.

Introduction

Melanoma is the number one cause of death in skin cancer [1, 2], and is one of the most commonly diagnosed cancers in adolescence and young adults (AYA), especially in young women during their reproductive age [3]. While most other cancer types have shown a decreasing trend of incidence rates over the past 24 years, melanoma remains one of the common cancer types with increasing trend[4]; and the epidemiological reasons are mostly attributed to ultraviolet radiation (UVR), including solar UV and indoor tanning bed [5, 6].

Risks for AYA melanoma include white ethnicity, female gender and environmental UV radiation [7]. Melanoma incidence rates increase with age for both genders but with different patterns [8, 9]**:** young women (<45 year old) have higher incidence rates than young men, but the trend reverses at older age – older women have lower incidence rates than older men [9]. It has been known for over 30 years that the melanoma incidence and mortality is higher in women than that in men at younger ages [10]. Most epidemiological studies attributed this cause to life style and tanning bed use for younger women [11, 12], i.e., younger women are less covered under the sun and use tanning beds more often [12, 13], hence they are more exposed to UVR. However, it was reported in a meta-analysis that in Europe tanning bed use only counted for 5.4% of all melanoma cases [14]. Therefore the question remains as to whether UVR can fully account for the gender difference observed in AYA melanoma, or alternatively, whether melanomas from all ages are equally affected by UVR.

Our previous studies strongly suggested negative answers to the above questions. We first described a unique female to male rate ratio change over age in melanoma which showed a peak difference at reproductive age [9]. Non-melanoma skin cancer, which was also caused by UV exposure, did not exhibit such age-dependent rate ratio difference between sexes [9]. More importantly, this rate ratio difference was observed in all ethnicities including African American group whose skin are well protected from UVR[9]. Further regression analysis on sex-specific age-standardized rates and daily average geographical UVI revealed that melanoma incidence rates in men showed a significant association with geographical UVI, but there was no such association in women [15]. These findings are very intriguing; they strongly suggest an independent role of sex , which has always been linked to

differential UV behavior between sexes. In this study we set out to examine whether we can separate the role between UVR, age and sex, and explore potential interactions among these factors in melanoma risk.

Materials and Methods:

Registry selection and melanoma classification: For melanoma cases, tumor classification was based on the standard of the International Classification of Diseases for Oncology, ICD-O-3, with code C43. In order to obtain a relatively homogeneous ethnic background, registries from northern Europe, United States and Australia were selected based on ethnic information. For northern Europe, countries with at least 50% light eye color of population were selected [16]. This excludes most of southern European countries even though they are Caucasians. Belgium was excluded because data was not available for a 10 year period of time. For the United States, race information is available so only white race was included in all selected registries. For Australia, it is known that the Northern Territory contains a large indigenous population, therefore the Northern Territory was excluded. For all registries, the most recent 10 years of incidence rates (case and population numbers in each 5 year age categories) were collected based on the data availability (Table 1), either from 1998 to 2007 or from 2000 to 2009. For European countries, data was obtained from Eureg (part of International Agency for Research of Cancer, IARC) website (http://eco.iarc.fr/eureg/Default.aspx). For the United States, data was downloaded from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute via SEER*Stat software. For Australia registries, data was obtained from IARC CI5, volume X plus.

Geographical UVI data and local latitude: The local UV indices were collected as described in our previous publication [15]. Briefly, UV indices were calculated from data collected by local satellite stations. The scale of UVI is proportional to the intensity of erythema-causing UV doses on the earth surface any day at noon [17]. Daily UVI were collected from July 1, 2002, the earliest time when the data was available, to June 30, 2014 when data was first collected for this study. Average daily UVI for this

period was used for analysis. The latitude value was that of roughly the central latitude of the registry area. More details are described in Supplemental Method.

Statistical methods: A negative binomial regression model was used to estimate association of age, sex and UVI with melanoma risk because, although the count data (case numbers) fit Poisson distribution, the data was over dispersed ($p < 0.0001$). In our model assessment, the Pearson Chi-Square values and degrees of freedom were used to estimate whether the data was over-dispersed when modeled with a negative binomial distribution. The time period was the same for all registries (10 years), but population size varied, therefore log-transformed population was used as an offset. A natural log link was used for a log linear model. Comparison between models was made via log likelihood ratios and chi square statistics.

