Environmental Exposures Such as Smoking and Low Vitamin D Are Predictive of Poor Outcome in Cutaneous Melanoma rather than Other Deprivation Measures

C.M. Hardie¹, F. Elliott¹, M. Chan¹, Z. Rogers¹, D.T. Bishop¹ and J.A. Newton-Bishop¹

A 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 2,183 population-ascertained primary cutaneous melanoma patients, clinical, demographic, and socio-economic variables were assessed as predictors of tumor 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 World Health Organization 25x25 risk factors for premature death, smoking and body mass index (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 the Townsend deprivation score were predictive in either 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.

Journal of Investigative Dermatology (2020) 140, 327–337; doi:10.1016/j.jid.2019.05.033

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; Ly ratzopoulos et al., 2013; MacKie and Hole, 1996; Rachet et al., 2008; Shack et al., 2007). It is hypothesized that late diagnosis could be one reason behind the association observed between thicker tumors and deprivation (Montella et al., 2002). The World Health Organization (WHO) plan for the prevention and control of non-communicable diseases 2013-2020 (World Health Organization, 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 25x25 risk factors include 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 tumor (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 took a wider look at factors reported to be associated with socioeconomic deprivation, including those that 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 the genes involved in the 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 (Bewick 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 to inform advice given to patients and to better understand the biology of host and/or tumor interaction.

RESULTS
Study population
The population studied was the Leeds Melanoma Cohort, and the median age of the participants was 56 years. Forty-four percent of subjects were male and 56% female. Ninety-nine percent of the participants were Caucasian and 1% other ethnicities. The median length of follow-up was 6.7 years at this analysis. A total of 574 patients (26%) have now died, including 426 (20%) deaths from melanoma. The mean Breslow thickness was 2.15 mm (Standard deviation ± 2.00). Fifty-nine participants did not have a Breslow thickness recorded, so they were excluded from the analysis of thickness. Missing data were usually attributable to technical issues with biopsies. Eligibility was based upon a diagnosis of stage I to IIIA melanoma, but the final staging after investigation at specialist centers was as follows: 11 (0.5%) stage 0, 1,204 (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 and/or 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 observed in multivariable analysis. The main confounding variable appeared to be age.

Lifestyle-related variables and the WHO 25x25 factors. Deficient vitamin D levels (< 20 nM) were independently associated with over 25% increased tumor thickness than that of suboptimal levels (20-60 nM) (25.60%, confidence interval [CI] = 10.85–40.35, P = 0.001). There were no significant associations with other thickness and the highest Townsend deprivation level when compared with the lowest. Smokers had thicker tumors than never smokers (13.67%, CI = 2.39–24.96, P = 0.02). Increasing BMI was also significantly associated with increasing tumor thickness (1.14%, CI = 0.37–1.90, 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 S1 shows the association of clinico-pathological, lifestyle, and WHO 25x25 factors with melanoma stage. In univariable analyses, increasing age, male sex, tumors sited in acral and/or sun-protected areas, and deficient vitamin D levels (< 20 nM) were associated with higher stage, and consuming >14 units of alcohol per week was associated with a 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 an increased Breslow thickness in a univariable analysis (16.55%, CI = 5.71–27.39, P = 0.003) but not in the multivariable model. No association was observed with reported housing problems, negative life events, history of anxiety and/or depression, or social support. Having a high ‘powerful others’ health locus of control (HLOC) 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 is shown in Table 3. The 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 and/or 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 25x25 factors. Deficient vitamin D levels (< 20 nM) were independently associated with an increased risk of melanoma death compared with suboptimal vitamin D levels (20-60 nM) (hazard ratio [HR] = 1.59, CI = 1.06–2.41, P = 0.03). Sufficient vitamin D levels (> 60 nM) were associated with a reduced risk of death in the univariable analysis compared with the suboptimal, but this was not significant in the multivariable model, although the HR remained similar, and this may reflect some loss of power. The Townsend deprivation score was not significantly associated with the risk of death from melanoma. Smoking at diagnosis was independently associated with an increased risk of death from melanoma (HR = 1.53, CI = 1.07–2.18, 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 the 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’ HLOC 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 = 1.02–1.82, 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. The 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 = 1.05–1.76, \( P = 0.02 \)).

