MAIN DOCUMENT

Title: Anthropometric factors and Breslow thickness: Prospective data on 2570 cutaneous melanoma cases in the population-based Janus Cohort

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SUMMARY

Background: Breslow thickness is the most important prognostic factor of localized cutaneous melanoma (CM), but associations with anthropometric factors have been sparsely and incompletely investigated.

Objectives: To examine pre-diagnostic body mass index (BMI), body surface area (BSA), height, weight and weight change in relation to Breslow thickness, overall and by anatomical site and histological subtype. Further, to assess possible non-linear associations between these anthropometric factors and Breslow thickness.

Methods: CMs in the Janus Cohort were identified 1972–2014. Linear regression was used to estimate geometric mean ratios (GMRs) of Breslow thickness with 95% confidence intervals (CIs) according to anthropometric factors. Restricted cubic splines in generalized linear models predicted adjusted mean Breslow thickness, and were used to assess possible non-linear relationships.

Results: Among 2570 CM cases, obese had a GMR of 1.16 (95% CI: 1.04, 1.30) of Breslow thickness *versus* normal weight cases. For BSA and weight, quintile 5 showed GMRs of 1.13 (95% CI: 1.00, 1.27) and 1.17 (95% CI: 1.03, 1.33) of Breslow thickness *versus* quintile 1, respectively. Associations seemed restricted to superficial spreading melanomas and CMs on the trunk and lower limbs. The associations plateaued at an adjusted mean Breslow thickness of about 2.5 mm (BMI 29 kg/m^2, BSA 2.05 m^2 and weight 90 kg), before declining for the highest values. No associations were found for height and weight change.

Conclusions: This large case-series of incident CM demonstrated positive associations between BMI, BSA, weight and Breslow thickness, and suggested that behavioral or other mechanisms apply at high values.

BULLET POINTS

What's already known about this topic?

- Several studies have reported associations between anthropometric factors and risk of cutaneous melanoma (CM).
- Two previous studies have reported an association between thick CMs and a body mass index (BMI) of ≥25 kg/m^2, but the relation between Breslow thickness and other anthropometric factors and the shape of these associations have remained unexplored to date.

What does this study add?

- This study is the first to model Breslow thickness as a continuous outcome in relation to pre-diagnostically measured BMI, body surface area (BSA), height weight, and weight change.
- This large case-series of 2570 incident CMs showed that Breslow increased with BMI, BSA and weight, but plateaued at an adjusted mean of about 2.5 mm when BMI exceeded 29 kg/m^2, BSA exceeded 2 m^2, and weight exceeded 90 kg.

INTRODUCTION

Cutaneous melanoma (CM) incidence and mortality rates have been increasing in fair-skinned populations worldwide[1], and in Europe CM is currently the third most frequent cancer after colorectal cancer and lung cancer.[2] Exposure to solar ultraviolet radiation (UVR) is the primary environmental risk factor, and it has been estimated to account for 85% of all CM cases.[3,4] Further, pigmentation characteristics such as nevi, hair and eye color and the skin's sensitivity to sunburns, are known CM risk factors.[5]

CM risk has been positively associated with body mass index (BMI), body surface area (BSA), weight and height in large population-based cohort studies with pre-diagnostic measurements,[6-9] and the latest meta-analysis confirmed a positive association between obesity and CM risk, most clearly seen in men probably due to confounding from solar UVR in women.[10]

Breslow thickness (*i.e.* vertical tumor thickness) is the most important prognostic factor of localized primary CM.[11] However, limited data exist on anthropometric factors in relation to Breslow thickness. To our knowledge, only three studies have addressed this; de Giorgi *et al.* found that overweight and postmenopausal women had increased risk of Breslow thickness >1mm,[12] Gandini *et al.* found a higher median Breslow thickness among CM cases with a BMI ≥25 *versus* <25 kg/m^2,[13] and Skowron *et al*. found a positive association between BMI and Breslow thickness.[14] However, these studies collected data on height and weight post-diagnostically, did not report associations stratified by anatomical site or histological subtype, and did not model Breslow thickness as a continuous outcome.

We recently examined CM risk according to anthropometric factors in the large population-based Janus Cohort.[9] In the present study, we examined pre-diagnostic BMI, BSA, height, weight and weight change in relation to Breslow thickness, in total and by anatomical site and histological subtype, among incident CM cases in the Janus Cohort. Further, we aimed to explore possible non-linear relationships between these anthropometric factors and Breslow thickness.

