

# Life-Course Trajectories of Physical Activity and Melanoma Risk in a Large Cohort of Norwegian Women

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**Purpose:** Physical activity (PA) is a cornerstone in disease prevention and varies throughout life. A pooled analysis of cohort studies and a meta-analysis of cohort studies found positive associations between PA and melanoma risk. However, previous studies focused on PA at specific ages and often lacked information on ultraviolet radiation (UVR) exposure. Using the population-based Norwegian Women and Cancer (NOWAC) cohort, including information on PA and UVR exposure, we estimated life-course PA trajectories from adolescence to adulthood and their associations with melanoma.

**Methods:** Total PA across different domains (recreation, occupation, transport, household) was reported for ages 14 and 30 years, and when responding to the questionnaire (31–76 years) using a 10-point scale, validated to rank PA levels in Norwegian females. We estimated life-course PA trajectories using a latent class mixed model in 152,248 women divided into three subcohorts depending on age at questionnaire completion: 31–39 (n = 27,098), 40–49 (n = 52,515) and ≥50 years (n = 72,635). The unique 11-digit identity number of Norwegian citizens was used to link NOWAC to the Cancer Registry of Norway for information on cancer diagnoses, emigration and death. Associations between PA trajectories and melanoma risk were estimated in each subcohort using multivariable Cox regression.

**Results:** Five classes of individual life-course PA trajectories were identified in subcohort 31–39 years (low, moderate, high, decreasing, increasing PA) and four in subcohorts 40–49 and ≥50 years (low, moderate, high, decreasing PA). No significant association was found between life-course PA trajectories and melanoma risk in any subcohort. Hazard ratios (95% confidence intervals) for the high versus moderate trajectory were 0.92 (0.66–1.29), 1.15 (0.97–1.37) and 0.90 (0.78–1.05) for subcohorts 31–39, 40–49 and ≥50 years, respectively.

**Conclusion:** Our results do not support a positive association between PA and melanoma risk found in previous studies, which is important for public health guidelines promoting regular PA.

**Keywords:** physical activity, cutaneous melanoma, trajectory, cohort, women, Norway

## Introduction

Physical activity (PA) varies during life in terms of frequency, duration and intensity. Thus, identifying life-course trajectories of PA is important to assess differences in PA behaviors and to understand the long-term effects of PA on health and disease risk. In recent years, several studies have estimated PA trajectories in specific age periods and associations with sociodemographic characteristics, health behaviors and outcomes such as chronic disease risk and mortality.<sup>1–8</sup> To our knowledge, no study to date has examined life-course trajectories of PA and cutaneous melanoma

occurrence. With 325,000 new cases and 57,000 deaths estimated globally in 2020, melanoma remains an important public health concern.<sup>9</sup>

PA is assumed to prevent cancer development by enhancing immune function, increasing DNA repair capacity, reducing oxidative stress, decreasing chronic inflammation and controlling weight.<sup>10–13</sup> The studies of PA and melanoma risk have reported mixed results, including positive,<sup>14–17</sup> inverse associations<sup>18</sup> and no association.<sup>19–22</sup> In particular, a pooled analysis of prospective cohort studies found a positive association between recreational PA and melanoma risk,<sup>15</sup> and a meta-analysis of cohort studies found a positive association between cardiorespiratory fitness and melanoma risk.<sup>17</sup> However, very few studies had information on ultraviolet radiation (UVR) exposure<sup>14,20,22</sup> and pigmentary characteristics,<sup>14,18,20,22</sup> the major melanoma risk factors, and none of the studies included in the pooled and meta-analysis adjusted for UVR.

Differences in the assessment of PA and geographical location may have also contributed to the mixed results. Apart from two studies that used occupational history to assess PA,<sup>14,21</sup> most studies assessed PA (recreational, occupational or combination of the two) at a specific time in adulthood. The large population-based Norwegian Women and Cancer (NOWAC) cohort includes information on PA, UVR exposure and pigmentary characteristics and is linked to the Cancer Registry of Norway (CRN). We aimed to i) estimate life-course trajectories of PA from age 14 through adulthood and ii) investigate the association between these trajectories and subsequent development of melanoma taking UVR exposure into account.

## Materials and Methods

### NOWAC Cohort

Between 1991 and 2007, questionnaires were sent to over 320,000 women aged 31–76 years, randomly drawn from the Norwegian National Population Register.<sup>23</sup> More than 172,000 participants answered (response 54%). A first and a second follow-up questionnaire was sent after five to seven years (response >79%). All women in NOWAC provided informed consent, and data were handled in accordance with the relevant ethical guidelines and regulations. The study has been approved by the Regional Committees for Medical Health Research Ethics of North Norway (2021/252094/REK Nord) and the Norwegian Centre for Research Data (2021/147992).

### Physical Activity (PA)

Participants reported their current level of PA at recruitment, first or second follow-up along with their past level of PA at ages 14 and 30, using a validated 10-point scale.<sup>24</sup> The scale was accompanied by the following explanation: “By physical activity we mean activity both at work and outside work, at home, as well as training/exercise and other physical activity, such as walking, etc. Please mark the number that best describes your level of physical activity; 1 being very low and 10 being very high”.<sup>25</sup> Based on this question, PA refers to total amount of PA across different domains (recreation, occupation, transport, and household) at ages 14 and 30, and age at PA questionnaire completion, either at recruitment or follow-up questionnaire. The scale has been validated to rank PA levels in the Norwegian female population, but not to quantify the “dose” of PA (intensity, duration, frequency).<sup>24</sup> The PA scale was compared with aerobic fitness (intra-class correlation coefficient 0.62), and PA energy expenditure acceleration and hours/day of moderate-to-vigorous intensity PA obtained from a heart rate and movement sensor (correlation coefficients 0.36–0.46). PA at questionnaire completion has previously been positively associated with sunbathing vacations and indoor tanning and inversely associated with sunburns.<sup>22</sup>

