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Environmental exposures such as smoking and low vitamin D are predictive of poor outcome in cutaneous melanoma rather than other deprivation measures

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Abstract

Lack of basic resources within a society (deprivation) is associated with increased cancer mortality and this relationship has been described for melanoma. We have previously reported the association of smoking and low vitamin D levels with melanoma death. In this study we further explored the associations of these with melanoma, in addition to deprivation and socio-economic stressors. In this analysis of 2183 population-ascertained primary cutaneous melanoma patients; clinical, demographic and socio-economic variables were assessed as predictors of tumour thickness, melanoma death and overall death. Using the Townsend deprivation score, the most deprived group did not have thicker tumors compared to the least deprived. Of the WHO 25×25 risk factors for premature death, smoking and BMI were independently associated with thicker tumors. Low vitamin D was also independently associated with thicker tumors. No socio-economic stressors were independent predictors of thickness. Smoking was confirmed as a key predictor of melanoma death and overall death as were low vitamin D levels, independent of other measures of deprivation. Neither BMI nor Townsend deprivation score were predictive in either

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CONFLICT OF INTEREST

The authors state no conflicts of interest.

DATA AVAILABILITY STATEMENT

Please contact the corresponding author if summary level data are required.

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survival analysis. We report evidence for the role of smoking, vitamin D and BMI in melanoma progression independent of a postcode derived measure of deprivation.

INTRODUCTION

The most important prognostic factors for cutaneous primary melanoma are Breslow thickness (thickness of the primary tumor in mm) (Balch et al., 2001; Breslow, 1979), microscopic ulceration status, the presence of tumor infiltrating lymphocytes, tumor mitotic rate, sex, age and tumor site (Downing et al., 2006). Although higher socio-economic status (SES) groups have an increased incidence of melanoma, deprivation is associated with thicker tumors and poorer prognosis (Idorn and Wulf, 2014; Kogevinas et al., 1991; Lyratzopoulos et al., 2012; MacKie and Hole, 1996; Rachet et al., 2008; Shack et al., 2007). It is hypothesised that late diagnosis could be one reason behind the association seen between thicker tumours and deprivation (Montella et al., 2002). The World Health Organisation (WHO) plan for prevention and control of non-communicable diseases 2013–20 (World Health Organisation, 2013) describes risk factors for early death from major non-communicable diseases (many of which are associated with deprivation) and aims to reduce these diseases by 25% by 2025. The 25×25 risk factors are: harmful use of alcohol; insufficient physical activity; current tobacco use; raised blood pressure; intake of salt; diabetes and obesity (Stringhini et al., 2017). We have previously reported that smoking and vitamin D deficiency are associated with increased melanoma specific death in this cohort (Newton-Bishop et al., 2009; Newton-Bishop et al., 2015) and that smoking and increased body mass index (BMI) were associated with microscopic ulceration of the primary (a marker of poor prognosis). These three factors are also associated with deprivation (Hiscock et al., 2012; Jääskeläinen et al., 2013; Mateo-Pascual et al., 2014; McLaren, 2007). In this paper we have taken a wider look at factors reported to be associated with socioeconomic deprivation including those which are more difficult to quantitate such as psychological stress.

The means by which co-morbidities and psychological stress may reduce cancer survival have been postulated to be via epigenetic modification of genes involved in control of inflammation (Stringhini et al., 2015), impaired immune response to cancer (McEwen and Gianaros, 2010), activation of the hypothalamus-pituitary axis, or by modification of pathways such as DNA damage (Chida et al., 2008; Cohen et al., 2007; Reiche et al., 2004; Steptoe and Feldman, 2001). We have previously reported financial stress to be significantly associated with melanoma related worry (Rogers et al., 2016) and melanoma relapse in an independent cohort (Beswick et al., 2008). Stressful neighborhood problems are more common in lower socioeconomic groups (Steptoe and Feldman, 2001) and negative events such as loss of employment have been linked to increased risk and recurrence of breast cancer (Lillberg et al., 2003; Palesh et al., 2007). Lower SES groups are also more likely to believe their quality of health is determined by chance, potentially leading to reduced health promotion behaviors (Wallston et al., 1978; Wardle and Steptoe, 2003). This study was designed to explore potentially modifiable components of deprivation as determinants of melanoma survival in order to inform advice given to patients and to better understand the biology of host/tumor interaction.

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RESULTS

Study population

The population studied was the Leeds Melanoma Cohort: median age of participants was 56 years. 44% of subjects were male and 56% female. 99% of participants were Caucasian and 1% other ethnicities. The median length of follow-up was 6.7 years at this analysis. 574 patients (26%) have now died including 426 (20%) deaths from melanoma. The mean Breslow thickness was 2.15mm (SD 2.00). 59 participants did not have a Breslow thickness recorded so were excluded from the analysis of thickness. Missing data were attributable usually to technical issues with biopsies. Eligibility was based upon a diagnosis of stage 1 to IIIA melanoma, but final staging after investigation at specialist centres was as follows: 11 (0.5%) stage 0, 1204 (55.2%) stage I, 649 (29.7%) stage II, 276 (12.6%) stage III, 13 (0.6%) stage IV and 30 (1.4%) unclassifiable.