METHODS

Study population and study design

This study is based on incident CM cases in the Janus Cohort; a population-based cohort for prospective cancer studies with serum samples, anthropometric measurements and questionnaire data from 292,851 Norwegians who participated in five health surveys between 1972 and 2003 (see supplemental Table S6). In one of these surveys, The Norwegian Counties Study, repeated measurements of weight were conducted, allowing for subgroup analyses according to weight change. The Janus Cohort, its data and establishment, have been described in detail previously.[15,16]

For the present study a comprehensive research file was created through linkage of anthropometric measurements and self-reported physical activity and smoking data from the Janus Cohort to individual information on education, occupation, cancer diagnoses, vital status and cause of death from national registries, and to group level information on ambient UVR data and sun tanning behavior in the Norwegian Women and Cancer (NOWAC) cohort study. Details of the linkage and the data sources are published elsewhere.[9,17]

Legal and ethical approvals were obtained from the Norwegian Data Inspectorate, the Regional Committee for Medical Research Ethics, and the Norwegian Directorate of Health.

Assessment of exposures

In the Janus Cohort, baseline height (to the nearest 1 cm) and weight (to the nearest 0.5 kg) were measured by trained staff according to a standardized protocol.[16] BMI was calculated as kg/m^2 and BSA (m^2) was calculated using the DuBois and DuBois' equation ($weight^{0.4253} \times height^{0.7253} \times 0.007184$).[18] Weight change was calculated by subtracting the latest weight measurement from the first (median time between the weight measurements was 10 years).[9] BSA, height and weight were categorized according to sex-specific quintiles (specified in Tables), and BMI (kg/m^2) according to the World Health Organization's BMI classification with additional cut-points: underweight (<18.5), normal weight 1 (18.5–22.9), normal weight 2 (23.0–24.9), overweight 1 (25.0–27.4), overweight 2 (27.5–29.9), and obese (≥30.0).[19] Weight change was categorized as <–2.0, –2.0 to 2.0, and >2.0 kg.[9] The questions about physical activity and smoking were worded somewhat differently in each survey and were harmonized as follows: physical activity: inactive, low, medium, high, unknown (see Stenehjem et al.[9]); and smoking status: current, former, never, unknown (see Hjerkind et al.[16]).

As detailed in Stenehjem et al.[9]; occupation at baseline (indoor, mixed, outdoor, unknown; categorized as in Alfonso et al.[20]) and highest attained educational level at baseline (none, compulsory, upper secondary, college/university, unknown) were obtained by linkage to Statistics Norway.

Ambient UVR exposure was based on region-specific cumulated doses of ultraviolet-B (UVB) radiation between 1972 and 1991 (when 97.5% of the Janus Cohort was recruited), derived from measurements and modelled values.[9,21] UVR exposure estimates were then linked to region of residence at baseline. Cumulative UVB doses were categorized in a decreasing order of UVB dose, as north, mid, southwest, southeast inland, southeast coast.

Annual mean numbers of sunburns on a group-level (specific to county of residence, age and time period) were obtained from the NOWAC study.[17,22] Then, sunburns were summed from birth to baseline and divided by the age at baseline to derive an average intensity measure. The rationale for applying group-level data from the NOWAC (women only) to the Janus Cohort (men and women) was based on a survey conducted by the Norwegian Cancer Society showing only small sex-differences for sunburns.[23]

Identification of cancer cases and assessment of Breslow thickness

Using unique personal identification numbers, the Janus Cohort was linked to the Cancer Registry of Norway (CRN) to provide a complete cancer history from 1953 until 31st December 2014 in all individuals with a CM diagnosis. Reporting of incident cancers to the CRN is compulsory in Norway, and data from several sources ensure high quality data.[24,25] Information on skin cancer localization was based on a CRN modified version of the International Classification of Diseases 7th revision (ICD-7 codes 1900-1909), converted into ICD-10 codes (head and neck = C43.0-4; trunk = C43.5; upper limbs = C43.6; lower limbs = C43.7; not otherwise specified = C43.9). Histological subtypes of CM were defined by using ICD-Oncology 3rd edition codes

(superficial spreading melanoma = 8743; nodular melanoma = 8721; other = 8000, 8723, 8730, 8742, 8744, 8745, 8770, 8772; not otherwise specified = 8720).

The Norwegian Malignant Melanoma Registry (NMMR) was established in 2008 under the CRN, and Breslow thickness has been routinely registered since then. For CM cases in the Janus Cohort diagnosed before 2008, information on Breslow thickness was manually extracted from histopathological reports by experienced CM registrars. Breslow tumour thickness was categorized by T-category as T1 (≤1.0 mm), T2 (>1.0-2.0 mm), T3 (>2.0-4.0 mm) and T4 (>4.0 mm) according to the American Joint Committee on Cancer 8th edition cancer staging manual.[11] Clinical stage was coded according to local CRN categories based on histopathological reports: localized (no metastases), regional metastasis (metastases in regional lymph nodes, satellites and in transit metastases), distant metastasis (organ metastases and non-regional lymph node metastases), and unspecified (no information).