### Other Exposures

Questions about pigmentation characteristics and UVR exposure in NOWAC have been described in detail,<sup>26–28</sup> and reproducibility was good (kappa/intraclass correlation coefficients 0.49–0.77) and independent of age, education and skin color.<sup>27</sup> Hair color (black/dark brown, brown, blond/yellow, or red) and untanned skin color (using a color scale graded from 1 (very fair) to 10 (very dark)) were reported. Ambient UVR of residence was categorized based on mean ambient UVR hours of the region of residence (latitudes, 70°–58°N), as low (northern Norway), medium-low (central Norway),

medium (southwestern Norway) and highest (southeastern Norway).<sup>28,29</sup> Annual number of severe sunburns, annual number of weeks spent on sunbathing vacations in countries of low (typically southern European countries) and high latitudes (within Norway/northern countries) and frequency of indoor tanning during various periods of adulthood were recorded at baseline and updated during follow-up.<sup>28</sup> For the most recent age period (5–10 years prior to the questionnaire), we categorized annual number of sunburns as never, 1, and  $\geq 2$ , annual number of weeks of sunbathing vacations as never, 1, 2–3 and  $\geq 4$ , and frequency of indoor tanning use as never, rarely and  $\geq 1$  time/month.

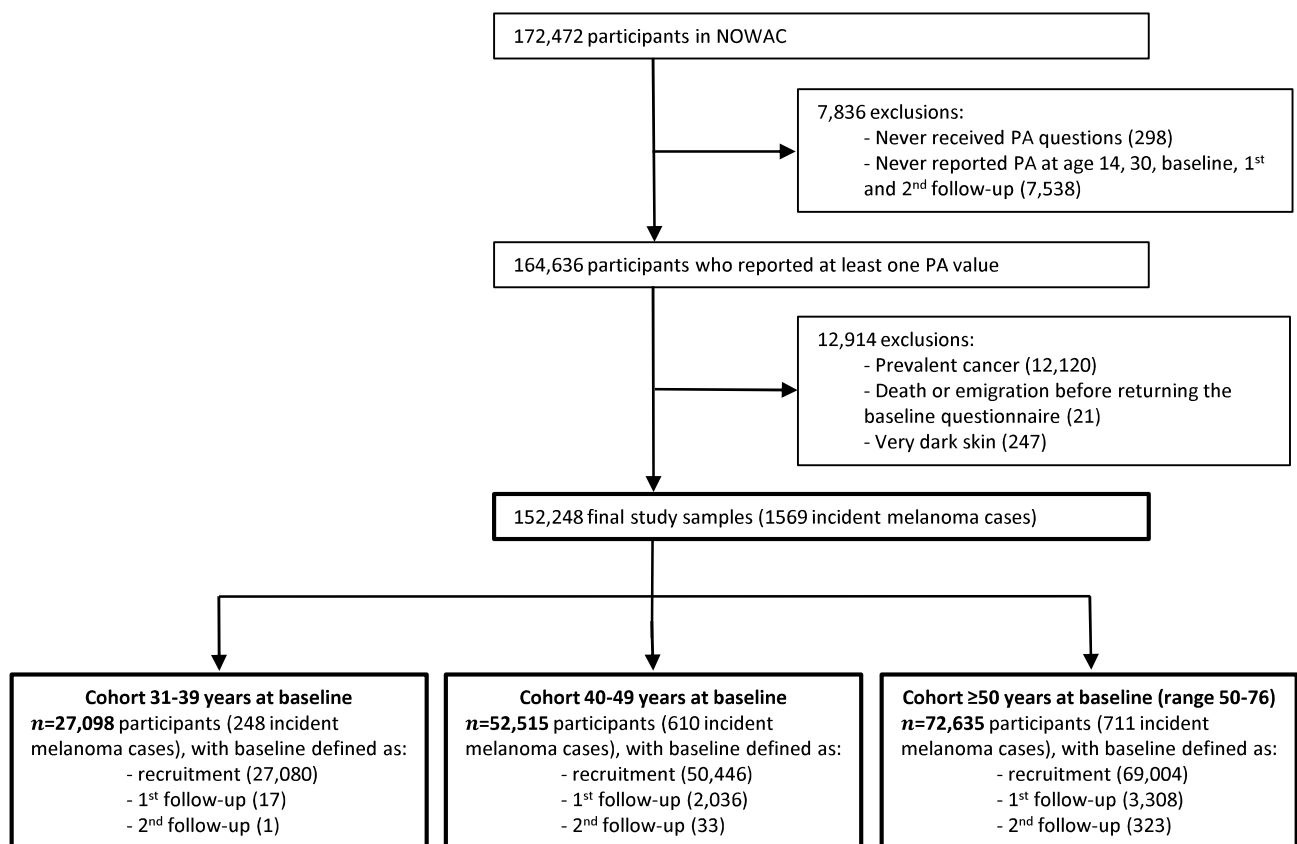
Participants also reported years of education (categorized as  $\leq 10$ , 11–13 and  $\geq 14$  years) and smoking status (never, former, current). Body mass index (BMI,  $\text{kg}/\text{m}^2$ ) was calculated from self-reported height and weight (categorized as normal weight  $< 25.0$ , overweight 25.0–29.9 and obese  $\geq 30.0$ )<sup>30</sup> at baseline and updated during follow-up.

## Follow-Up and Endpoints

Using the unique 11-digit identity number of Norwegian citizens, the NOWAC cohort was linked to the CRN for information on cancer incidence, emigration and death. Melanoma cases were defined as first incident invasive melanoma.