Factors predicting Breslow thickness

Clinico-pathological variables—Table 1 shows the association of Breslow thickness with clinico-pathological variables in univariable and multivariable analyses. Increasing age, male sex and tumor sited in acral/ sun-protected areas were independently predictive of thicker tumors. Tumors on the head and neck were significantly thicker in univariable analysis than tumors on the limbs but this association was not seen in multivariable analysis. The main confounding variable appeared to be age.

Lifestyle related variables and the WHO 25×25 factors—Deficient vitamin D levels (<20 nmol/L) were independently associated with over 25% increased tumor thickness compared to suboptimal levels (20–60 nmol/L) (25.60%, CI 10.85 to 40.35, p=0.001). There were no significant associations with tumour thickness and the highest Townsend deprivation level when compared with the lowest. Smokers had thicker tumors than never smokers (13.67%, CI 2.39 to 24.96, p=0.02). Increasing BMI was also significantly associated with increasing tumor thickness (1.14%, CI 0.37 to 1.90, p=0.004). Alcohol consumption did not show any association with thickness in the univariable analysis but consuming >14 units per week was associated with thinner tumors in the multivariable model. (−14.87%, CI −14.01 to −4.60, p=0.003). Reported exercise was not associated with Breslow thickness.

Supplementary Table 1 shows the association of clinico-pathological, lifestyle and WHO 25×25 factors with melanoma stage. In univariable analyses, increasing age, male sex, tumors sited in acral/ sun-protected areas and deficient vitamin D levels (<20 nmol/L) were associated with higher stage and consuming >14 units of alcohol per week was associated with lower stage compared with low alcohol intake. The associations for tumor site, vitamin D levels and alcohol intake persisted in multivariable analyses.

Financial and home environment stressors—Table 2 shows the association of Breslow thickness with variables related to financial and environmental stressors. Perceived financial hardship in more than one domain was associated with increased Breslow thickness in univariable analysis (16.55%, CI 5.71 to 27.39, p=0.003), but not in the multivariable

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model. No association was seen with reported housing problems, negative life events, history of anxiety/depression or social support. Having a high 'powerful others' health locus of control was associated with increased tumor thickness in univariable analysis, but this association did not persist in the multivariable model. The main confounding variable was participant age.

Melanoma specific survival

Clinico-pathological variables—The association of clinico-pathological variables with melanoma specific survival (MSS) is shown in Table 3. Breslow thickness was independently associated with death from melanoma. Older age and male sex were also significantly associated with increasing risk. Tumors on the back were independently associated with death from melanoma compared with tumors on the limbs. Tumors on the trunk and head/neck and in sun-protected sites were significantly associated with increased risk of death from melanoma in univariable analysis.

Lifestyle related variables and the WHO 25×25 factors—Deficient vitamin D levels (<20 nmol/L) were independently associated with increased risk of melanoma death compared with suboptimal vitamin D levels (20–60 nmol/L) (HR 1.59, CI 1.06 to 2.41, p=0.03). Sufficient vitamin D levels (>60 nmol/L) were associated with reduced risk of death in univariable analysis compared with suboptimal but this was not significant in the multivariable model, although the HR remained similar and this may reflect some loss of power. Townsend deprivation score was not significantly associated with risk of death from melanoma. Smoking at diagnosis was independently associated with increased risk of death from melanoma (HR 1.53, CI 1.07 to 2.18, p=0.02). Neither BMI, alcohol nor exercise were significantly associated.

Financial and home environment stressors—Perceived financial hardship was associated with death from melanoma in the univariable analysis but not in multivariable (table 4). Housing problems, reported negative life events, previous anxiety or depression and level of social support were not related to death from melanoma. 'Internal' health locus of control was not associated but having a high score in the 'chance' health locus domain was independently associated with death from melanoma (HR 1.37, CI 1.02 to 1.82, p=0.03). A high score for 'powerful others' was significantly associated with melanoma specific death in univariable analysis, but this did not persist in the multivariable model.

Overall survival

Clinico-pathological variables—Table 5 demonstrates the association of clinico-pathological variables with overall survival. Breslow thickness, older age and male sex were independently associated with death. Tumors on the back were independently associated with death compared to tumors on the limbs (HR 1.36, CI 1.05 to 1.76, p=0.02).

Lifestyle related variable and the WHO 25×25 factors—Deficient vitamin D levels were independently associated with an increased risk of death (HR 1.57, CI 1.10 to 2.25, p=0.01) and sufficient vitamin D levels (>60 nmol/L) were associated with reduced risk of death in the univariable analysis but not the multivariable. Townsend deprivation score was

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not associated with overall survival. Smoking at diagnosis was independently associated with increased risk of death (HR 1.66, CI 1.21to 2.28, p=0.002). BMI, alcohol intake and exercise were not associated.

Financial and home environment stressors—Reported financial hardship, housing problems, negative life events, history of anxiety or depression and level of social support were not associated with risk of death. An 'internal' or 'powerful others' health locus of control was not independently associated with death. High 'chance' locus of health control was significantly associated with death in univariable analysis but this did not reach significance in the multivariable model.

Smoking and increased BMI were found to be significantly associated with an increased deprivation score (more deprived) although a low vitamin D level was not (supplementary table 2).

DISCUSSION

This study modelled known melanoma clinico-pathological prognostic factors, the majority of the 25×25 WHO risk factors, vitamin D levels and socio-economic stressors together to explore the complex relationship between melanoma and deprivation. Although lower SES has been reported to be associated with poorer survival from melanoma, these analyses were not adjusted for deprivation related variables such as smoking and vitamin D deficiency included here.