Results

All three factors and interactions between each two contribute significantly to melanoma risk

Table 1 lists the registries and countries, years of data collection, age-standardized gender-specific melanoma incidence rates, geographical UVIs and latitudes. As described in Supplemental Methods, negative binomial regression was used to assess melanoma risk. In the base model (Model 1) which include three factors only, all three variables (age, sex and UVI) were significant contributors to melanoma risk (Table 2). Sequentially adding an interaction between UVI*sex, or UVI*age, or age*sex to base model, we generated Model 2, 3 and 4. Each interaction significantly improved the prediction of melanoma risk as judged by the significant p values for either the interaction, or the model comparison, or both (Table 2). Model 5 included all three possible 2x2 interactions, and again it is a significantly better model than Model 4. When latitude was used instead of UVI, the results were similar (Supplemental Table S1), all three variables and their interactions showed significant contributions to melanoma risk. Note that in all models, sex exhibited a negative coefficient, revealing that overall females showed a protective effect against melanoma risk as the regression models used male sex as a baseline.

The female sex is an independent risk factor for melanoma diagnosed at younger age

The interaction between UVI and sex was not well documented. We next examined UVI*sex interaction using the same negative binomial model for each age category. As shown in Table 3, both models suggested that UVI was significantly associated with melanoma risk across all age categories except for the very young age (Agecat 1).

Sex association with melanoma risk was age-dependent in both models, with different patterns. At very young age (0-14 years) the role of sex was uncertain as the p values ranged from non-significant to significant in model A for various age groups (Table 3). Adding UVI*sex interaction did not improve the model, meaning sex at these age groups did not modify UVI effect.

Age 15-19 group was a unique group in which sex was significantly associated with melanoma in both models; adding UVI*sex interaction significantly improved model (Table 3). The interaction between UVI and sex contributed significantly in determining melanoma risk as indicated by its significant p value (p=0.0304, Table 3). Therefore sex alone and the interaction between sex and UVI both are crucial.

For the 20-44 age group (the major reproductive age group), sex alone played a significant role in both models, while the UVI*sex interaction impact was not significant, as reflected by the p values for both the model comparison and for the interaction (Table 3).

Age 45-49 is a transition group, in which sex showed marginally significant impact in Model A (p=0.063) but shows significant impact in Model B (p=0.0076). The interaction between sex and UVI is also significant in this age group (p = 0.038). Therefore this age group and the age group 15-19 are the only two groups where both sex and UVI-sex interaction play significant roles in determining melanoma outcome. For both groups Model B is better than Model A, which emphasizes the importance of the interaction.

Sex does not play a role in the age 50-54 group in either model. This is consistent with our previous findings: the rate ratio between sexes for this age group is nearly 1.0 [9]. When the UVI and sex

interaction is taken into consideration, sex is still not a significant contributor (p = 0.064), but the interaction is (p = 0.0325) (Table 3).

After age 54, Model B was significantly better than Model A; therefore sex alone is no longer a significant risk factor, even though we know that men's rates are higher than women's in these ages. In these older age groups, it is the interaction between sex and UVI that becomes important (Table 3).

Discussion and Conclusions

The role of sex in melanoma development was well known before, but it was mostly focused on the incidence rate difference at different ages. Here we reveal a significant interaction between sex and UVI which has been under-reported. What was more striking was that the interaction between sex and UVI was age-dependent. Before age 45 there is no significant interaction between sex and UVI; and sex and UVI independently contribute to melanoma risk. After age 49 the UVI and sex interaction played a significant role in melanoma risk, while sex itself was no longer significant. These results may suggest that, 1) sex plays an independent role in early onset melanoma development, and 2) sex exhibited a modification role on UVI impact in melanoma occurring later in life; specifically the female sex exhibited protective role against ambient UV exposure.

It is worth to note that the interaction was dependent on age, with 15-19 and 45-49 years as two switching ages. The age group 15-19 is the group just about to complete puberty changes and reach their life time high sexual hormonal levels [18, 19]. Meanwhile this group is also reported to use tanning beds more often than other age groups [20]. There may be a link between the tanning bed use and geographical UVI, so it seems multiple factors may be at play for this particular age group. The 15-19 and 45-49 age groups are also the exact ages when sex hormones exhibit the most dramatic changes in human life span [21]. In particular, both estrogen and testosterone levels dramatically increase during the ages of 15-19 and they both dramatically decrease in the 45-49 year age group. This coincidence may suggest a link of these hormonal changes with melanoma risk, and these changes interact with geographical UVI to impact melanoma development. The role of hormonal impact is further supported

by the non-significant role of sex for melanomas diagnosed before age 15 when the sexual biological difference is not as dramatic as later ages.