## Study Samples

Baseline was defined as the first returned questionnaire (recruitment, first or second follow-up) with information on current PA. Among 172,472 participants who answered the recruitment questionnaire, we excluded 7836 women with missing information on PA in all questionnaires (Figure 1), ie, who never received PA questions ( $n = 298$ ) or who never reported PA at ages 14 and 30, recruitment, 1st and 2nd follow-up ( $n = 7538$ ). Baseline was set at recruitment for participants who did not report current PA in any of the questionnaires (neither recruitment nor follow-up questionnaires)



**Figure 1** Flowchart of the subcohorts from the Norwegian Women and Cancer (NOWAC) study for the analysis of life-course trajectories of physical activity (PA) and risk of melanoma, 1991–2018.

but who reported past PA at age 14 and/or 30. We further excluded women with melanoma or other cancers diagnosed prior to baseline ( $n = 12,120$ ), women who died or emigrated before returning the baseline questionnaire ( $n = 21$ ) and women who reported very dark skin color (grades 9–10,  $n = 247$ ).<sup>31</sup> In total, 152,248 participants were included in this study, aged 31–76 years, and had the opportunity to retrospectively report PA at ages 14, 30 and at baseline. Because of the wide age range at baseline, participants were analyzed in three subcohorts based on age when reporting PA at baseline: 31–39 years ( $n = 27,098$ ), 40–49 years ( $n = 52,515$ ) and  $\geq 50$  years ( $n = 72,635$ ).

## Statistical Analyses

### Trajectories

LCMM (also known as growth mixture modeling) was used to estimate life-course PA trajectories, ie, classes (groups) of participants following a similar PA pattern over time,<sup>32</sup> separately in each subcohort (31–39 years, 40–49 years and  $\geq 50$  years at baseline). Age (14, 30 and age at baseline) was set as time indicator and included as fixed terms (linear and quadratic) and class-specific terms (linear and quadratic). For each subcohort, trajectory models including 2, 3, 4 and 5 classes were evaluated. We chose the number of classes ( $k$ ) that best fit with our data based on Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), entropy, classes' distribution and posterior probability. A grid of 100 initial values was used to prevent any convergence toward a local maximum. Participants who reported PA at least once were included (LCMM takes into account incomplete exposure).

### Three-Step Approach

To assess the association between PA trajectories and melanoma risk, we used a three-step approach<sup>33,34</sup> combined with Cox proportional hazards regression. The trajectory analysis, described above, is the first step. The second step consists in assigning class membership to each participant. Posterior probabilities of belonging to each of the  $k$  classes were computed for each participant. We then used the proportional assignment method,<sup>34,35</sup> ie, each participant was replicated  $k$  times in the dataset and assigned to each of the  $k$  classes together with its related posterior probabilities. In the third step, we investigated the association between class membership of PA trajectories from step 2 and melanoma risk in a Cox proportional hazard model estimating hazard ratios (HRs) and 95% confidence intervals (CIs). To take the uncertainty of classification into account, the posterior probabilities from step 2 were used as weights. We used age as time-scale, calculating person-years from baseline to date of diagnosis of first melanoma or any other primary cancer, emigration, death or end of follow-up (31st December 2018) whichever occurred first. A directed acyclic graph (DAG) was used to model the relationship between PA trajectories and melanoma risk, based on current knowledge on melanoma risk factors ([Figure S1](#)). Based on this DAG, we used three adjustment sets of covariates. Model 0 is the age-adjusted model. In model 1, we additionally adjusted for education and smoking corresponding to the minimal set of covariates necessary to control for confounding when estimating the total effect of PA on melanoma risk based on the DAG. In model 2, we further adjusted for hair color as a proxy of sensitivity to UVR exposure,<sup>26</sup> residential ambient UVR exposure and height, corresponding to the maximal set of covariates based on the DAG. Sunbathing vacations, sunburn, indoor tanning and obesity were not included in the maximal set of covariates identified by the DAG as they are mediators on the path from PA trajectories to melanoma. Only participants with complete information for all adjustment covariates were included in step 3.

Additional adjustment for sunbathing vacations, sunburn, indoor tanning and BMI (as a proxy of obesity) was also carried out. We also conducted sensitivity analysis based on an alternative DAG in which the arrow between PA trajectories and obesity was reversed ([Figure S2](#)). Based on this alternative DAG, we further adjusted for BMI in model 1 and for BMI and indoor tanning in model 2.

### Naïve Approach

In addition to the 3-step approach, we also implemented a naïve approach. For this approach, PA at ages 14, 30 and baseline were regrouped into three categories: low (1–4), moderate (5–6) and high (7–10).<sup>36</sup> Thus, there were 27 possible naïve trajectories combining the three categories of PA at the three time points. We regrouped the 27 possible naïve trajectories into five groups: low, moderate, high, decreasing and increasing ([Table S1](#)). The association between the

naïve trajectories and melanoma risk was then investigated using Cox proportional hazard models with the same adjustment sets as in the three-step approach in each subcohort. Only participants with complete information for PA at ages 14, 30 and baseline were included in the naïve trajectories.

For graphical representations of predicted life-course trajectories and Sankey diagrams of PA trajectory classes obtained with latent class mixed model (LCMM) and naïve life-course trajectory analysis, participants needed to belong to a unique trajectory class. Thus, the modal assignment method was used (ie, each participant was assigned to the class with the highest posterior probability computed in step 2 above).

Statistical analyses were carried out using the R software (<https://www.r-project.org/>), including lcmm package for the LCMM trajectory's analysis.<sup>37</sup> We used two-sided tests and a 5% statistical significance level. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines were used ([Supplementary Materials](#)).