**Lifestyle-related variables and the WHO 25x25 factors.** Deficient vitamin D levels were independently associated with an increased risk of death (HR = 1.57, CI = 1.10–2.25, \( P = 0.01 \)), and sufficient vitamin D levels (> 60 nM) were associated with a reduced risk of death in the univariable analysis but not the multivariable. The Townsend deprivation score was not associated with overall survival. The Townsend deprivation was independently associated with an increased risk of death (HR = 1.66, CI = 1.21–2.28, \( P = 0.002 \)). BMI, alcohol intake, and exercise were not associated.

**Financial and home environment stressors.** Reported financial hardship, housing problems, negative life events, a history of anxiety or depression, and level of social support were not associated with risk of death. An ‘internal’ or ‘powerful others’ HLOC was not independently associated with death. A high ‘chance’ locus of health control was significantly associated with death in univariable analysis, but this did not reach significance in the multivariable model (Table 6).

---

### Table 1. The Association of Clinico-Pathological variables with Breslow Thickness in Univariable and Multivariable Linear Regression Analysis

| Factor                     | Univariable | Multivariable (\( n = 1,662 \)) |
|----------------------------|-------------|----------------------------------|
|                            | % Breslow change (95% CI) | \( p \) | % Breslow change (95% CI) | \( p \) |
| Age (years)                | 1.03 (0.81, 1.25) | < 0.001 | 0.93 (0.66, 1.21) | < 0.001 |
| Sex                        | Reference    | Reference | Reference | Reference |
| Male                       | 13.17 (7.10, 19.34) | < 0.001 | 9.81 (1.74, 17.87) | 0.02 |
| Breslow thickness           | Reference    | Reference | Reference | Reference |
| Back                       | 6.12 (-1.35, 13.58) | 0.11 | 2.61 (-6.18, 11.39) | 0.56 |
| Trunk                      | 5.28 (-5.27, 15.84) | 0.33 | 1.81 (-10.52, 14.16) | 0.77 |
| Head/neck                  | 15.62 (4.94, 26.30) | 0.004 | 10.95 (-0.86, 22.75) | 0.07 |
| Acral/sun protected         | 39.39 (27.04, 51.74) | < 0.001 | 29.55 (14.62, 44.47) | < 0.001 |

**Vitamin D**1 nM

| Vitamin D1 nM | Univariable | Multivariable |
|---------------|-------------|---------------|
| 20-60         | Reference   | Reference     |
| < 20          | 23.94 (9.48, 38.40) | 0.001 | 25.60 (10.85, 40.35) | 0.001 |
| > 60          | -2.65 (-10.44 to 5.15) | 0.51 | -1.72 (-9.62, 6.19) | 0.67 |

**Townsend score**

| Townsend score | Univariable | Multivariable |
|----------------|-------------|---------------|
| Least deprived | Reference   | Reference     |
| Moderate       | -6.69 (-14.30, 0.93) | 0.09 | -8.91 (-17.30, -0.53) | 0.04 |
| Most deprived  | -0.80 (-8.45, 6.84) | 0.84 | -3.94 (-12.62, 4.73) | 0.37 |

**WHO 25x25 factors**

| Smoking | Univariable | Multivariable |
|---------|-------------|---------------|
| Never   | Reference   | Reference     |
| Ex-smoker | 9.56 (2.67, 16.45) | 0.007 | 4.39 (-6.18, 11.39) | 0.56 |
| Smoker  | 11.14 (1.07, 21.21) | 0.03 | 13.67 (2.39, 24.96) | 0.02 |

| BMI     | Univariable | Multivariable |
|---------|-------------|---------------|
| 0       | 1.41 (0.74, 2.07) | < 0.001 | 1.14 (0.37, 1.90) | 0.004 |
| > 0 ≤ 7 | Reference   | Reference     |
| > 7 ≤ 14 | 2.94 (-6.27, 12.14) | 0.53 | -1.17 (-11.21, 8.88) | 0.82 |
| > 14    | -5.55 (-13.75, 2.65) | 0.19 | -14.38 (-24.02, -4.75) | 0.003 |

| Exercise MET hrs/week | Univariable | Multivariable |
|-----------------------|-------------|---------------|
| 0                     | Reference   | Reference     |
| 0.1 – 10              | -2.69 (-11.72) | 0.56 | 2.29 (-7.58, 12.18) | 0.65 |
| 10.1 – 20             | 0.34 (-8.27, 8.94) | 0.94 | 3.92 (-5.63, 13.47) | 0.42 |
| > 20                  | -2.39 (-11.40, 6.62) | 0.60 | 5.63 (-4.39, 15.66) | 0.27 |

Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent of task; WHO, world health organization.

Boldface indicates \( P < 0.05 \).