The strength of the study was its size, the wealth of data collected, population-based ascertainment and use of melanoma specific survival. There was a long duration of follow up during a period where moderation of survival by treatment was minimal. The weaknesses were the relative lower participation of patients with low SES, use of self reporting. Causal pathways cannot be reported and there may be confounding variables not accounted for.

We confirmed that increasing age, male sex, and acral/sun-protected site were independently associated with increased tumor thickness. Thicker tumors were also associated with head and neck site although this relationship was confounded by age. The observation of thicker tumors arising in sun-protected sites may reflect difficulty in diagnosis, but the age related association with thicker head and neck tumors may reflect the *NRAS* and double wild type driven melanomas more common in older groups (Cirenajwis et al., 2017; Ellerhorst et al., 2011).

We confirmed that vitamin D deficiency (<20 nmol/L) was associated with thicker tumors which we first reported in a subset of these data (Newton-Bishop et al., 2009) and has subsequently been replicated (Fang et al., 2016; Gambichler et al., 2013; Saiag et al., 2015; Wyatt et al., 2015). Vitamin D/*VDR* signalling has been identified as an inhibitor of β-catenin signalling in colon cancer (Larriba et al., 2013) and our group has similar data for melanoma submitted for publication as evidence for a causal relationship between vitamin D and stage at diagnosis (Muralidhar et al., 2018).

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Townsend deprivation score (postal code derived) was not a consistent independent predictor of thickness. However, factors known to be related to deprivation were. Smoking was shown to be associated with increased Breslow thickness: to our knowledge this is previously unreported in a large study (Grange et al., 2012; Koh et al., 1984). BMI was also shown to be associated with increased tumor thickness which is corroborated by other recent studies (de Giorgi et al., 2013; Stenehjem et al., 2018). An explanation could be delayed presentation which has been associated with obesity (Risica et al., 2008). Possible biological mechanisms exist including the production of angiogenic factors (Cao, 2007) and the excretion of exosomes by adipocytes (Lazar et al., 2016).

Reported consumption of over 14 units of alcohol per week was associated with thinner tumors. In analysis stratified by sex (not reported) the protective effect of alcohol was only seen in women. The association seen between increased alcohol intake and decreased Breslow has not been described before and is unexpected (Freedman et al., 2003; Millen et al., 2004). Alcohol has however been reported to be protective of diseases associated with systemic inflammation which is recognised as a driver of cancer (Mostofsky et al., 2016), and this observation may reflect a biological mechanism of interest. We saw no effect of reported exercise on thickness.

Alcohol intake >14 units per week was also associated with lower stage. Although comparisons between the stage and Breslow thickness analysis cannot be directly made, smoking and BMI were not associated with stage at diagnosis and Breslow thickness appeared to be more closely related to these deprivation related factors.

Reporting financial hardship was significantly associated with increased Breslow thickness in univariable analysis. This is consistent with findings from our group demonstrating an association between perceived hardship and melanoma recurrence (Beswick et al., 2008). Lack of money can impact on psychological stress, which is hypothesised to induce immune suppression via pathways involving the hypothalamic-pituitary-adrenocortical axis or the sympathetic nervous system (Jin Shin et al., 2016; McEwen and Gianaros, 2010; Reiche et al., 2004). No association was seen with other measured stress related factors.

We postulated that a high ‘chance’ perception of health control may be associated with increased Breslow thickness as this has been related to delay in seeking medical care (Tromp et al., 2005) but we did not find any evidence for this. High ‘powerful others’ perception of health control was associated with increased thickness but this belief has been associated with older age (Lumpkin, 1986) and there was no association demonstrated in multivariable analysis.

For melanoma specific survival, the association of increasing age, male sex and tumor site on the back with increased risk of death were replicated. Data reported here show the protective effects of vitamin D levels on MSS were independent of Townsend deprivation score and 25×25 factors. This result may form evidence against the view vitamin D levels are acting as a surrogate marker of social status related “better health”. As previously demonstrated, smoking was associated with MSS and we have theorised that smoking could mediate melanoma development via promotion of systemic inflammation (Newton-Bishop et

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al., 2015). Obesity has previously been demonstrated to be associated with relapse in a subset of this cohort (Newton-Bishop et al., 2009) and is associated with poorer outcomes in other cancers (Calle et al., 2003). BMI and alcohol consumption were not independently associated with MSS in this data set but may contribute by association with thickness. Exercise was not associated.

In addition to association with increased Breslow thickness, perceived financial hardship was also associated with death from melanoma in univariable analysis. It is possible that individual questions are more likely to identify deprivation than the Townsend score. However the association was not significant in multivariable analysis. There was no evidence for association between other home and environment stress factors examined and death from melanoma. However, an association was seen with a high ‘chance’ health locus of control. Reported explanations include increased unhealthy lifestyle factors such as smoking in this group (Luszczynska and Schwarzer, 2005) but these were adjusted for. Belief in ‘chance’ is also related to poorer concordance with treatment regimes (Náfrádi et al., 2017) which could be related to poorer outcomes. High ‘chance’ has been linked to low SES (Beeken et al., 2011) although it was not associated with Townsend score here (supplementary table 2). As there was multiple testing the effect of health locus of control, which has not previously been examined in melanoma thickness/survival, would need further exploration.