## Results

### Characteristics of Study Participants

Women in the youngest subcohort (31–39 years at baseline) were recruited earlier, followed for a longer period and were younger at end of follow-up and at diagnosis compared to the other subcohorts (40–49 years and  $\geq 50$  years at baseline, [Table 1](#)). Participants from the youngest subcohort were also more likely to be in the highest category of education, currently smoking, have a lower BMI, report fewer sunburns and sunbathing vacations, and use indoor tanning devices more often ([Table 1](#)). PA at age 14 and baseline were similar in the three subcohorts (mean PA at age 14: 6.5, 6.5 and 6.8,

**Table 1** Baseline Characteristics of the Study Sample from the Norwegian Women and Cancer Study (1991–2018, n = 152,248), Stratified by Subcohorts Labelled According to Age at Baseline

	Subcohorts		
	31–39 years <sup>a</sup>	40–49 years <sup>a</sup>	$\geq 50$ years <sup>a,b</sup>
<b>Number of participants, n (%)</b>	27,098 (17.8)	52,515 (34.5)	72,635 (47.7)
<b>Melanoma cases, n (%)</b>	248 (15.8)	610 (38.9)	711 (45.3)
<b>Year of recruitment, %</b>			
1991–1992	86.5	53.9	2.1
1997–1998	13.5	20.5	32.9
2003–2007	0.0	25.5	64.9
<b>Birth cohort, %</b>			
1927–1944	0.0	10.6	35.2
1945–1952	19.8	56.2	49.0
1953–1965	80.2	33.2	15.7
<b>Follow-up time (years), mean (SD)</b>	24.6 (5.6)	20.3 (6.9)	14.4 (5.0)
<b>Age at recruitment, mean (SD)</b>	36.7 (2.1)	45.8 (2.8)	56.6 (4.7)
<b>Age at end of follow-up, mean (SD)</b>	61.3 (6.1)	66.1 (6.2)	71.0 (6.8)
<b>Age at diagnosis, mean (SD)</b>	52.8 (8.2)	59.8 (7.4)	66.8 (7.6)
<b>Education, %</b>			
$\leq 10$	27.2	31.9	35.2
11–13	32.7	30.0	26.0
$\geq 14$	38.9	34.6	31.9
Missing	1.2	3.5	6.9
<b>Smoking, %</b>			
Never	31.8	33.3	37.0
Former	27.0	33.2	37.6
Current	39.7	32.5	24.8
Missing	1.5	1.0	0.6

(Continued)

**Table 1** (Continued).

	Subcohorts		
	31–39 years <sup>a</sup>	40–49 years <sup>a</sup>	≥50 years <sup>a,b</sup>
<b>BMI (kg/m<sup>2</sup>), mean (SD)</b>	22.6 (3.3)	23.9 (3.7)	25.2 (4.1)
<b>BMI category, %</b>			
Normal and underweight (<25.0 kg/m <sup>2</sup> )	80.7	68.8	54.5
Overweight (25.0–29.9 kg/m <sup>2</sup> )	14.2	22.9	32.0
Obese (≥30 kg/m <sup>2</sup> )	3.5	6.5	11.1
Missing	1.6	1.8	2.4
<b>Hair color, %</b>			
Black/dark brown	14.3	15.1	16.8
Brown	33.7	38.1	37.8
Blond/yellow	34.1	36.1	37.5
Red	2.4	2.8	3.1
Missing	15.6	7.9	4.7
<b>Ambient UVR of residence, %</b>			
Low (northern Norway)	11.2	18.5	26.6
Medium-low (central Norway)	14.3	12.9	8.9
Medium (southwestern Norway)	20.0	17.3	18.9
Highest (southeastern Norway)	54.6	51.3	45.5
<b>Sunburns (per year)<sup>c</sup>, %</b>			
Never	24.8	19.9	14.6
I	27.3	23.6	28.6
≥2	38.3	36.6	49.7
Missing	5.5	17.4	9.2
<b>Sunbathing vacations (weeks/year)<sup>c</sup>, %</b>			
Never	24.8	19.9	14.6
I	27.3	23.6	28.6
2–3	32.5	30.0	38.2
≥4	5.8	6.6	11.5
Missing	9.6	20.0	7.1
<b>Indoor tanning<sup>c</sup>, %</b>			
Never	35.2	36.9	41.6
Rarely	44.1	33.8	40.7
≥1 per month	13.7	13.2	12.1
Missing	6.9	16.1	5.6
<b>PA at age 14, mean (SD)<sup>d</sup></b>	6.5 (2.0)	6.5 (2.0)	6.8 (2.0)
<b>PA at age 30, mean (SD)<sup>e</sup></b>	5.8 (1.8)	6.2 (1.8)	6.7 (1.8)
<b>PA at baseline, mean (SD)<sup>f</sup></b>	5.7 (1.9)	5.7 (1.9)	5.7 (1.9)