Study samples

Out of 3477 CM cases in the Janus Cohort, we excluded 907 CM cases (16 not histologically verified as CM, 447 with a CM diagnosis before baseline, 14 with missing county of residence, and 430 missing Breslow thickness), leaving 2570 CM cases available for the main analysis of Breslow thickness in relation to anthropometric factors (Figure 1). Breslow thickness according to weight change was examined in a subsample of 284 individuals with repeated anthropometric measurements (Figure 1).

For CM cases from the full cohort, baseline was defined as the year of first participation in a health survey recruiting to the Janus Cohort. For CM cases in the

subsample with repeated weight measurements, baseline was defined as the year of the second weight measurement conducted between 1985 and 1988.

Data analysis

Continuous variables were described as means with standard deviations (SDs) or range, or as medians with 25^{th}–75^{th} percentiles, depending on the data skewness. Categorical variables were presented as frequencies (%).

To examine the relationship between the anthropometric factors and Breslow thickness as a continuous outcome, linear regression with $\log_e$-transformed Breslow thickness was used to estimate regression coefficients with 95% confidence intervals (CIs). Backtransformed estimates; geometric mean ratios (GMRs; the geometric mean relative to the reference group) with 95% CIs are presented. To account for group level data (ambient UVR and sunburns), standard errors that allow for intragroup correlation were used (cluster option in the specification of the variance-covariance matrix in Stata).[26] We adjusted for age at diagnosis, sex, ambient UVR of residence, average intensity of sunburns, occupational UV exposure, physical activity, education, and smoking status. We also adjusted for height in the analyses of BMI, weight and weight change, and adjusted for BMI in the analyses of height (specified in Tables and Figure legends).

To explore the shape of the associations between anthropometric factors and Breslow thickness (not $\log_e$-transformed), we estimated adjusted mean values of Breslow thickness (in mm) by restricted cubic splines in generalized linear regression models, specified with gamma distribution, log link and robust variance, using the Stata commands -mkspline2-, and -adjustrcsspline-.[27,28]

To check for interactions between anthropometric factors and sex, product-terms were included in initial models. We also checked for interactions between anthropometric factors *versus* time period of diagnosis, site and subtype using likelihood ratio tests. The assumption of normally distributed residuals was evaluated by Q-Q and Kernel density plots, and was found satisfactory.

To compare our data with those of de Giorgi *et al.*[12], we also performed a logistic regression analysis in women and estimated odds ratios (ORs) with 95% CIs for CM >1 mm *vs.* ≤1 mm for BMI categorized as <25 and ≥25 kg/m^2.

In a supplemental analysis, we imputed missing data on a combined dataset of the 2570 CM cases with Breslow thickness and the 430 CM cases without to check whether GMRs differed and to evaluate possible selection bias. For these 3000 CM cases, with and without Breslow thickness, 642 CM cases had missing data on one or more of the variables used in the models (mainly occupation and smoking, in addition to Breslow thickness), and we completed the data set by using multiple imputation with chained equations that were ran 25 times (See supplemental material for details).[29]

Tests for significance were two-sided and a 5% level of significance was used. All data analyses were performed using Stata version 15.1 (StataCorp, College Station, TX, USA).

RESULTS

We found no significant interaction effects between anthropometric factors and sex; neither overall ($0.108 \leq P_{interaction} \leq 0.953$) or for each anatomical site ($0.059 \leq P_{interaction} \leq 0.970$), results are therefore presented for men and women combined.

Breslow thickness ranged from 0.08 mm to 40 mm in the total sample of 2570 incident CM cases. Table 1 shows characteristics of the cases, in total and by T category. Men and women were evenly distributed among T1 cases, while the proportion of men increased with increasing T category. BMI increased slightly from T1 to T4. BSA, height and weight increased from T1 to T3, and levelled off or decreased in T4. The proportion of head and neck cases increased from 9% in T1 to 20% in T4, while no clear trend was seen for the other anatomical sites. Nodular melanomas of the head and neck had the highest median Breslow thickness of 3.5 mm (Supplemental Table S1).

Table 2, shows that continuous variables of BMI, BSA and weight, Breslow thickness increased significantly with increasing values (P_{trend} *0.009, 0.029* and *0.007*, respectively), while no significant trend was found for height (P_{trend} 0.557. When modelling these variables in categories, CM cases with BMI ≥30 kg/m^2 had significantly higher Breslow thickness than cases with BMI 18.5-22.9 kg/m^2 (GMR 1.16, 95% CI: 1.04, 1.30) . Increased GMRs were also found in the highest quintiles of BSA and weight (GMRs 95% CIs: 1.13 (1.00, 1.27) and 1.17 (1.03, 1.33), respectively). No significant association was found between Breslow thickness and weight change. No significant interaction effects between anthropometric factors and time period of diagnosis were found (results not shown).