Overall survival demonstrated comparable results to melanoma specific survival in that Breslow thickness, older age, male sex, tumour site on the back, deficient vitamin D and smoking at diagnosis were also associated with risk of overall death.

In summary, increased thickness of primary tumors was independently associated with increased age, male sex, tumor in sun-protected sites and low vitamin D. Interesting findings were that smoking and increased BMI were also independently associated with increased Breslow thickness and that higher alcohol consumption was protective. Although an association was seen with perceived financial hardship, objective measures of increased deprivation were not associated and neither were other stress related variables.

Independent predictors of melanoma death included the well-known prognostic factors of increased age, male sex, tumor thickness, tumor site, low vitamin D levels and smoking. Townsend score was not an independent predictor of death. This finding fits the narrative that the association seen by others between melanoma death and deprivation is connected to factors related to deprivation, not deprivation itself. The finding of the association of high ‘chance’ locus of control with increased risk of melanoma specific death is to our knowledge previously unreported. Smoking, BMI and vitamin D levels are potentially modifiable elements of deprivation that could be targeted in treatment and prevention of melanoma. This study is consistent with the WHO view that tackling the 25×25 factors should produce improvements in premature mortality.

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MATERIALS AND METHODS

Study design

2183 patients were recruited to the Leeds Melanoma Cohort (LMC) between 2000 and 2012 (Newton-Bishop et al., 2015). Patients were identified from pathology and clinical registers in a defined area of England, with additional recruitment from 32 other centres (342 recruits) carrying out sentinel node biopsy and treating rare subtypes of cases (76 recruits). Eligible patients were aged 18–75 and had a new diagnosis of stage 1 to IIIA primary melanoma. 2183/3360 (65%) eligible patients took part. Non-participants were younger, more deprived (higher Townsend scores) and had thicker tumors than participants (Rogers et al., 2016). The median time to interview from diagnosis was 5.2 months. This cohort was built prior to the advent of targeted/immuno therapies therefore few received checkpoint therapies having significant effects on survival. Participants gave written informed consent and approval was obtained from our institution, the MultiCentre Research Ethics (MREC/1/3/57) and the Patient Information Advisory Group [PIAG 3-09(d)/2003].

Data on age, sex and tumor site (limbs, back, trunk, head/neck and acral/sun protected) were collected. Tumor characteristics were extracted from histopathology reports. Serum 25-Hydroxyvitamin D_2/D_3 levels were measured at study entry. AJCC 7^{th} edition was used for staging (Edge and Compton, 2010). Data were adjusted for season and batch (Newton-Bishop et al., 2015), referred to as the vitamin D level. A postcode derived score (Townsend Material Deprivation) (Townsend et al., 1988) was used to estimate deprivation.

Smoking was categorised as “current smoker, ex-smoker or never smoked.” BMI was estimated using self-reported height and weight. Presence of diabetes was self reported. Alcohol intake was self-reported as number of glasses of wine, single measures of spirits/fortified wine and pints of beer per week.

Questionnaires measuring perceived financial hardship and problems with housing/neighborhood were developed in-house and tested on melanoma patients in clinic. Negative life events were measured using questions derived from Oei and Zwarts life events questionnaire (Oei and Zwart, 1986). For variables see supplementary table 3. A three-tier score was created for presence of: no financial hardship; one element of or more than one element of financial hardship. Three-tier scores were also created for housing problems and negative life events. Previous anxiety or depression was self-reported. A modification of the Norbeck Social Support Questionnaire was used to measure social support (Norbeck et al., 1981).

The Multidimensional Health Locus of Control scale (Wallston et al., 1978) was used to assess participants’ health beliefs indicating the degree individuals believed their behaviour affected their health: three domains: *internal*: personal behaviour affects health, *chance*: health is a matter of chance or *powerful others*: health is controlled by others.

Melanoma specific survival and overall survival

Participants were followed up by annual re-contact, review of medical records and national registers. For patients who died their medical records and death certificate or cause of death

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was obtained from the Office of National Statistics, prior to reorganisation of these services as NHS Digital. To determine melanoma specific death, this evidence was reviewed and participants who died of non-melanoma causes were censored at time of death. Overall follow up was censored on 03/31/2018.

Statistical analysis

Vitamin D levels (nmol/L) were available for 1780 subjects and grouped into three categories; deficient (<20), suboptimal 20–60 (reference), >60 (sufficient) (Newton-Bishop et al., 2015). Townsend score was grouped into approximate tertiles as were health locus of control scores. BMI was a continuous measure. To calculate units (8g alcohol) per week, number of pints was multiplied by 2.15 and glasses of wine by 1.6 (UK Chief Medical Officer, 2016). Alcohol consumption was grouped by units per week: none, 0–7 (reference), 7–14, >14 (UK Chief Medical Officer, 2016). Exercise was calculated by allocating metabolic equivalent (MET) values to activities (Ainsworth et al., 1993). MET hours/week were summed for each participant and grouped: 0 (reference), 0–10, 10–20 and >20.

Unadjusted linear regression was used to assess predictors of Breslow thickness. 100 × natural log was taken so coefficients were interpreted as percentage change. The clinico-pathological variables and variables related to financial and home environment stressors were taken into multivariable models. Diabetes was not included as it was collinear with BMI.