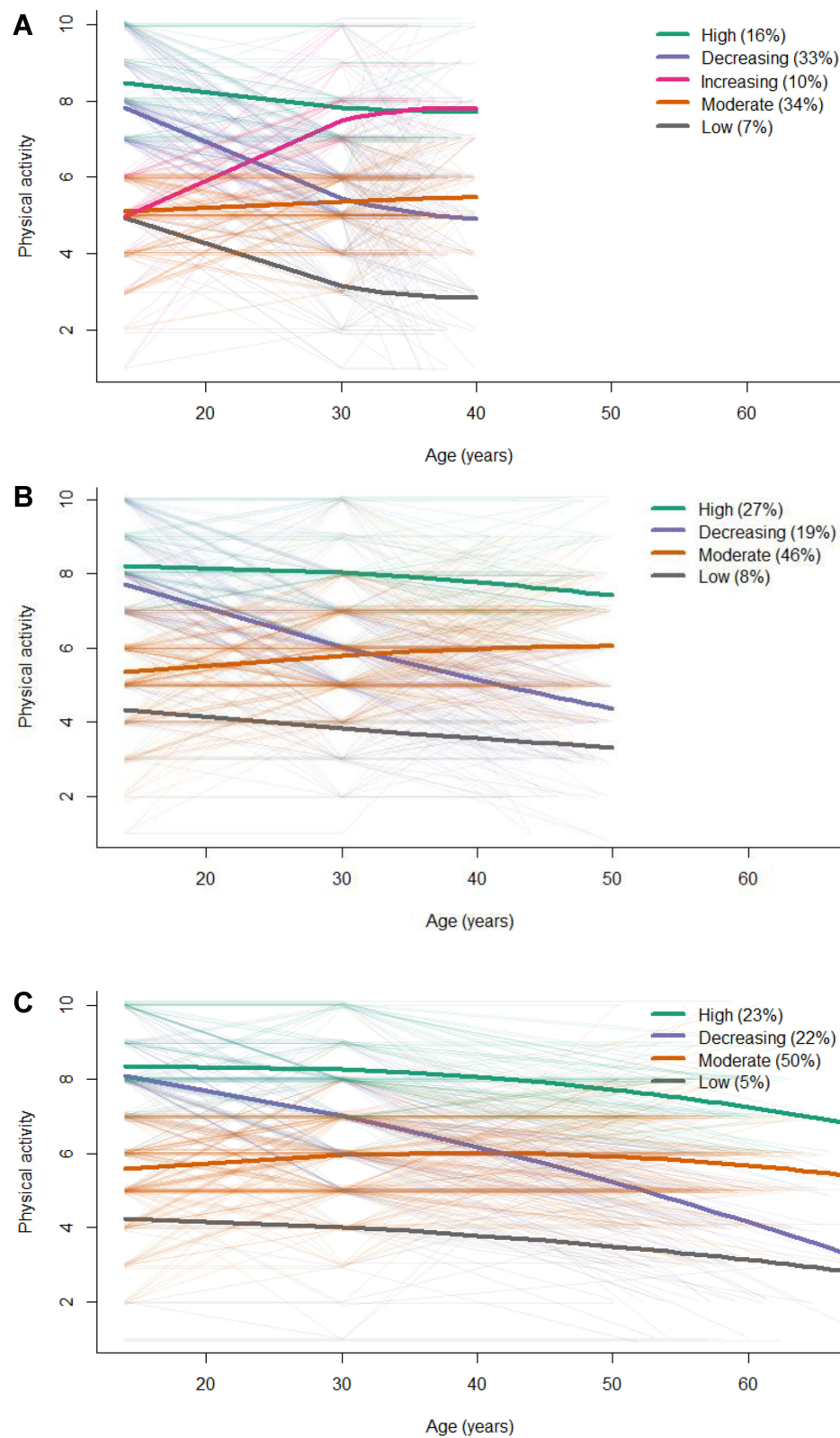
**Notes:** <sup>a</sup>Age when recording information on current physical activity; <sup>b</sup>Range 50–76 years at baseline; <sup>c</sup>During the last decade. <sup>d</sup>Missing: 31–39 (n = 257), 40–49 (n = 2760), ≥50 (n = 7473). <sup>e</sup>Missing: 31–39 (n = 1108), 40–49 (n = 1631), ≥50 (n = 4665). <sup>f</sup>Missing: 31–39 (n = 133), 40–49 (n = 174), ≥50 (n = 347).

**Abbreviations:** BMI, body mass index; PA, physical activity; SD, standard deviation; UVR, ultraviolet radiation.

for subcohorts 31–39, 40–49 and >50 years at baseline, respectively, and mean PA at baseline: 5.7 for all the subcohorts), while PA at age 30 was highest in the oldest subcohort (mean PA: 5.8, 6.2 and 6.7, for subcohorts 31–39, 40–49 and >50 years, respectively) (Table 1 and Figure S3). A total of 248, 610 and 711 women were diagnosed with primary incident melanoma in subcohorts 31–39, 40–49 and ≥50 years, respectively.

## Trajectory Analysis

Based on the best compromise between discrimination capacity (high entropy), model quality (low AIC and BIC), classes' distribution and posterior probabilities (Tables S2 and S3), LCMM identified five life-course PA trajectory classes (low, moderate, high, decreasing and increasing) for subcohort 31–39 years (Figure 2A) and four (low, moderate,



**Figure 2** Class-specific average predicted life-course trajectories (bold lines) of physical activity for each subcohort: 31–39 years (**A**), 40–49 years (**B**) and  $\geq 50$  years (**C**) at baseline, the Norwegian Women and Cancer study, 1991–2018,  $n = 152,248$ .

**Note:** The thinner lines in the background represent observed individual trajectories of 500 participants randomly selected in each subcohort.

high and decreasing) for subcohorts 40–49 and  $\geq 50$  years (Figure 2B and C). Most participants in the youngest subcohort were in the moderate (34%) or decreasing (33%) classes. An increasing life-course trajectory class (10%) was only identified in the youngest subcohort. Trajectory patterns and participants' distribution in the four classes were similar up to age 50 in the two oldest subcohorts (Figure 2), except for a steeper decrease by increasing age in the decreasing class in the 40–49 subcohort. In the  $\geq 50$  years subcohort, PA decreased in all the classes after age 50. Almost half of the participants in the older cohorts were allocated to the moderate class (46% for 40–49 years and 50% for  $\geq 50$  years). In all three subcohorts, participants in the high PA class were more likely to have a lower BMI, less sunburns, use indoor tanning more often and spend more time on sunbathing vacations (Tables S4–S6).

With the naïve approach, most participants were assigned to the moderate or high PA life-course trajectory classes for all subcohorts, and there was major overlap between the LCMM and naïve classes (Figure 3 and Figure S4). For subcohorts 40–49 and  $\geq 50$  years, the main difference between the two approaches was that the naïve-increasing class was part of the LCMM-moderate class.