When stratified by anatomical site (Supplemental Table S2), similar significant positive trends were found for continuous variables of BMI (GMR 1.10, P_{trend} 0.004), BSA (GMR 1.02, P_{trend} 0.026) and weight (GMR 1.03, P_{trend} 0.004) in trunk and lower limb CMs, but not head/neck and upper limb CMs. No significant interaction effects

between anatomical sites and anthropometric factors were found ($0.193 \leq P_{interaction} \leq 0.745$).

When stratified by histological subtype (Supplemental Table S3), significant positive trends were only found for BMI (GMR 1.07, P_{trend} *0.027*) and weight (GMR 1.02, P_{trend} *0.020*) in superficial spreading melanomas. No significant interaction effects between histological subtypes and anthropometric factors were found ($0.623 \leq P_{interaction} \leq 0.771$).

In Figure 2, associations between anthropometric factors and Breslow thickness are presented using restricted cubic splines. For BMI, estimated mean Breslow thickness increased from *ca* 1.7 mm for underweight until *ca* 2.5 mm for overweight, and then declined (Figure 2). For BSA, mean Breslow increased from *ca* 1.6 mm at 1.35 m^2 to 2.25 mm at 2.05 m^2, and then declined (Figure 2). Mean Breslow thickness was fluctuating around 2 mm across height from 145 cm to 200 cm. The association with weight showed a similar pattern as for BSA, where mean Breslow thickness increased from *ca* 1.6 mm at 40 kg to *ca* 2.3 mm at 90 kg, and then declined. No association was found for Breslow thickness according to weight change (data not shown).

In the analysis, replicating that of de Giorgi *et al.*[12], we found an OR of 1.19 (95% CI: 0.93, 1.53) for CM >1 mm *versus* ≤1 mm when comparing women with a BMI ≥25 to women with BMI <25 kg/m^2.

The 2570 CM cases with Breslow thickness differed from the 430 CM cases without this information with respect to sex, birth year, age at diagnosis, time period of diagnosis, clinical stage, anatomical site and histological subtype (Supplemental

Table S4). The results based on imputed data (n=3000) did not differ materially from those based on the non-imputed (n=2570), see Supplemental Table S5.

DISCUSSION

In the present study, we prospectively examined Breslow thickness in relation to pre-diagnostic anthropometric factors among 2570 incident CM cases. Categorical analyses showed increased GMRs of Breslow thickness for the highest categories of BMI, BSA and weight, but not for height. The shape of the associations between Breslow thickness and BMI, BSA and weight were non-linear, with exposure-response curves that increased before levelling off or decreasing.

To our knowledge, this is the first study to examine Breslow thickness as a continuous outcome according to anthropometric factors. de Giorgi *et al.* examined Breslow thickness as a dichotomous outcome according to BMI, and found a statistically significant increased risk of thick CMs >1 mm in overweight and postmenopausal women.[12] When replicated on our data, we found no statistically significant result, but we were unable to conduct analyses stratified by menopausal status due to few postmenopausal female participants at baseline.[30] The difference between our results and those of de Giorgi *et al.*[12], Gandini *et al.*[13], and Skowron *et al.*[14] might be explained by the fact that their studies were conducted in Italian and French populations with different phenotypes (*e.g.* skin, eye, and hair colour), sun tanning behaviour, ambient UVR, BMI distribution[31] and access to physicians[32] compared with our Norwegian cohort, and hence a different risk profile to develop thick CMs.[33]

The shape of the exposure-response curves between anthropometric factors and Breslow thickness has, to our knowledge, not been explored previously. Mean Breslow thickness increased until a BMI of 29 kg/m^2, a BSA of 2.05 m^2 and a weight of 90 kg, then plateaued at a mean of *ca.* 2.5 mm before declining for the highest anthropometric values. A similar shape was seen for weight change. In line with our recent discussion of CM risk,[9] the plateauing pattern of Breslow thickness might be explained by residual confounding of UVR exposure. In contrast to our CM risk analysis,[9] we found no association with height and Breslow thickness, which suggest that underlying biological mechanisms such as insulinlike growth factor binding protein 3 (IGFBP-3) and loci that influence height are more likely to be associated with occurrence than progression of CM.[34,35]

When stratified by anatomical site and histological subtype, the associations seemed restricted to superficial spreading melanomas and CMs localized on the trunk and lower limbs, possibly representing divergent pathways of CM development,[36] although we did not find any significant interaction effects between anthropometric factors and site or subtype.