For melanomas diagnosed at older age, although sex no longer contributes independently to melanoma risk, the female sex shows a protective role against UV radiation. Without age stratification, the female sex exhibits an overall protective effect (Table 2). These results provide a possible explanation and validation of our previous observation that the incidence rates in women are not significantly associated with UVI in a linear model [15]. In contrast, the incidence rates in men are significantly associated with ambient UVI and the association levels increase with age [15] .

The limitation of this study is that the interaction between sex and UVI is based on geographical UV which may not reflect how much UV radiation a person receives, which is also difficult to separate from other environmental factors such as temperature and latitude. Confounding factors such as indoor tanning device use cannot be separated from the gender factor as females are more intent on having tanned skin either through tanning devices or sun bathing[22]. However, females also tend to use significantly more sunscreen [23-25] . Furthermore, from our previous observation, it is known that young females did not show a particular higher incidence rate for non-melanoma skin cancer [9], which is also caused by UV radiation. Therefore it is highly likely that it is the female sex, and not their sun behavior, that contributes significantly to melanoma risk at young ages.

In summary our results suggest that the ambient UV exposure and sex each contributes to melanoma risk independently for those diagnosed at younger age (≤ 44 years old), that the ambient UV plays a significant role in melanoma risk for those diagnosed at older age (≥45 years old). However there is a significant interaction between sex and UVI for melanomas occurring at older age, manifesting as a protective role of female sex against UV-associated melanoma risk. The significance of these observations guarantees further investigations in the mechanism of sex difference and how this difference can be utilized in developing effective prevention strategies.

Disclosure of Potential Conflicts of Interest:

The authors declare that they have no conflicts of interest.

Author's contribution:

FLS conceived the idea, collected data, performed statistical analysis and wrote the manuscript. AZ provided statistical advice, examined statistical model and edited the manuscript.

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244 Figure legend:

245 Figure 1. Melanoma. Histogram of case numbers (numbers for each 5 year age category from each
246 registry) distribution suggested a Poisson distribution.

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Table 1. Cancer registry, years, rates and local UVI and latitude

Country	Registry	Years	asr-M	asr-F	UVI	Latitude
Australia	Queensland	1998-2007	60.7	43.9	9.4	20.9
	New South Wales	1998-2007	44.6	30.2	7.2	33.9
	Tasman	1998-2007	37.5	34.9	5.6	41.4
	Victoria	1998-2007	32.9	26.5	6.3	37.5
	South Australia	1998-2007	32.6	26.5	7.0	30.5
	West Australia	1998-2007	49.3	33.8	7.7	27.7
Austria	Austria	2000-2009	11.0	9.7	4.1	47.5
Czech	Czech	1998-2007	12.4	10.8	3.5	49.8
Denmark	Denmark	1998-2007	14.5	17.9	3.0	56.3
Estonia	Estonia	1998-2007	6.2	7.9	2.3	58.6
Finland	Finland	1998-2007	11.0	9.1	1.8	61.9
France	Manche/Haut-Rhin	2000-2009	12.8	13.8	3.8	47.9
Iceland	Iceland	1998-2007	11.4	20.2	1.9	65.0
Ireland	Ireland	2000-2009	11.0	14.0	3.0	53.4
Netherland	Netherland	1998-2007	13.1	16.8	3.2	52.1
Norway	Norway	1998-2007	16.6	17.5	1.9	60.5
Sweden	Sweden	2000-2009	15.5	15.9	2.2	60.1
Switzerland	Zurich	2000-2009	21.0	18.9	4.1	47.4
Germany	Brandenburg	2000-2009	8.2	7.9	3.1	52.0
	Mecklenburg	2000-2009	8.1	8.3	2.8	53.6
	Schleswig-Holstein	2000-2009	14.3	16.4	2.8	54.2
	Thuringen	2000-2009	9.8	9.6	3.5	51.0
United Kingdom	East England	2000-2009	10.1	11.0	3.0	52.2
	NW England	2000-2009	8.7	11.4	2.2	52.4
	Northern Ireland	1998-2007	9.1	12.0	3.0	54.8
	Scotland	1998-2007	10.8	12.9	2.6	56.5
	Wales	1998-2007	9.8	10.8	3.0	52.1
United States	Atlanta	2000-2009	37.7	26.3	6.7	33.7
	Greater Georgia	2000-2009	24.5	17.2	6.7	32.2
	Connecticut	2000-2009	22.9	17.3	4.9	41.6
	Detroit	2000-2009	19.7	16.4	4.9	42.3
	Hawaii	2000-2009	61.2	39.3	10.5	19.9
	Iowa	2000-2009	18.3	15.8	4.9	41.9
	Kentucky	2000-2009	22.1	16.3	5.7	37.8
	Los Angeles	2000-2009	18.4	10.8	6.9	34.1
	Louisiana	2000-2009	17.4	11.4	8.9	31.0
	New Mexico	2000-2009	18.6	11.9	6.7	34.5
	New Jersey	2000-2009	23.5	16.9	5.6	40.1
	San Francisco	2000-2009	26.8	18.2	5.7	37.8
	San Jose	2000-2009	23.3	16.3	5.7	37.8
	Seattle	2000-2009	27.5	23.6	4.3	47.6
	Utah	2000-2009	29.5	19.4	6.1	39.3