To test associations with melanoma specific survival and overall survival, Cox proportional hazard models were used in univariable then multivariable analysis. Survival time was measured from date of surgical excision to date of death or last follow-up. Analysis was censored at 10 years. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated.

Univariable and multivariable linear regression models were performed to assess predictors of Townsend deprivation score. Univariable and multivariable generalized linear models with a log link and risk ratios were estimated to assess predictors of stage III-IV melanomas compared with lower stages. Stata S.E. 12.1 was used for analyses (StataCorp, 2011).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AJCC	*American Joint Committee on Cancer*
BMI	body mass index
CI	confidence interval
MSS	melanoma specific survival
HLOC	health locus of control
HR	hazard ratio
SES	socio-economic status
WHO	World Health Organisation
MET	metabolic equivalent

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Table 1.

The association of clinico-pathological variables with Breslow thickness in univariable and multivariable linear regression analysis.

		Univariable		Multivariable (n = 1662)	
Factor	**n (%)**	**% Breslow change (95% CI)**	***p***	**% Breslow change (95% CI)**	***p***
Age (years)	2124	1.03 (0.81, 1.25)	**<0.001**	0.93 (0.66, 1.21)	**<0.001**
Sex	2124				
Female	1206 (57)	Reference	-	Reference	-
Male	918 (43)	13.17 (7.10, 19.34)	**<0.001**	9.81 (1.74, 17.87)	**0.02**
Site	2124				
Limbs	1011(48)	Reference	-	Reference	-
Back	543 (26)	6.12 (−1.35, 13.58)	0.11	2.61 (−6.18, 11.39)	0.56
Trunk	214(10)	5.28 (−5.27, 15.84)	0.33	1.81 (−10.52, 14.16)	0.77
Head/neck	208(10)	15.62 (4.94, 26.30)	**0.004**	10.95 (−0.86, 22.75)	0.07
Acral/sun protected	148 (7)	39.39 (27.04, 51.74)	**<0.001**	29.55 (14.62, 44.47)	**<0.001**
Vitamin D[1] nmol/L	1739				
20–60	1164 (67)	Reference	-	Reference	-
<20	106 (6)	23.94 (9.48, 38.40)	**0.001**	25.60 (10.85, 40.35)	**0.001**
>60	469 (27)	−2.65 (−10.44 to 5.15)	0.51	−1.72 (−9.62, 6.19)	0.67
Townsend score	2081				
Least deprived	681	Reference	-	Reference	-
Moderate	706	−6.69 (−14.30, 0.93)	0.09	−8.91 (−17.30, −0.53)	**0.04**
Most deprived	694	−0.80 (−8.45, 6.84)	0.84	−3.94 (−12.62, 4.73)	0.37
WHO 25×25 factors					
Smoking	2042				
Never	1125(55)	Reference	-	Reference	-
Ex smoker	677 (33)	9.56 (2.67, 16.45)	**0.007**	4.39 (−6.18, 11.39)	0.56
Smoker	240 (12)	11.14 (1.07, 21.21)	**0.03**	13.67 (2.39, 24.96)	**0.02**
BMI	2091	1.41 (0.74, 2.07)	**<0.001**	1.14 (0.37, 1.90)	**0.004**
Alcohol units/week	2082				
0	410 (20)	6.22 (−3.16, 15.61)	0.19	−1.83 (−12.14, 8.49)	0.73
>0<7	560 (30)	Reference	-	Reference	-
>7≤14	430 (21)	2.94 (−6.27, 12.14)	0.53	−1.17 (−11.21, 8.88)	0.82
>14	682 (33)	−5.55 (−13.75, 2.65)	0.19	−14.38 (−24.02, −4.75)	**0.003**
Exercise MET[2] hrs/week	2021				
0	518 (26)	Reference	-	Reference	-
0.1 – 10	468 (23)	−2.69 (−11.72)	0.56	2.29 (−7.58, 12.18)	0.65
10.1 – 20	565 (28)	0.34 (−8.27, 8.94)	0.94	3.92 (−5.63, 13.47)	0.42
>20	470 (23)	−2.39 (−11.40, 6.62)	0.60	5.63 (−4.39, 15.66)	0.27

[1] Vitamin D adjusted for season and batch.

[2] Metabolic Equivalence of Task

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Table 2.

Association of financial and home environment stressors with Breslow thickness in univariable and multivariable linear regression analysis.