The proportions of men diagnosed as T3/T4 were around twice that of women. That men are diagnosed with CM at a later stage than women, has also been reported in two recent Norwegian studies,[37,38] and may be a result of lower awareness (patient delay) or a higher tumour growth rate in men.[39] Our finding that 24% of the cases were diagnosed as T3/T4 is in sharp contrast to the 15% reported from the US and Australia.[40,41] The high proportions of T3/T4 CMs in our data are likely to be explained mainly by low disease awareness, hazardous sun seeking behaviour,[42-44] and possibly insufficient numbers of dermatologists per inhabitant.[32]

In turn, these factors may contribute to the high CM mortality rate in Norway compared to other fair-skinned populations in the northern hemisphere.[45]

Our findings could also be explained by both behavioural and biological mechanisms. Obesity and body dissatisfaction have been associated with reduced skin self-examination and delayed presentation in CM patients,[46] which might explain the higher BMI in T4 cases, while the decline in adjusted mean Breslow thickness for the highest anthropometric values might reflect a less sun-seeking behaviour in larger individuals and those who gain weight compared to normal size individuals and those who lose weight. Possible biological mechanisms include activation of adipocytes that produce high levels of vascular endothelial growth factor, which has been shown to contribute to angiogenesis and tumour growth.[47] CM progression has also been related to diet-induced obesity in mice models, by involvement of Cav-1 and FASN, which control CM cell proliferation.[48] Leptin is released by adipose tissue and positively associated with body weight,[49] and high levels at diagnosis have been associated with an increased risk of CM[50] that might be mediated by an increase in neoangiogenesis and impaired melanocyte DNA repair.[51] Moreover, obesity has been associated with low vitamin D levels (and *vice versa*).[52,53] Further, low vitamin D levels have been associated with increased Breslow thickness,[54,55] which might suggest that the observed association between adiposity and Breslow thickness in our data could be altered by insufficient vitamin D levels, although direct evidence is lacking.

Strengths of the present study include the large number of incident CM cases from a population-based cancer registry and pre-diagnostic measurements of height and weight performed according to standardized protocol by trained staff. Self-

reported height and weight could lead to biased associations with Breslow thickness.[56] The lack of individual information on UVR exposure and pigmentary traits are important limitations of our study, and we cannot exclude residual confounding from these factors. Moreover, we had no information on hormone use among our female participants which potentially could have confounded the results.[57]

In summary, this large case-series of incident CM from a population-based cohort, demonstrated positive associations between BMI, BSA, weight and Breslow thickness, and showed that Breslow thickness increased with increasing BMI, BSA and weight in a monotonic manner before levelling off or declining at high values.

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TABLES

Table 1. Characteristics of the 2570 melanoma cases in the Janus Cohort stratified by T category