asr-M: age-standardized rate for males; asr-F: age-standardized rate for females

Table 2: Parameter estimate from different models using UVI

		Coefficient	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq	p value for model comparison
Model 1	Intercept	-12.312	0.0754	-12.4597	-12.164	26640.5	<.0001	
	uvi	0.1673	0.0107	0.1463	0.1883	244.47	<.0001	
	sex	-0.1383	0.0475	-0.2314	-0.0452	8.48	0.0036	
	age	0.0631	0.0012	0.0607	0.0654	2724.68	<.0001	
	LL*	-8854.7						NA
Model 2	Intercept	-12.1	0.0909	-12.2779	-11.922	17730.3	<.0001	
	uvi	0.1222	0.0148	0.0931	0.1513	67.79	<.0001	
	sex	-0.558	0.1103	-0.7741	-0.3418	25.59	<.0001	
	age	0.063	0.0012	0.0606	0.0653	2753.02	<.0001	
	uvi*sex	0.0892	0.0212	0.0477	0.1308	17.74	<.0001	
	LL	-8844.1						< 0.0001
Model 3	Intercept	-11.945	0.1384	-12.2165	-11.674	7448.36	<.0001	
	uvi	0.0898	0.0265	0.0377	0.1418	11.43	0.0007	
	sex	-0.1398	0.0473	-0.2325	-0.0472	8.76	0.0031	
	age	0.0549	0.0028	0.0494	0.0605	378.59	<.0001	
	uvi*age	0.0017	0.0005	0.0007	0.0028	9.98	0.0016	
	LL	-8848.7						0.0005
Model 4	Intercept	-11.761	0.0926	-11.9425	-11.58	16127.2	<.0001	
	uvi	0.1662	0.0103	0.146	0.1863	261.08	<.0001	
	sex	-1.1858	0.1131	-1.4076	-0.9641	109.84	<.0001	
	age	0.0504	0.0016	0.0472	0.0537	937.02	<.0001	
	age*sex	0.0232	0.0023	0.0187	0.0277	103	<.0001	
	LL	-8795.6						< 0.0001
Model 5	Intercept	-11.313	0.1522	-11.6114	-11.015	5528.3	<.0001	
	uvi	0.0689	0.0275	0.015	0.1227	6.29	0.0122	
	sex	-1.5477	0.1481	-1.8381	-1.2574	109.15	<.0001	
	age	0.0447	0.0029	0.0389	0.0504	231.08	<.0001	
	uvi*sex	0.0808	0.0204	0.0409	0.1207	15.76	<.0001	
	uvi*age	0.0013	0.0005	0.0002	0.0023	5.78	0.0163	
	age*sex	0.0228	0.0023	0.0183	0.0272	100.78	<.0001	
	LL	-8782.7						< 0.0001