1 Vitamin D adjusted for season and batch.
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 S2).

DISCUSSION

This study modeled known melanoma clinico-pathological prognostic factors, the majority of the 25x25 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 the use of melanoma-specific survival. There was a long duration of follow-up during a period where the moderation of survival by treatment was minimal. The weaknesses were the relative lower participation of patients with low SES and the 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 or sun-protected site were independently associated with increased tumor thickness. Thicker tumors were also associated with head and neck sites, 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 nM) 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 and vitamin D receptor signaling has been identified as an inhibitor of β-catenin signaling 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).

The 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).

The 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). However, alcohol has been reported to be protective of diseases associated with systemic inflammation, which is recognized 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.

Table 3. Association of Clinico-Pathological Factors with Melanoma Specific Death in Univariable and Multivariable Cox Proportional Hazard Analysis

| Factor                        | Censored (n=1,757) | Died of melanoma (n=426) | Univariable | Multivariable (n=1,648) |
|-------------------------------|---------------------|---------------------------|-------------|-------------------------|
| Breslow (mm)                  | n (%)               | n (%)                     | Hazard ratio (95% CI) | Hazard ratio (95% CI) |
| Age (years)                   | -                   | -                         | < 0.001      | < 0.001                 |
| Sex                           | -                   | -                         | < 0.001      | < 0.001                 |
| Townsend score                | Least deprived      | 563 (81)                  | 0.79 (0.60, 1.04) | 0.09                    |
| Smoking                       | Never               | 964 (83)                  | 1.01 (0.98, 1.03) | 0.54                    |
| WHO 25x25 factors             | Tobacco            | 462 (83)                  | 1.01 (0.98, 1.03) | 0.54                    |
| Alcohol units/week            | 0                   | 318 (78)                  | 1.31 (0.39, 1.74) | 0.06                    |
| Exercise MET hrs/week         | 0                   | 431 (81)                  | 1.00 (0.76, 1.30) | 0.95                    |
| Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent of task; WHO, world health organization.

Boldface indicates \( P < 0.05 \).

1Vitamin D adjusted for season and batch.
Alcohol intake >14 units per week was also associated with a lower stage. Although comparisons between the stage and Breslow thickness analysis cannot be directly made, smoking and BMI were not associated with the 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 a 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 hypothesized to induce immune suppression via pathways involving the hypothalamic-pituitary-adrenocortical axis or the sympathetic nervous system (Shin et al., 2016; McEwen and Gianaros, 2010; Reiche et al., 2004). No association was seen with other stress-related factors measured.

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 a 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. The data reported here show that the protective effects of vitamin D levels on melanoma-specific survival were independent of the Townsend deprivation score and the 25x25 factors. This result may form evidence against the view that vitamin D levels are acting as a surrogate marker of social status related to “better health”. As previously demonstrated, smoking was associated with melanoma-specific survival, and we have theorized that smoking could mediate melanoma development via the promotion of systemic inflammation (Newton-Bishop et 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.

### Table 4. Association of Financial and Home Environment Stressors with Melanoma Specific Death in Univariable and Multivariable Cox Proportional Hazard Analysis