	All	T1 (≤1.0 mm)	T2 (1.0–2.0 mm)	T3 (>2.0–4.0 mm)	T4 (>4.0 mm)
n (%)	2570 (100)	1373 (100)	587 (100)	376 (100)	234 (100)
Breslow thickness, median mm (25^{th}–75^{th} percentile)	1.00 (0.6–2.0)	0.6 (0.5–0.9)	1.5 (1.2–1.8)	3.0 (2.5–3.51)	6.0 (5.0–9.0)
Sex, n (%)					
Men	1423 (55)	692 (50)	324 (55)	247 (66)	160 (68)
Women	1147 (45)	681 (50)	263 (45)	129 (34)	74 (32)
Year of birth, mean (range)	1943 (1922–1972)	1944 (1922–1972)	1942 (1922–1962)	1942 (1922–1962)	1939 (1922–1955)
Age at diagnosis, mean (range)	60 (29–90)	59 (31–90)	60 (40–89)	61 (29–86)	66 (42–90)
Anatomical site, n (%)					
Head and neck	289 (11)	127 (9)	56 (10)	59 (16)	47 (20)
Trunk	1307 (51)	720 (52)	290 (49)	192 (51)	105 (45)
Upper limbs	319 (12)	175 (13)	78 (13)	39 (10)	27 (12)
Lower limbs	617 (24)	330 (24)	153 (26)	84 (22)	50 (21)
Not otherwise specified	38 (2)	21 (2)	10 (2)	2 (<1)	5 (2)
Histological subtype, n (%)					
Superficial spreading melanoma	1624 (63)	1100 (80)	343 (59)	128 (34)	53 (23)
Nodular melanoma	487 (19)	48 (4)	136 (23)	179 (48)	124 (53)
Not otherwise specified	359 (14)	171 (12)	89 (15)	58 (15)	41 (18)
Other[a]	100 (4)	54 (4)	19 (3)	11 (3)	16 (7)
Clinical stage, n (%)					
Localized	2029 (79)	1130 (82)	475 (81)	284 (75)	140 (60)
Regional metastasis	92 (4)	10 (<1)	13 (2)	29 (8)	40 (17)
Distant metastasis	37 (1)	6 (<1)	5 (1)	10 (3)	16 (7)
Unspecified	412 (16)	227 (17)	94 (16)	53 (14)	38 (16)
BMI, mean kg/m^2 (SD)[b]	24.7 (3.3)	24.5 (3.3)	24.9 (3.4)	25.1 (3.2)	25.3 (3.3)
BSA, mean m^2 (SD)[b]	1.89 (0.20)	1.87 (0.19)	1.89 (0.20)	1.92 (0.20)	1.92 (0.18)
Height, mean cm (SD)[b]	173.2 (9.0)	172.6 (8.9)	173.2 (9.1)	174.8 (9.0)	174.1 (8.9)
Weight, mean kg (SD)[b]	74.5 (13.1)	73.3 (13.1)	75.0 (13.3)	76.9 (13.2)	76.9 (12.0)
Weight change, median kg (25^{th}–75^{th} percentile)[c]	3.0 (0.5–6.5)	3.5 (0.5–5.5)	3.0 (0.0–7.0)	3.0 (0.5–6.0)	3.0 (0.0–6.5)
Ambient UVR of residence, n (%)					
North	161 (6)	81 (6)	39 (7)	24 (6)	17 (7)
Mid	313 (12)	159 (11)	91 (16)	30 (8)	33 (14)
Southwest	366 (14)	217 (16)	73 (12)	47 (13)	29 (12)
Southeast inland	1196 (47)	618 (45)	271 (46)	184 (49)	123 (53)
Southeast coast	534 (21)	298 (22)	113 (19)	91 (24)	32 (14)
Sunburns, mean (SD)[d]	0.91 (0.11)	0.92 (0.10)	0.90 (0.11)	0.90 (0.12)	0.87 (0.13)
Occupational UV exposure, n (%)					
Indoor	1576 (61)	856 (63)	358 (61)	222 (59)	140 (60)
Mixed	723 (28)	386 (28)	157 (27)	117 (31)	63 (27)
Outdoor	163 (7)	71 (5)	44 (7)	21 (6)	27 (11)
Unknown	108 (4)	60 (4)	28 (5)	16 (4)	4 (2)
Physical activity, n (%)					
Inactive	454 (18)	235 (17)	107 (18)	63 (17)	49 (21)
Low	1492 (58)	818 (60)	341 (58)	209 (56)	124 (53)
Medium	552 (21)	282 (21)	127 (22)	91 (24)	52 (22)
High	60 (2)	33 (2)	8 (1)	12 (3)	7 (3)
Unknown	12 (<1)	5 (<1)	4 (<1)	1 (<1)	2 (<1)
Smoking status, n (%)					
Never	1009 (39)	557 (41)	222 (38)	142 (38)	88 (37)
Former	687 (27)	362 (26)	165 (28)	100 (27)	60 (26)
Current	791 (31)	403 (29)	183 (31)	123 (33)	82(35)
Unknown	83 (3)	51 (4)	17 (3)	11 (33)	4 (2)
Education, n (%)					
None	8 (<1)	1 (<1)	3 (<1)	4 (1)	0 (0)
Compulsory	574 (22)	274 (20)	137 (23)	90 (24)	73 (31)
Upper secondary	1367 (53)	740 (54)	309 (53)	194 (52)	124 (53)
College/university	617 (24)	356 (26)	136 (23)	88 (23)	37 (16)
Unknown	4 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)

Abbreviations: BMI = body mass index; BSA = body surface area; SD = standard deviation; UVR = ultraviolet radiation.

[a]Lentigo maligna melanoma included in other (n=61)

[b]Missing: weight (n=8); height (n=7); BMI and BSA (n=8)

[c]Weight change only available in a subsample with repeated measurements (n=284).

[d]Group-level data (age-, county- and time period-specific) on the average intensity of sunburns from birth to baseline.

Table 2. Geometric mean ratios (GMRs) and 95% confidence intervals (CIs) from linear regression of Breslow thickness on anthropometric factors, n=2570 cutaneous melanoma cases.