*LL, log likelihood value

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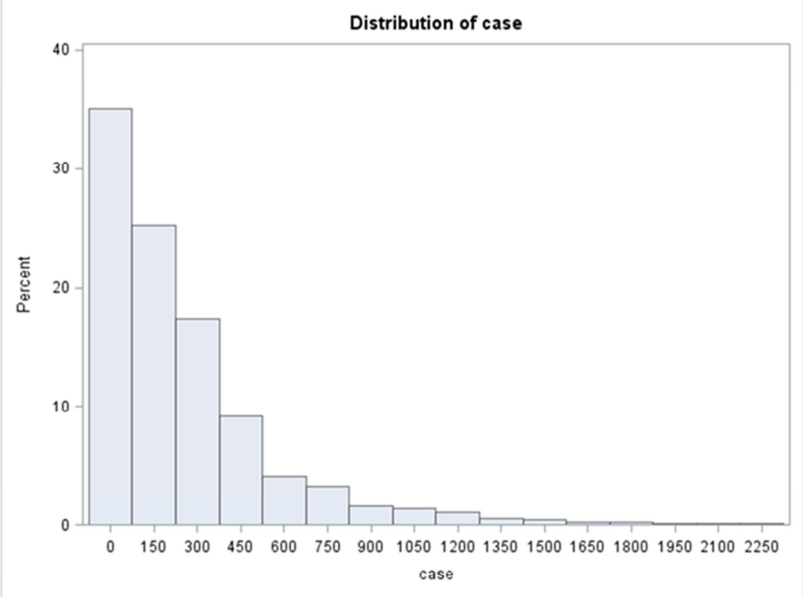
Table 3: UVI, sex and UVI-sex interaction in different age strata

		Model A (UVI, Sex)			Model B (UVI, Sex, UVI*Sex)				Model Comparison	
Agecat	age	LL	p_uvi	p_sex	LL	p_uvi	p_sex	p_uvi*sex	LLR	p_model
1	0-4	-91.25	0.1418	0.19	-91.25	0.281	0.606	0.9997	0.000	1.0000
2	5-9	-122.19	0.0075	0.0099	-121.49	0.0048	0.9529	0.2477	1.391	0.2380
3	10-14	-187.39	<.0001	0.2065	-187.24	0.0042	0.3325	0.6093	0.302	0.5820
4	15-19	-328.50	<.0001	**0.0019**	-325.82	0.0055	**0.001**	**0.0304**	5.374	**0.0204**
5	20-24	-389.39	<.0001	**<.0001**	-387.88	0.0008	**<.0001**	0.0941	3.013	0.0826
6	25-29	-441.87	<.0001	**<.0001**	-440.45	0.0055	**0.001**	0.1074	2.848	0.0915
7	30-34	-464.84	<.0001	**<.0001**	-463.72	0.0009	**0.0002**	0.1505	2.243	0.1342
8	35-39	-480.52	<.0001	**<.0001**	-478.63	<.0001	**<.0001**	0.0597	3.785	0.0517
9	40-44	-497.01	<.0001	**0.0002**	-496.04	<.0001	**0.0056**	0.177	1.936	0.1641
10	45-49	-512.55	<.0001	0.063	-510.28	<.0001	**0.0076**	**0.038**	4.523	**0.0334**
11	50-54	-520.73	<.0001	0.8234	-518.35	<.0001	0.0643	**0.0325**	4.753	**0.0292**
12	55-59	-529.92	<.0001	**0.0056**	-525.27	<.0001	0.1288	**0.0025**	9.309	**0.0023**
13	60-64	-528.54	<.0001	**<.0001**	-525.71	<.0001	0.8396	**0.0185**	5.674	**0.0172**
14	65-69	-528.40	<.0001	**<.0001**	-524.73	<.0001	0.823	**0.0073**	7.339	**0.0068**
15	70-74	-527.74	<.0001	**<.0001**	-524.59	<.0001	0.2765	**0.0132**	6.282	**0.0122**
16	75-79	-523.19	<.0001	**<.0001**	-518.21	<.0001	0.5581	**0.0016**	9.967	**0.0016**
17	80-84	-496.91	<.0001	**<.0001**	-492.64	<.0001	0.1813	**0.0037**	8.550	**0.0035**
18	85+	-473.15	<.0001	**<.0001**	-468.35	<.0001	0.3123	**0.0021**	9.613	**0.0019**

LL: log likelihood; LLR: log likelihood ratio



Liu and Ziogas, Figure 1

Supplemental Method:

1. **Calculation of age-standardized rates:** Age-standardized rates were calculated based on the standard world population 2025 (obtained from SEER website).