		Univariable		Multivariable models[1]	
Factor	**n (%)**	**% change in Breslow (95% CI)**	***p***	**% change in Breslow (95% CI)**	***p***
Perceived financial hardship		n = 1924		n=1556	
0	196 (10)	Reference	-	Reference	-
1	428 (22)	15.12 (2.92, 27.33)	**0.02**	5.41 (−7.77, 18.59)	0.42
>1	1300 (68)	16.55 (5.71, 27.39)	**0.003**	8.95 (−2.71, 20.60)	0.13
Housing problems		n = 2005		n = 1556	
0	1511(75)	Reference	-	Reference	-
1	211 (11)	−8.91 (−19.32, 1.51)	0.09	−5.97 (−17.54, 5.61)	0.31
>1	283 (14)	2.20 (−6.98, 11.38)	0.64	−0.79 (−10.91, 9.33)	0.88
Negative life events		n = 2037		N = 1629	
0	1400 (69)	Reference	-	Reference	-
1	438 (220	3.23 (−4.54, 10.99)	0.42	6.49 (−2.06, 15.05)	0.14
>1	199(10)	−5.59 (−16.44, 5.05)	0.30	−4.14 (−15.85, 7.58)	0.49
Previous depression/anxiety		n = 2016		n = 1648	
No	1547(77)	Reference	-	Reference	-
Yes	469(23)	−2.02 (−9.49, 5.44)	0.66	−3.30 (−11.73, 5.14)	0.44
Social support		n = 2124		n = 1648	
Score	-	−0.05 (−1.27, 1.16)	0.93	1.20 (−0.26, 2.66)	0.12
Internal HLOC		n = 2035		n = 1604	
Low	547 (27)	Reference	-	Reference	-
Moderate	690 (34)	3.58 (−4.41, 11.66)	0.39	0.20 (−9.15, 8.74)	0.96
High	798 (39)	3.31 (−4.53, 11.15)	0.41	1.15 (−7.51, 9.82)	0.79
Chance HLOC		n = 2014		n = 1584	
Low	638 (32)	Reference	-	Reference	-
Moderate	640 (21)	−0.74 (−8.59, 7.12)	0.85	−2.86 (−11.60, 5.87)	0.52
High	736 (37)	4.21 (−3.38, 11.80)	0.27	1.13 (−7.39, 9.66)	0.79
Powerful others HLOC		n = 2013		n = 1591	
Low	607 (30)	Reference	-	Reference	-
Moderate	737 (37)	4.80 (−2.88, 12.47)	0.22	1.69 (−6.88, 10.26)	0.70
High	669 (33)	17.15 (9.19, 24.99)	**<0.001**	6.07 (−3.15, 15.27)	0.20

[1] Multivariable models with age, sex, site, vitamin D (adjusted for season and batch), Townsend score, BMI, smoking, alcohol intake and exercise

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Table 3.

Association of clinico-pathological factors with melanoma specific death in univariable and multivariable Cox proportional hazard analysis.

	Censored (n=1757)	Died of melanoma (n=426)	Univariable		Multivariable (n = 1648)	
Factor	**n (%)**	**n (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Breslow (mm)	-	-	1.23 (1.20, 1.26)	**<0.001**	1.23 (1.19, 1.27)	**<0.001**
Age (years)	-	-	1.04 (1.03, 1.05)	**<0.001**	1.03 (1.02, 1.04)	**<0.001**
Sex						
Female	1038 (84)	195(16)	1	-	1	-
Male	719(76)	231 (24)	1.71 (1.41, 2.07)	**<0.001**	1.51 (1.16, 1.97)	**0.002**
Tumor site						
Limbs	882 (87)	133 (13)	1	-	1	-
Back	421(77)	124 (23)	1.81 (1.42, 2.31)	**<0.001**	1.51 (1.12, 2.01)	**0.006**
Trunk	168(78)	47 (22)	1.78 (1.28, 2.49)	**0.001**	1.42 (0.95, 2.12)	0.09
Head/neck	166(78)	46 (22)	1.63 (1.17, 2.28)	**0.004**	0.98 (0.67, 1.44)	0.93
Acral/sun protected	120 (61)	76 (29)	3.98 (3.00, 5.28)	**<0.001**	1.41 (0.93, 2.13)	0.11
Vitamin D[1] nmol/L						
20–60	949 (80)	240 (20)	1	-	1	-
<20	79 (72)	31 (28)	1.62 (1.11, 2.35)	**0.01**	1.59 (1.06, 2.41)	**0.03**
>60	405 (84)	76 (16)	0.76 (0.59, 0.99)	**0.04**	0.79 (0.60, 1.04)	0.09
T ownsend score						
Least deprived	563 (81)	136(19)	1	-	1	-
Moderate	594 (82)	133 (18)	0.91 (0.72, 1.16)	0.46	0.92 (0.70, 1.21)	0.56
Most deprived	564 (79)	150 (21)	1.06 (0.84, 1.34)	0.62	0.81 (0.65, 1.16)	0.34
WHO 25×25 factors						
Smoking						
Never	964 (83)	193(17)	1	-	1	-
Ex smoker	543(78)	153(22)	1.38 (1.12, 1.71)	**0.003**	1.02 (0.80, 1.31)	0.87
Smoker	186 (76)	58 (24)	1.40 (1.04, 1.88)	**0.02**	1.53 (1.07, 2.18)	**0.02**
BMI	-	-	1.02 (1.00, 1.04)	0.05	1.01 (0.98, 1.03)	0.54
Alcohol units/week						
0	318 (78)	92 (22)	1.31 (0.89, 1.74)	0.06	1.14 (0.81, 1.59)	0.45
>0 ≤7	462 (83)	98(18)	1	-	1	-
>7 ≤14	343 (80)	87 (20)	1.14 (0.86, 1.52)	0.37	1.05 (0.75, 1.47)	0.79
>14	558(82)	124 (18)	1.00 (0.76, 1.30)	0.98	0.83 (0.60, 1.17)	0.29
Exercise MET[2] **hrs/ week**						
0	431 (81)	103 (19)	1	-	1	-

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	Censored (n=1757)	Died of melanoma (n=426)	Univariable		Multivariable (n = 1648)	
Factor	**n (%)**	**n (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
0.1 – 10	381 (79)	100 (21)	1.11 (0.76, 1.31)	0.48	1.20 (0.87, 1.66)	0.26
10.1 – 20	474 (82)	107 (18)	1.00 (0.76, 1.31)	0.99	0.96 (0.70, 1.33)	0.80
>20	391 (81)	89 (19)	1.01 (0.76, 1.34)	0.95	1.09 (0.78, 1.52)	0.63

[1]Vitamin D adjusted for season and batch.