| Factor               | Censored (n = 1,757) | Died of melanoma (n = 426) | Univariable | Multivariable models | Hazard ratio (95% CI) | P   | Hazard ratio (95% CI) | P   |
|----------------------|----------------------|-----------------------------|-------------|----------------------|----------------------|-----|----------------------|-----|
| Financial hardship   |                      |                             |             |                      |                      |     |                      |     |
| 0 (n = 1,937)        | n (%)                | 173 (87)                   | 1           | 1                    | 1.937                |     | 1.556                |     |
| 1 (n = 354)          | 79 (21)              | 26 (13)                    | 1.73 (1.12, 2.68) | 0.01                | 1.35 (0.82, 2.20)   | 0.24|
| > 1 n ( = 1067)      | 261 (20)             | 1.66 (1.11, 2.49)          | 0.01        | 1.23 (0.78, 1.94)   | 0.38                |
| Housing problems     |                      |                             |             |                      |                      |     |                      |     |
| 0 (n = 2060)         | n (%)                | 1,260 (81)                 | 1           |                      | 1.260                |     | 1.621                |     |
| 1 (n = 18)           | 83 (17)              | 37 (17)                    | 0.89 (0.63 to 1.25) | 0.63                | 1.18 (0.80, 1.72)   | 0.41|
| > 1 n ( = 225)       | 66 (23)              | 1.12 (0.86 to 1.46)        | 0.42        |                      | 0.98 (0.71, 1.34)   | 0.90|
| Negative life events |                      |                             |             |                      |                      |     |                      |     |
| 0 (n = 2,092)        | n (%)                | 1,169 (81)                 | 1           |                      | 2,092                |     | 1.629                |     |
| 1 (n = 355)          | 80 (20)              | 89 (20)                    | 1.05 (0.83 – 1.34) | 0.68                | 0.96 (0.72, 1.27)   | 0.76|
| > 1 (n = 164)        | 82 (17)              | 37 (18)                    | 0.93 (0.66 – 1.31) | 0.69                | 1.04 (0.70, 1.55)   | 0.84|
| Hx depression/ anxiety|                    |                             |             |                      |                      |     |                      |     |
| No (n = 1,276)       | n (%)                | 1,260 (81)                 | 1           |                      | 1,276                |     | 1                    |     |
| Yes (n = 394)        | 83 (17)              | 317 (20)                   | 1.00 (0.99 – 1.01) | 0.98                | 1.01 (0.99, 1.02)   | 0.28|
| Social support scale |                      |                             |             |                      |                      |     |                      |     |
| Score -              | -                    | 1.00 (0.99 – 1.01)          | 0.98        |                      | 1.00 (0.99, 1.02)   | 0.28|
| Internal HLOC        |                      |                             |             |                      |                      |     |                      |     |
| Low (n = 458)        | 81 (19)              | 105 (19)                   | 1           |                      | 1                    |     | 1                    |     |
| Middle (n = 569)     | 80 (20)              | 140 (20)                   | 1.08 (0.84 to 1.39) | 0.55                | 1.07 (0.79, 1.45)   | 0.65|
| High (n = 656)       | 80 (20)              | 162 (20)                   | 1.06 (0.83 to 1.36) | 0.63                | 0.96 (0.72, 1.28)   | 0.80|
| Chance HLOC          |                      |                             |             |                      |                      |     |                      |     |
| Low (n = 540)        | 83 (17)              | 110 (17)                   | 1           |                      | 540                  |     | 1                    |     |
| Middle (n = 542)     | 82 (18)              | 116 (18)                   | 1.02 (0.78 to 1.32) | 0.89                | 1.03 (0.76, 1.41)   | 0.87|
| High (n = 585)       | 77 (23)              | 175 (23)                   | 1.35 (1.06 to 1.71) | 0.02                | 1.37 (1.02, 1.82)   | 0.03|
| Powerful others HLOC |                      |                             |             |                      |                      |     |                      |     |
| Low (n = 528)        | 85 (15)              | 92 (15)                    | 1           |                      | 528                  |     | 1                    |     |
| Middle (n = 621)     | 82 (18)              | 132 (18)                   | 1.22 (0.94 to 1.59) | 0.14                | 0.85 (0.62, 1.16)   | 0.30|
| High (n = 514)       | 74 (26)              | 180 (26)                   | 1.90 (1.48 to 2.44) < 0.001 | 0.99(0.72, 1.36)   | 0.96|

Abbreviations: CI, confidence interval; HLOC, health locus of control.

Boldface indicates P < 0.05.

1 Multivariable models including Breslow thickness, site, age, sex, vitamin D (adjusted for season and batch), Townsend score, smoking, body mass index, alcohol intake and exercise.
in other cancers (Calle et al., 2003). BMI and alcohol consumption were not independently associated with melanoma-specific survival in this data set but may contribute by association with thickness. Exercise was not associated.

In addition to the association with increased Breslow thickness, perceived financial hardship was also associated with death from melanoma in a 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 a multivariable analysis. There was no evidence for the association between other home and environment stress factors examined and death from melanoma. However, an association was seen with a high ‘chance’ HLOC. 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 the Townsend score here (Supplementary Table S2). As there was multiple testing on the effect of HLOC, which has not previously been examined in melanoma thickness and/or survival, would need further exploration.