2. **More on UVI collection:** UVI information was obtained as previously described from local satellite stations (Liu-Smith et al., JAAD, 2017) , except for a few areas where no station was placed. UVI was estimated for these areas based on the similarity of latitude from another area where monitoring station was available. Local median latitude was obtained as where the central line lays for that area, without weighing out the area shape.

3. **Statistical Models:** As shown in Supplemental Figure 1, the histogram shows that case numbers follow a Poisson distribution. The dispersion calculated by maximum likelihood estimation was 2.035 with 95% Wald confidence interval of 1.888 to 2.169, significantly different than 0, suggesting a negative binomial model was more suitable for parameter estimation. Estimated by Pearson chi square the data fitted well into negative binomial distribution (data not shown). Log-transformed case number was dependent variable; and log-transformed population was used as an offset. Scale was defined as deviance. The age category was converted into numerical age using the middle point of that category. For example, numerical age for age category 5 (20-24 years old) is 22.5, and so on.

   The base model (Model 1) included sex, age and UVI as independent variables. Next we added potential interactions among sex, age and UVI in Model 1 and sequentially generated Model 2 (with interaction between UVI and sex, UVI*sex), Model 3 (UVI*age) and Model 4 (age*sex). Model 5 included all three 2x2 interactions.

   Model A and Model B were also based on the negative binomial regression on each age strata. Model A included only UVI and sex and Model B included UVI*sex interaction as an additional variable.

Supplemental Table 1

Supplemental Table 1: parameter estimate from different models using latitude

		Coeeficient	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq	p value for model comparison
Model 1	Intercept	-10.149	0.1123	-10.369	-9.929	8162.22	<.0001	
	latitude	-0.0307	0.002	-0.0346	-0.027	229	<.0001	
	sex	-0.1374	0.048	-0.2314	-0.044	8.22	0.0042	
	age	0.0631	0.0012	0.0607	0.066	2679.83	<.0001	
	LL*	-8867.5						NA
Model 2	Intercept	-10.548	0.1405	-10.823	-10.27	5638.65	<.0001	
	latitude	-0.0218	0.0028	-0.0273	-0.016	59.82	<.0001	
	sex	0.6568	0.1856	0.293	1.021	12.52	0.0004	
	age	0.063	0.0012	0.0607	0.065	2711.69	<.0001	
	latitude*sex	-0.0177	0.004	-0.0256	-0.010	19.56	<.0001	
	LL	-8855.8						<0.0001
Model 3	Intercept	-10.86	0.2342	-11.32	-10.40	2150.4	<.0001	
	latitude	-0.0147	0.0051	-0.025	-0.005	8.51	0.0035	
	sex	-0.1389	0.0477	-0.232	-0.046	8.5	0.0036	
	age	0.0788	0.0048	0.0695	0.0882	272.97	<.0001	
	latitude*age	-0.0004	0.0001	-0.0006	-0.0001	11.66	0.0006	
	LL	-8860.5						<0.0001
Model 4	Intercept	-9.6074	0.1222	-9.8468	-9.3679	6182.3	<.0001	
	latitude	-0.0305	0.002	-0.0343	-0.0267	244.79	<.0001	
	sex	-1.1911	0.1143	-1.4152	-0.967	108.55	<.0001	
	age	0.0504	0.0017	0.0472	0.0537	918.54	<.0001	
	age*sex	0.0233	0.0023	0.0188	0.0278	102.07	<.0001	
	LL	-8808.9						<0.0001
Model 5	Intercept	-10.499	0.2476	-10.984	-10.014	1798.35	<.0001	
	latitude	-0.0109	0.0052	-0.0211	-0.0006	4.34	0.0373	
	sex	-0.4523	0.2052	-0.8546	-0.05	4.86	0.0275	
	age	0.0621	0.0048	0.0528	0.0715	169.7	<.0001	
	latitude*age	-0.0003	0.0001	-0.0005	-0.0001	6.72	0.0096	
	latitude*sex	-0.016	0.0039	-0.0236	-0.0085	17.35	<.0001	
	age*sex	0.0229	0.0023	0.0184	0.0273	99.86	<.0001	
	LL	-8794.3						< 0.0001

*LL, log likelihood value