## PA Trajectories and Melanoma Risk

Using the moderate trajectory as reference, LCMM life-course PA trajectories were not significantly associated with melanoma in any subcohorts with models 0, 1 and 2 (Table 2; HR (95% CI) for high versus moderate with model 2 were 0.92 (0.66–1.29), 1.15 (0.97–1.37) and 0.90 (0.78–1.05) for subcohorts 31–39, 40–49 and  $\geq 50$  years at baseline, respectively). In the youngest subcohort, women who increased their level of PA from adolescence to adulthood had a non-significant lower risk of melanoma compared to moderately active women (HR = 0.77, 95% CI = 0.54–1.08, model 2). Further adjustment for sunbathing vacations, sunburns, indoor tanning and BMI did not change the results (Table S7). Sensitivity analysis using an alternative DAG where the arrow between PA and obesity was reversed also gave similar results (Table S8).

As for LCMM trajectories, the naïve PA trajectories were not associated with melanoma risk in any subcohort, regardless of adjustment for UVR exposure (Table 3). In the oldest subcohort, a non-significantly reduced risk of melanoma was found for women in the low compared to the moderate trajectory (HR = 0.69, 95% CI = 0.46–1.04, model 2). The 40–49 years subcohort was the only subcohort with positive (though non-significant) associations.

## Discussion

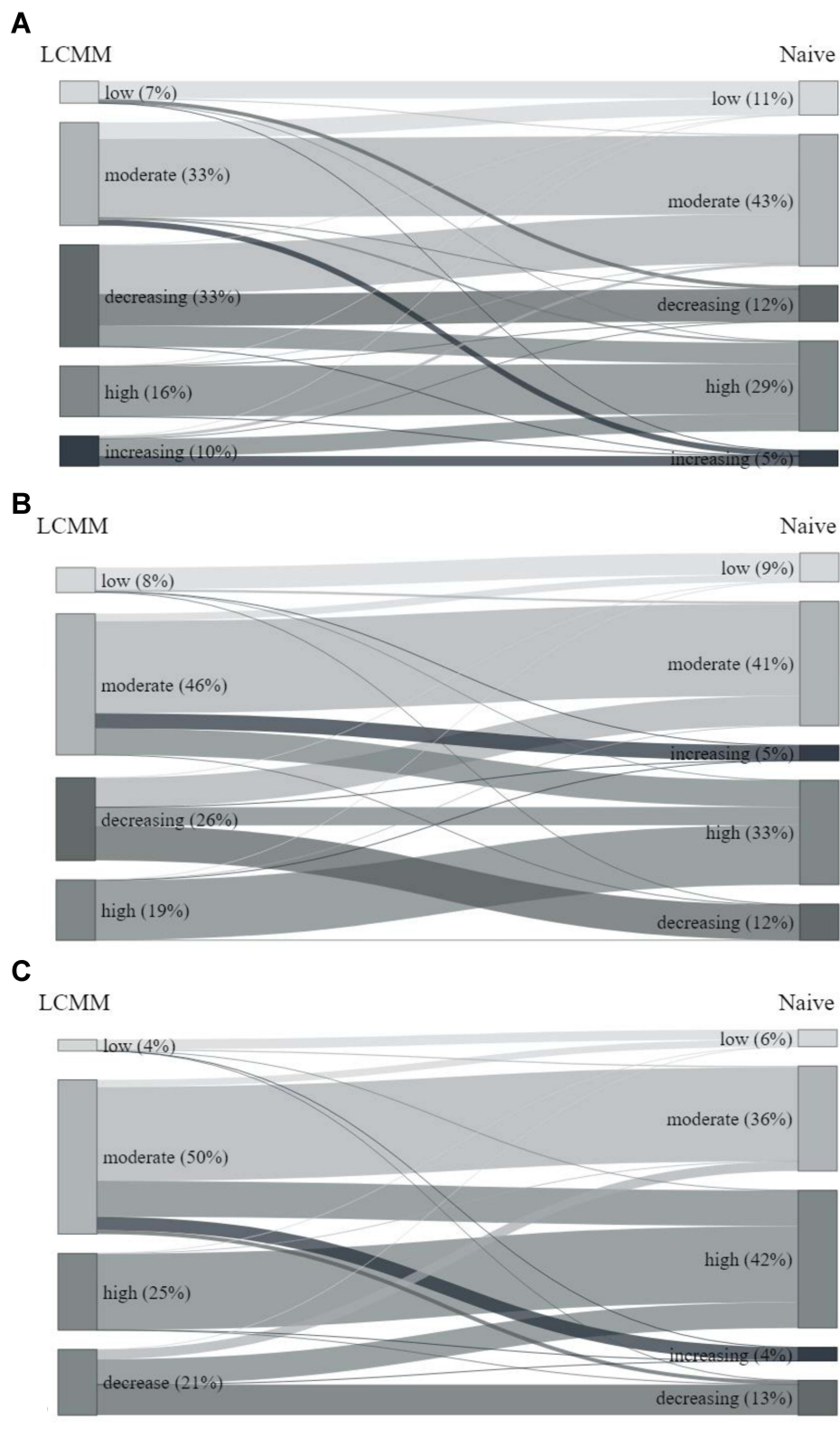
Using three measures of PA from adolescence through adulthood, the LCMM approach identified five life-course trajectory classes for the subcohort aged 31–39 years at baseline (low, moderate, high, decreasing and increasing) and four for the subcohorts 40–49 and  $\geq 50$  years at baseline (low, moderate, high and decreasing). These trajectory classes overlapped largely in all subcohorts with the five naïve classes (low, moderate, high, decreasing and increasing). We did not find any significant associations between the LCMM or naïve life-course PA trajectory classes and melanoma risk.