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

Table 5. Association of Clinico-Pathological Factors with Overall Survival in Univariable and Multivariable Cox Proportional Hazard Analysis

| Factor                        | Censored (n = 1,607) | Died (n = 576) | Univariable | Multivariable (n = 1,640) |
|-------------------------------|---------------------|---------------|-------------|--------------------------|
|                              | 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)               | 1.68 (1.42, 1.98) | < 0.001      | 1.41 (1.12, 1.78)     | 0.004      |
|                              | Male                | 639 (67)      | 311 (33)               | 1.05 (1.04, 1.06) | < 0.001      | 1.05 (1.04, 1.06)     | < 0.001      |
| Tumor site                    | Limbs               | 825 (81)      | 190 (19)               | 1.60 (1.29, 1.98) | < 0.001      | 1.36 (1.05, 1.76)     | 0.02      |
|                              | Back                | 387 (71)      | 158 (29)               | 1.98 (1.26, 2.33) | < 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 (67)      | 93 (47)                | 3.54 (2.76, 4.53) | < 0.001      | 1.22 (0.85, 1.76)     | 0.29      |
| Vitamin D1 nM                 | 20-60               | 870 (73)      | 319 (27)               | 1.52 (1.10, 2.11) | 0.01         | 1.57 (1.10, 2.25)     | 0.01      |
|                              | < 20                | 69 (63)       | 41 (37)                | 0.83 (0.67, 1.03) | 0.08         | 0.79 (0.62, 1.00)     | 0.05      |
|                              | > 60                | 370 (77)      | 111 (23)               | 1.10 (0.90, 1.35) | 0.34         | 0.97 (0.76, 1.25)     | 0.83      |
| Townsend score                | Least deprived      | 522 (75)      | 177 (25)               | 1.42 (1.18, 1.70) | <0.001       | 1.09 (0.88, 1.36)     | 0.42      |
|                              | Moderate            | 542 (75)      | 185 (25)               | 0.96 (0.78, 1.21) | 0.68         | 1.05 (0.88, 1.36)     | 0.67      |
|                              | Most deprived       | 508 (71)      | 206 (29)               | 1.31 (1.01, 1.69) | 0.04         | 1.66 (1.21, 2.28)     | 0.002     |
| WHO 25x25 factors             | Smoking             | 897 (78)      | 260 (22)               | 1.28 (1.01, 1.64) | 1.08 (0.81, 1.44) | 0.60       |
|                              | 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     |
| MAC                           | 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)               | 1.04 (0.81, 1.35) | 0.74         | 1.00 (0.75, 1.35)     | 0.99      |
|                              | > 7 ≤14             | 324 (75)      | 106 (25)               | 0.96 (0.77, 1.20) | 0.72         | 0.79 (0.59, 1.06)     | 0.12      |
|                              | > 14                | 509 (75)      | 173 (25)               | 1.04 (0.81, 1.35) | 0.74         | 1.00 (0.75, 1.35)     | 0.99      |
| Exercise MET hrs/week         | 0                   | 388 (73)      | 146 (27)               | 0.98 (0.77, 1.25) | 0.88         | 0.99 (0.75, 1.30)     | 0.92      |
|                              | > 20                | 316 (75)      | 119 (25)               | 0.98 (0.77, 1.25) | 0.88         | 0.97 (0.73, 1.29)     | 0.84      |

Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent of task; WHO, world health organization. Boldface indicates P < 0.05.

1Vitamin D adjusted for season and batch.
In summary, an 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. The 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 a 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 the treatment and prevention of melanoma. This study is consistent with the WHO view that tackling the 25x25 factors should produce improvements in premature mortality.

**MATERIALS AND METHODS**

**Study design**

A total of 2,183 patients were recruited to the Leeds Melanoma Cohort between 2000 and 2012 (Newton-Bishop et al., 2015). The patients were identified from pathology and clinical registers in a defined area of England with additional recruitment from 32 other centers (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 I to IIIA primary melanoma. A total of 2,183 of 3,360 eligible patients (65%) took part. Non-participants were younger, more deprived (higher Townsend scores) and had thicker tumors than the 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 and/or immuno therapies.

**Table 6. Association of Financial and Home Environment Stressors with Overall Survival in Univariable and Multivariable Cox Proportional Hazard Analysis**