[2]Metabolic Equivalence of Task

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Table 4.

Association of financial and home environment stressors with melanoma specific death in univariable and multivariable Cox proportional hazard analysis.

	Censored	Died of melanoma	Univariable		Multivariable models[1]	
Factor	**(n=1757) n (%)**	**(n=426) n (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Financial hardship			n = 1937		n = 1556	
0	173(87)	26(13)	1	-	1	-
1	354 (79)	92 (21)	1.73 (1.12, 2.68)	**0.01**	1.35 (0.82, 2.20)	0.24
>1	1067(80)	261 (20)	1.66 (1.11, 2.49)	**0.01**	1.23 (0.78, 1.94)	0.38
Housing problems			n = 2060		n = 1621	
0	1260 (81)	294 (19)	1	-	1	
1	18(83)	37 (17)	0.89 (0.63 to 1.25)	0.63	1.18 (0.80, 1.72)	0.41
>1	225 (77)	66(23)	1.12 (0.86 to 1.46)	0.42	0.98 (0.71, 1.34)	0.90
Negative life events			n = 2092		N = 1646	
0	1169 (81)	278 (19)	1	-	1	-
1	355(80)	89 (20)	1.05 (0.83 – 1.34)	0.68	0.96 (0.72, 1.27)	0.76
>1	164 (82)	37 (18)	0.93 (0.66 – 1.31)	0.69	1.04 (0.70, 1.55)	0.84
Hx depression/ anxiety			n = 2070		N = 1629	
No	1276(80)	317 (20)	1	-	1	
Yes	394 (83)	83 (17)	0.86 (0.68 – 1.10)	0.23	0.87 (0.65, 1.16)	0.34
Social support scale			n = 2081		N = 1633	
Score	-	-	1.00 (0.99 – 1.01)	0.98	1.01 (0.99, 1.02)	0.28
Internal HLOC			n = 2090		N = 1604	
Low	458(81)	105(19)	1	-	1	-
Middle	569(80)	140 (20)	1.08 (0.84 to 1.39)	0.55	1.07 (0.79, 1.45)	0.65
High	656 (80)	162 (20)	1.06 (0.83 to 1.36)	0.63	0.96 (0.72, 1.28)	0.80
Chance HLOC			n = 2068		N = 1584	
Low	540 (83)	110(17)	1	-	1	-
Middle	542 (82)	116(18)	1.02 (0.78 to 1.32)	0.89	1.03 (0.76, 1.41)	0.87
High	585 (77)	175(23)	1.35 (1.06 to 1.71)	**0.02**	1.37 (1.02, 1.82)	**0.03**
Powerful others HLOC			n = 2069		n = 1591	
Low	528(85)	92(15)	1	-	1	-
Middle	621(82)	132(18)	1.22 (0.94 to 1.59)	0.14	0.85 (0.62, 1.16)	0.30
High	514 (74)	180 (26)	1.90 (1.48 to 2.44)	**<0.001**	0.99(0.72, 1.36)	0.96

[1] Multivariable models including Breslow thickness, site, age, sex, vitamin D (adjusted for season and batch), Townsend score, smoking, BMI, alcohol intake and exercise

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Table 5.

Association of clinico-pathological factors with overall survival in univariable and multivariable Cox proportional hazard analysis.