PA trajectories have been studied during different periods in life, including childhood/adolescence<sup>6</sup> and different periods of adulthood (early, mid and old).<sup>3–5,36,38,39</sup> A recent systematic review found that three to five PA trajectory classes were reported by most studies.<sup>1</sup> However, a maximum of 10 classes has also been reported.<sup>8</sup> Differences between studies in number of trajectories might be explained by differences in age periods, length of trajectory period, number of PA measures used, PA type, sex, sample size and method used to estimate the trajectories.

Since age when assessing current PA at baseline ranges over several age decades in women participating in the NOWAC study, we divided the cohort into three subcohorts and investigated PA trajectories in each subcohort separately. Different patterns of PA trajectories were obtained in the subcohorts. In particular, no increasing PA class was found for the two oldest subcohorts. Participants in the increasing PA class in the youngest subcohort might decrease their level of PA later in life and thereby move to the moderate PA class when reaching the age of the oldest subcohort. Indeed, in subcohorts 40–49 and  $\geq 50$  years at baseline, participants assigned to the increasing PA class using the naïve method were assigned to the moderate PA class by LCMM. The absence of increasing class was also reported by a systematic review of PA trajectories, for the studies including the oldest participants.<sup>1</sup>

To our knowledge, this is the first study investigating the association between trajectories of life-course PA and melanoma. Our result of no association between PA trajectories and incident invasive melanoma is in agreement with





**Figure 3** Sankey diagrams of physical activity trajectory classes obtained with latent class mixed model (LCMM) and naïve life-course trajectory analysis, for each subcohort: 31–39 years (A), 40–49 years (B) and ≥50 years (C) at baseline, in the Norwegian Women and Cancer study, 1991–2018, n = 137,800.

**Table 2** Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for Melanoma Risk in Life-Course Physical Activity Trajectories (Latent Class Mixed Model) Using the Moderate Trajectory Class as Reference in Each Subcohort of the Norwegian Women and Cancer Study, 1991–2018, n = 130,259

Classes	n (Cases) <sup>b</sup>	Model 0 <sup>c</sup>	Model 1 <sup>d</sup>	Model 2 <sup>e</sup>
<b>31–39 years<sup>a</sup></b>	<b>21,129 (220)</b>			
Low	1769 (16)	0.89 (0.59–1.34)	0.90 (0.60–1.35)	0.91 (0.60–1.36)
Moderate	7181 (77)	1.00	1.00	1.00
High	3535 (35)	0.93 (0.67–1.30)	0.94 (0.67–1.31)	0.92 (0.66–1.29)
Decreasing	7420 (73)	0.93 (0.74–1.15)	0.93 (0.75–1.16)	0.93 (0.75–1.16)
Increasing	2224 (18)	0.75 (0.53–1.06)	0.76 (0.54–1.07)	0.77 (0.54–1.08)
<b>40–49 years<sup>a</sup></b>	<b>45,839 (540)</b>			
Low	4245 (44)	0.85 (0.68–1.08)	0.87 (0.69–1.10)	0.87 (0.69–1.10)
Moderate	19,387 (227)	1.00	1.00	1.00
High	9388 (119)	1.11 (0.93–1.32)	1.13 (0.95–1.35)	1.15 (0.97–1.37)
Decreasing	12,819 (151)	1.02 (0.89–1.18)	1.03 (0.90–1.19)	1.03 (0.90–1.19)
<b>≥50 years<sup>a</sup></b>	<b>63,291 (617)</b>			
Low	3678 (31)	0.84 (0.65–1.07)	0.85 (0.66–1.09)	0.84 (0.65–1.08)
Moderate	29,132 (304)	1.00	1.00	1.00
High	15,419 (146)	0.88 (0.75–1.02)	0.89 (0.77–1.04)	0.90 (0.78–1.05)
Decreasing	15,063 (136)	0.88 (0.77–1.00)	0.91 (0.80–1.03)	0.92 (0.81–1.04)

**Notes:** <sup>a</sup>Subcohorts are labelled by age at baseline. <sup>b</sup>Weighted class-specific sample size (n) is the sum of participants' weights in the class and weighted class-specific number of cases (cases) is the sum of cases' weights in the class (see Statistical analyses). <sup>c</sup>Model 0: Cox proportional hazards model stratified by year of recruitment, and with age as time scale. <sup>d</sup>Model 1: model 0 + education and smoking status. <sup>e</sup>Model 2: model 1 + hair color, ambient ultraviolet radiation of residence and height.

**Table 3** Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for Melanoma Risk in Life-Course Naïve Trajectories of Physical Activity Using the Moderate Trajectory Class as Reference for Each Subcohort in the Norwegian Women and Cancer Study, 1991–2018, n = 119,768

Classes	n (Cases) <sup>b</sup>	Model 0 <sup>c</sup>	Model 1 <sup>d</sup>	Model 2 <sup>e</sup>
<b>31–39 years<sup>a</sup></b>	<b>21,596 (215)</b>			
Low	2387 (20)	0.74 (0.46–1.20)	0.75 (0.46–1.20)	0.75 (0.46–1.21)
Moderate	9277 (104)	1.00	1.00	1.00
High	6350 (58)	0.82 (0.60–1.13)	0.82 (0.60–1.13)	0.82 (0.59–1.12)
Decreasing	2489 (22)	0.80 (0.51–1.27)	0.83 (0.52–1.31)	0.83 (0.52–1.32)
Increasing	1093 (11)	0.90 (0.48–1.67)	0.91 (0.49–1.70)	0.92 (0.49–1.71)
<b>40–49 years<sup>a</sup></b>	<b>42,388 (510)</b>			
Low	3978 (47)	1.00 (0.73–1.38)	1.02 (0.74–1.41)	1.02 (0.74–1.40)
Moderate	17,202 (191)	1.00	1.00	1.00
High	14,232 (183)	1.18 (0.97–1.45)	1.20 (0.98–1.47)	1.21 (0.99–1.48)
Decreasing	4887 (60)	1.12 (0.84–1.49)	1.14 (0.86–1.53)	1.15 (0.86–1.54)
Increasing	2089 (29)	1.23 (0.83–1.81)	1.25 (0.84–1.84)	1.25 (0.85–1.85)
<b>≥50 years<sup>a</sup></b>	<b>55,784 (553)</b>			
Low	3355 (26)	0.70 (0.46–1.05)	0.70 (0.47–1.05)	0.69 (0.46–1.04)
Moderate	20,067 (224)	1.00	1.00	1.00
High	23,252 (228)	0.89 (0.74–1.07)	0.90 (0.75–1.08)	0.91 (0.75–1.09)
Decreasing	69,55 (59)	0.76 (0.57–1.01)	0.79 (0.59–1.05)	0.80 (0.60–1.07)
Increasing	2155 (16)	0.75 (0.46–1.23)	0.75 (0.46–1.23)	0.75 (0.46–1.23)