	GMR[a] (95% CI)	GMR[b] (95% CI)	P_{trend}[c]
Body mass index (kg/m²)[d]			
Continuous (per 5)	1.13 (1.08, 1.19)	1.07 (1.02, 1.13)	*0.009*
<18.5	1.03 (0.80, 1.33)	1.10 (0.89, 1.35)	
18.5-22.9	1.00 (1.00, 1.00)	1.00 (reference)	
23.0-24.9	1.13 (1.05, 1.23)	1.06 (0.97, 1.15)	
25.0-27.4	1.21 (1.09, 1.34)	1.10 (0.98, 1.23)	
27.5-29.9	1.22 (1.09, 1.35)	1.09 (0.98, 1.22)	
≥30.0	1.26 (1.13, 1.40)	1.16 (1.04, 1.30)	
Body surface area (m²)			
Continuous (per 0.05)	1.03 (1.02, 1.04)	1.01 (1.00, 1.02)	*0.029*
SQ1 (M: 1.39-1.85; W: 1.35-1.60)	1.00 (1.00, 1.00)	1.00 (reference)	
SQ2 (M: 1.86-1.93; W: 1.61-1.68)	0.97 (0.85, 1.09)	0.98 (0.86, 1.11)	
SQ3 (M: 1.94-2.01; W: 1.69-1.75)	0.99 (0.83, 1.19)	0.99 (0.81, 1.21)	
SQ4 (M: 2.02-2.10; W: 1.76-1.83)	0.98 (0.83, 1.16)	1.00 (0.84, 1.20)	
SQ5 (M: 2.11-2.62; W: 1.84-2.35)	1.12 (0.97, 1.29)	1.13 (1.00, 1.27)	
Height (cm)[e]			
Continuous (per 5)	1.04 (1.02, 1.06)	1.01 (0.99, 1.02)	*0.557*
SQ1 (M: 155-172; W: 148-160)	1.00 (1.00, 1.00)	1.00 (reference)	
SQ2 (M: 173-176; W: 161-163)	0.94 (0.80, 1.10)	0.96 (0.81, 1.13)	
SQ3 (M: 177-179; W: 164-166)	0.94 (0.86, 1.03)	0.97 (0.89, 1.06)	
SQ4 (M: 180-183; W: 167-170)	0.92 (0.80, 1.05)	0.97 (0.85, 1.11)	
SQ5 (M: 184-201; W: 171-184)	0.97 (0.89, 1.06)	1.02 (0.95, 1.10)	
Weight (kg)[d]			
Continuous (per 5)	1.04 (1.03, 1.05)	1.02 (1.01, 1.04)	*0.007*
SQ1 (M: 43-70; W: 41-57)	1.00 (1.00, 1.00)	1.00 (reference)	
SQ2 (M: 71-76; W: 58-61)	1.00 (0.86, 1.17)	1.01 (0.86, 1.19)	
SQ3 (M: 77-81; W: 62-66)	0.97 (0.83, 1.14)	0.98 (0.82, 1.18)	
SQ4 (M: 82-88; W: 67-73)	1.03 (0.86, 1.24)	1.05 (0.86, 1.28)	
SQ5 (M: 89-148; W: 74-120)	1.16 (1.03, 1.32)	1.17 (1.03, 1.33)	
Weight change (kg)[d,f]			
<-2.0	1.24 (0.98, 1.55)	1.22 (0.84, 1.77)	
-2.0 to 2.0	1.00 (reference)	1.00 (reference)	
>2.0	1.00 (0.49, 2.04)	0.99 (0.55, 1.76)	

Abbreviations: M = men; SQ = sex-specific quintile; W = women.
Missing: weight (n=8); height (n=7); body mass index and body surface area (n=8)

[a]Adjusted for age at diagnosis

[b]Adjusted for age at diagnosis, sex, ambient UVR of residence, average intensity of sunburns, occupation, physical activity, education, smoking.

[c]Modelled as a continuous variable to test for linear trend.

[d]Adjusted for height in addition to covariates in b

[e]Adjusted for body mass index in addition to covariates in b

[f]Weight change only available in a subsample with repeated measurements (n=284).