	Censored (n=1607)	Died (n= 576)	Univariable		Multivariable (n = 1648)	
Factor	**n (%)**	**n (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Breslow (mm)	-	-	1.21 (1.19, 1.24)	**<0.001**	1.20 (1.16, 1.24)	**<0.001**
Age (years)	-	-	1.05 (1.04, 1.10)	**<0.001**	1.05 (1.04, 1.06)	**<0.001**
Sex						
Female	968(79)	265 (21)	1	-	1	-
Male	639 (67)	311 (33)	1.68 (1.42, 1.98)	**<0.001**	1.41 (1.12, 1.78)	**0.004**
Tumor site						
Limbs	825(81)	190 (19)	1	-	1	-
Back	387 (71)	158 (29)	1.60 (1.29, 1.98)	**<0.001**	1.36 (1.05, 1.76)	**0.02**
Trunk	151(70)	64 (30)	1.98 (1.26, 2.23)	**<0.001**	1.35 (0.96, 1.91)	0.09
Head/neck	141 (67)	71 (33)	1.69 (1.27, 2.22)	**<0.001**	0.98 (0.71, 1.35)	0.90
Acral/sun protected	103(53)	93 (47)	3.54 (2.76, 4.53)	**<0.001**	1.22 (0.85, 1.76)	0.29
Vitamin D[1] nmol/L						
20–60	870(73)	319 (27)	1	-	1	-
<20	69(63)	41 (37)	1.52 (1.10, 2.11)	**0.01**	1.57 (1.10, 2.25)	**0.01**
>60	(370 (77)	111 (23)	0.83 (0.67, 1.03)	0.08	0.79 (0.62, 1.00)	0.05
Townsend score						
Least deprived	522 (75)	177 (25)	1	-	1	-
Moderate	542 (75)	185 (25)	0.96 (0.78, 1.12)	0.68	1.05 (0.88, 1.361	0.67
Most deprived	508 (71)	206 (29)	1.10 (0.90, 1.35)	0.34	0.97 (0.76, 1.25)	0.83
WHO 25×25 factors						
Smoking						
Never	897(78)	260 (22)	1	-	1	-
Ex smoker	485(70)	211 (30)	1.42 (1.18, 1.70)	**<0.001**	1.09 (0.88, 1.36)	0.42
Smoker	169 (69)	75 (31)	1.31 (1.01, 1.69)	**0.04**	1.66 (1.21, 2.28)	**0.002**
BMI	-	-	1.02 (1.00, 1.04)	**0.03**	1.00 (0.98, 1.02)	0.84
Alcohol intake units/week						
0	284 (69)	126 (31)	1.28 (1.01, 1.64)		1.08 (0.81, 1.44)	0.60
>0 ≤7	426 (76)	134 (24)	1	-	1	-
>7 ≤14	324 (75)	106 (25)	1.04 (0.81, 1.35)	0.74	1.00 (0.75, 1.35)	0.99
>14	509 (75)	173 (25)	0.96 (0.77, 1.20)	0.72	0.79 (0.59, 1.06)	0.12
Exercise MET[2] **hrs/week**						
0	388 (73)	146 (27)	1	-	1	-
0.1 – 10	356 (74)	125 (26)	0.98 (0.77, 1.25)	0.88	0.99 (0.75, 1.30)	0.92
10.1 – 20	431 (74)	150 (26)	0.98 (0.78, 1.24)	0.90	0.87 (0.67, 1.17)	0.39

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	Censored (n=1607)	Died (n= 576)	Univariable		Multivariable (n = 1648)	
Factor	**n (%)**	**n (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
>20	361(75)	119 (25)	0.98 (0.77, 1.25)	0.88	0.97 (0.73, 1.29)	0.84

[1]Vitamin D adjusted for season and batch.

[2]Metabolic Equivalence of Task

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Table 6.

Association of financial and home environment stressors with overall survival in univariable and multivariable Cox proportional hazard analysis.

	Censored	Died	Univariable		Multivariable models[1]	
Factor	**(n=1607) n (%)**	**(n=576) n (%)**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Financial hardship			n = 1973		n = 1556	
0	164 (82)	35 (18)	1	-	1	-
1	323 (72)	123 (28)	1.59 (1.04, 2.41)	**0.03**	1.26 (0.82, 1.91)	0.29
>1	976(73)	352 (27)	1.42 (0.97, 2.10)	0.07	1.22 (0.83, 1.81)	0.31
Housing problems			n = 2060		n = 1621	
0	1164(75)	390 (25)	1	-	1	-
1	164 (76)	51 (24)	0.91 (1.00, 1.22)	0.54	1.21 (0.87, 1.68)	0.30
>1	193 (66)	98 (34)	1.25 (1.00, 1.56)	0.05	1.09 (0.84, 1.42)	0.52
Negative life events			n = 2092		n = 1646	
0	1055 (72)	392 (27)	1	-	1	-
1	332(75)	112 (25)	0.94 (0.76, 1.16)	0.59	1.00 (0.79, 1.28)	0.97
>1	159(79)	42 921)	0.73 (0.53, 1.01)	0.06	0.84 (0.58, 1.22)	0.36
Hx depression/ anxiety			n = 2070		n = 1629	
No	1165 (73)	428 (27)	1	-	1	-
Yes	366(77)	111 (23)	0.84 (0.68, 1.04)	0.11	0.84 (0.65, 1.07)	0.16
Norbeck social support scale			n = 2081		n = 1633	
Score	-	-	0.99 (0.98, 1.01)	0.32	1.01 (0.99, 1.02)	0.40
Internal HLOC			n = 2090		n = 1604	
Low	420 (75)	143 (25)	1	-	1	-
Middle	525 (74)	184 (26)	1.08 (0.87, 1.35)	0.48	1.14 (0.88, 1.48)	033
High	603(74)	215 (26)	1.10 (0.89, 1.36)	0.85	0.99 (0.77, 1.27)	0.92
Chance HLOC			n = 2068		n = 1584	
Low	506 (78)	144 (22)	1	-	1	-
Middle	495 (75)	163(25)	1.06 (0.84, 1.32)	0.63	0.83 (0.83, 1.42)	0.55
High	529(70)	231 (30)	1.30 (1.06, 1.60)	**0.01**	1.28 (0.99, 1.65)	0.06
Powerful others HLOC			n = 2069		n = 1591	
Low	511(82)	109(18)	1	-	1	-
Middle	582 (77)	173(23)	1.31 (1.03, 1.66)	0.03	0.94 (0.70, 1.25)	0.66
High	439 (63)	255 (36)	2.26 (1.81, 2.83)	**<0.001**	1.16 (0.87, 1.54)	0.32

[1] Multivariable models including Breslow thickness, site, age, sex, vitamin D (adjusted for season and batch), Townsend score, smoking, BMI, alcohol intake and exercise