**Notes:** <sup>a</sup>Subcohorts are labelled by age at baseline. <sup>b</sup>Class-specific sample size (n) and number of cases (cases). <sup>c</sup>Model 0: Cox proportional hazards model stratified by year of recruitment, and with age as time scale. <sup>d</sup>Model 1: model 0 + education and smoking status. <sup>e</sup>Model 2: model 1 + hair color, ambient ultraviolet radiation of residence and height.

some previous studies that used measures of PA at one specific time,<sup>16,19–21</sup> and with our previous study in NOWAC investigating PA at recruitment and updated during follow-up.<sup>22</sup> However, some studies found a positive association between PA and melanoma risk.<sup>14,15,17</sup> Regular physical activity is recommended by public health authorities,<sup>40</sup> thus our finding of no association of increased PA over lifetime with melanoma is reassuring.

Most studies examining the association between trajectory classes and an outcome used modal assignment (assignment of the class with the highest posterior probability) without including posterior probabilities as weights in the analysis of the association between trajectory classes and an outcome.<sup>2,4,6,8,41</sup> We used proportional assignment for PA trajectory classes to take the classification uncertainty into account in the Cox regression.

Our study included population-based data from a large prospective cohort and a combination of occupational and recreational PA, reported at baseline for up to three different time points (ages 14, 30 and study baseline) for more than 150,000 Norwegian women. The linkage to the CRN is also an important strength. Reporting of incident cancers to the CRN is compulsory in Norway, and 99.9% of the melanomas are morphologically verified.<sup>42,43</sup> However, some misclassification of PA may exist. Questionnaires were used to record PA by a 10-point scale validated to rank current PA levels in the Norwegian female population,<sup>24</sup> thus considered a suitable measure to differentiate PA in our study. However, no validation study has been conducted for the retrospective assessment of PA at ages 14 and 30. PA included any type of PA (occupational, recreational, commuting, home duties, etc.) and has been used to investigate PA and risk of other cancer sites.<sup>36,44–46</sup> Depending on the subcohort, PA trajectories were estimated based on up to three PA measures over an average period of 13 to 33 years. A strength of the LCMM method applied in the current study is that it includes participants with incomplete data (ie, who did not report PA for all time points).<sup>37</sup> As PA might change from age 30 to age at baseline, more PA measures would have improved the estimation of PA trajectories. Moreover, there may be more misclassification of PA at ages 14 and 30 years in the oldest subcohort, since the time period from age 30 to baseline was much longer (20–46 years) than for the youngest subcohort (1–9 years). Importantly, misclassification is likely non-differential since this is a cohort study with exposure recorded prior to cancer diagnosis. In addition, the PA assessment lacks information of whether PA was practiced indoor or outdoor, and the intensity, frequency and duration of PA. Studies with cardiorespiratory fitness measures would be needed to validate our findings.

The NOWAC women live in a high-latitude country. In a previous study from this cohort, we found positive associations between PA and sunbathing vacations and indoor tanning, and an inverse association between PA and sunburns.<sup>22</sup> The latter is in contrast to studies from other climates where a positive association has been found between PA and sunburns.<sup>47–50</sup> Our analysis was based on DAGs, taking UVR sensitivity and UVR exposure into account. Adjusting for UVR sensitivity (model 2) and UVR exposure (sensitivity analysis) did not change the results. An explanation might be that PA included both indoor and outdoor activities and UVR exposure referred to general UVR habits and did not include UVR exposure while practicing PA. Thus, our findings might not be generalizable to populations in more sunny climates where the association between PA and sun exposure is more important.<sup>50</sup>

## Conclusion

In this prospective cohort study of Norwegian women aged 31–76 years at inclusion, we investigated PA trajectories over the life course with retrospective assessments of PA in adolescence and early adulthood. We identified five classes of life-course PA trajectories in the youngest subcohort and four trajectory classes in the oldest subcohorts. We did not find any associations between PA trajectories and melanoma risk. Our result does not support a positive association between PA and cutaneous melanoma risk found in previous studies, which is important for public health guidelines promoting regular PA.

## Abbreviation

AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, Confidence interval; CRN, Cancer Registry of Norway; DAG, Directed acyclic graph; BMI, Body mass index; HR, Hazard ratio; LCMM, Latent class mixed model; NOWAC, Norwegian Woman and Cancer; PA, Physical activity; UVR, Ultraviolet radiation.

## Data Sharing Statement

The data generated and/or analysed in the current study can be accessed upon reasonable request to the originating cohort (NOWAC@uit.no). Access will be conditional to adherence to local ethical and security policy. The R code used to conduct specific analyses will be shared on reasonable request (of the specific code) to the corresponding author.

## Ethics Approval and Consent to Participate

All women provided informed consent, and data were handled in accordance with the relevant ethical regulations. 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) and complies with the Declaration of Helsinki.

## Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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