FIGURES

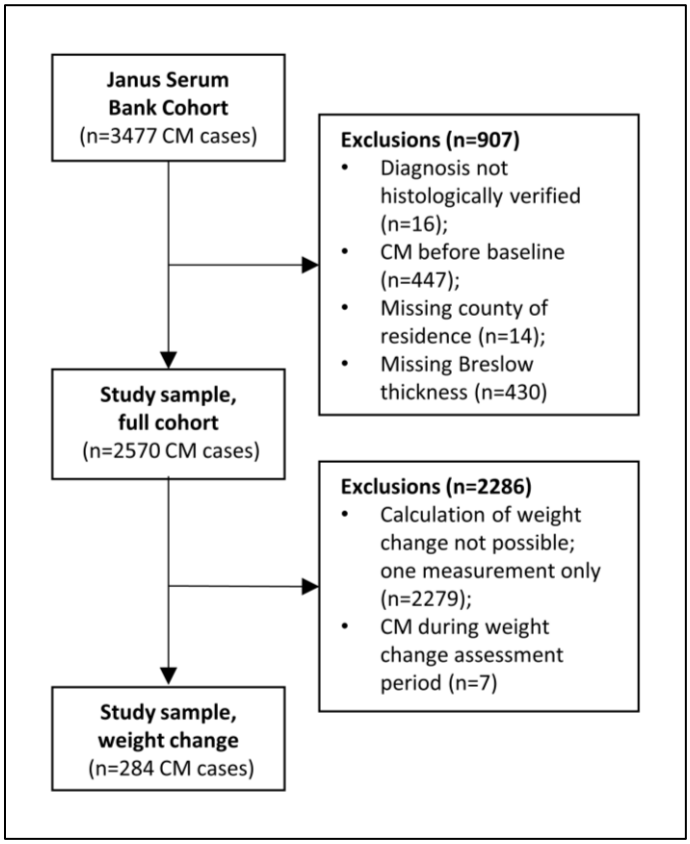

Figure 1. Overview of study samples and exclusions

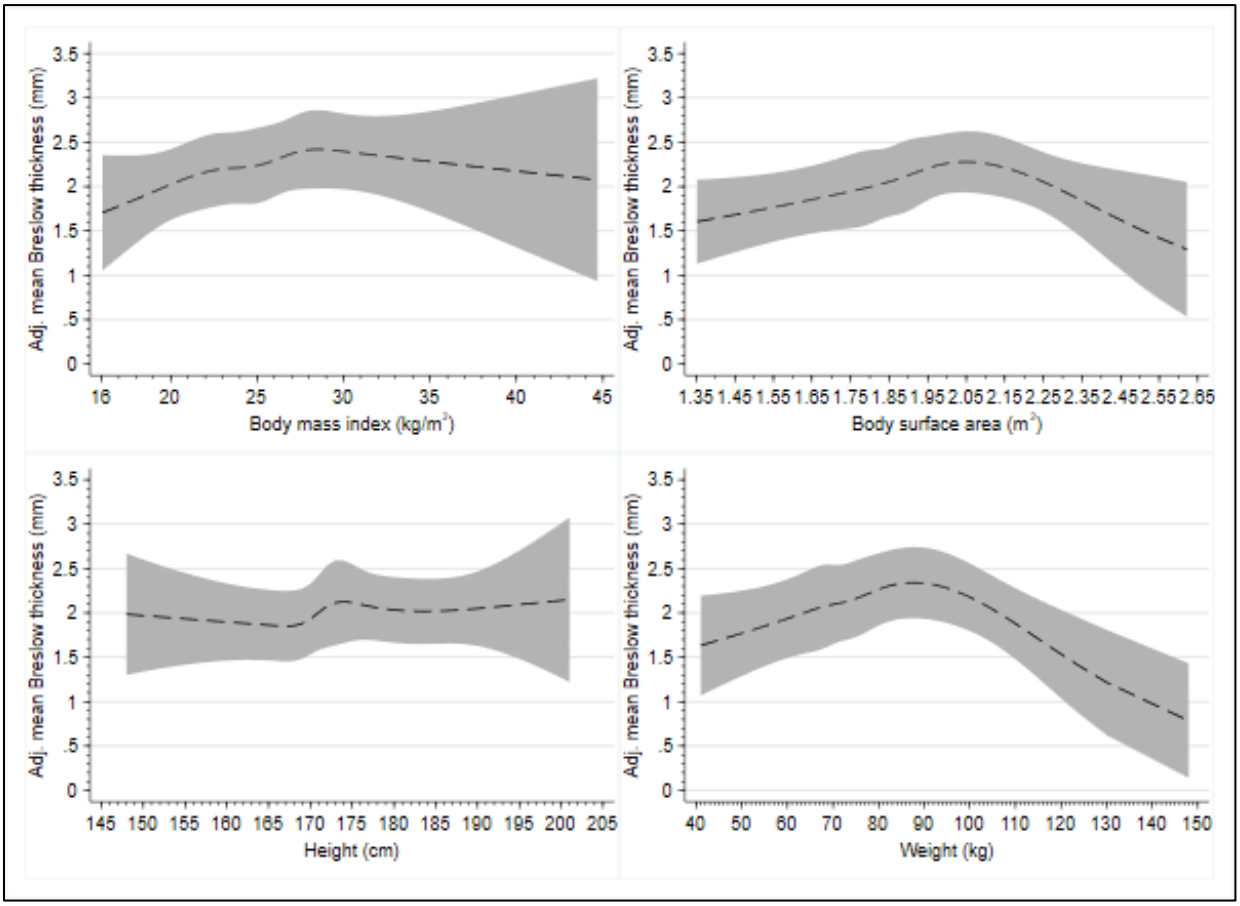

Figure 2: Restricted cubic splines displaying adjusted means of Breslow thickness (mm) with 95% confidence intervals according to anthropometric factors, adjusted for age at diagnosis, sex, ambient UVR of residence, average intensity of sunburns, occupation, physical activity, education and smoking status, in 2570 cutaneous melanoma cases. Models according to body mass index and weight were additionally adjusted for height. The model according to height was additionally adjusted for body mass index.