| Factor                  | Censored (n = 1,607) | Died (n = 576) | Univariable | Multivariable models | p    | Hazard ratio (95% CI) | p    | Hazard ratio (95% CI) |
|-------------------------|----------------------|---------------|-------------|----------------------|------|----------------------|------|----------------------|
| Financial hardship      |                      |               |             |                      |      |                      |      |                      |
| 0                       | 164 (82)             | 35 (18)       | 1           | 1                    |      | 1.26 (0.82, 1.91)    | 0.29 |                      |
| 1                       | 323 (72)             | 123 (28)      | 1.59 (1.04, 2.41) | 0.03    | 1.22 (0.83, 1.81)    | 0.31 |                      |
| > 1                     | 976 (73)             | 352 (27)      | 1.42 (0.97, 2.10) | 0.07    | 1.22 (0.83, 1.81)    | 0.31 |                      |
| Housing problems        |                      |               |             |                      |      |                      |      |                      |
| 0                       | 1,164 (75)           | 390 (25)      | 1           | 1                    |      | 1.21 (0.87, 1.68)    | 0.30 |                      |
| 1                       | 164 (76)             | 51 (24)       | 0.91 (1.00, 1.22) | 0.54    | 1.09 (0.84, 1.42)    | 0.52 |                      |
| > 1                     | 193 (66)             | 98 (34)       | 1.25 (1.00, 1.56) | 0.05    | 1.09 (0.84, 1.42)    | 0.52 |                      |
| Negative life events    |                      |               |             |                      |      |                      |      |                      |
| 0                       | 1,055 (72)           | 392 (27)      | 1           | 1                    |      | 1.26 (0.82, 1.91)    | 0.29 |                      |
| 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 (21)       | 0.73 (0.53, 1.01) | 0.06    | 0.84 (0.58, 1.22)    | 0.36 |                      |
| Hx depression/ anxiety  |                      |               |             |                      |      |                      |      |                      |
| No                      | 1,165 (73)           | 428 (27)      | 1           | 1                    |      | 1.21 (0.87, 1.68)    | 0.30 |                      |
| 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 |          |               |             |                      |      |                      |      |                      |
| Score                   | -                    | -             | 0.99 (0.98, 1.01) | 0.32    | 1.01 (0.99, 1.02)    | 0.40 |                      |
| Internal HLOC           |                      |               |             |                      |      |                      |      |                      |
| Low                     | 420 (75)             | 143 (25)      | 1           | 1                    |      | 1.14 (0.88, 1.48)    | 0.33 |                      |
| Middle                  | 525 (74)             | 184 (26)      | 1.08 (0.87, 1.35) | 0.48    | 0.99 (0.77, 1.27)    | 0.92 |                      |
| High                    | 603 (74)             | 215 (26)      | 1.10 (0.89, 1.36) | 0.85    | 0.99 (0.77, 1.27)    | 0.92 |                      |
| Chance HLOC             |                      |               |             |                      |      |                      |      |                      |
| Low                     | 506 (78)             | 144 (22)      | 1           | 1                    |      | 1.28 (0.99, 1.65)    | 0.06 |                      |
| 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    |                      |               |             |                      |      |                      |      |                      |
| Low                     | 511 (82)             | 109 (18)      | 1           | 1                    |      | 1.16 (0.87, 1.54)    | 0.32 |                      |
| 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 |                      |

Abbreviations: CI, confidence interval; HLOC, health locus of control. Boldface indicates $P < 0.05$.

1Multivariable models including Breslow thickness, site, age, sex, vitamin D (adjusted for season and batch), Townsend score, smoking, body mass index, alcohol intake and exercise.
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 and/or neck and acral and/or sun protected) were collected. Tumor characteristics were extracted from histopathology reports. Serum 25-Hydroxyvitamin D$_2$/D$_3$ levels were measured at study entry. The American Joint Committee on Cancer 7th edition was used for staging (Edge and Compton, 2010). The 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 categorized as ‘current smoker, ex-smoker, or never smoked.’ BMI was estimated using self-reported height and weight. The presence of diabetes was self-reported. Alcohol intake was self-reported as number of glasses of wine, single measures of spirits and/or fortified wine, and pints of beer per week.

Questionnaires measuring perceived financial hardship and problems with housing and/or neighborhood were developed in-house and tested on melanoma patients in the clinic. Negative life events were measured using questions derived from the Oei and Zwarts life events questionnaire (Oei and Zwart, 1986). See Supplementary Table S3 for the variables. A three-tier score was created for the 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 HLOC scale (Wallston et al., 1978) was used to assess participants’ health beliefs indicating the degree individuals believed their behavior affected their health was classified into the following three domains: (i) internal: personal behavior affects health, (ii) chance: health is a matter of chance or (iii) powerful others: health is controlled by others.

Melanoma-specific survival and overall survival

The participants were followed up by annual re-contact, a review of medical records, and national registers. The medical records and death certificate or cause of death for patients who died was obtained from the Office of National Statistics, prior to the reorganization of these services as NHS Digital. To determine melanoma-specific death, this evidence was reviewed, and the participants who died of non-melanoma causes were censored at the time of death. The overall follow-up was censored on March 31, 2018.

Statistical analysis

Vitamin D levels (nM) were available for 1,780 subjects and grouped into three categories; deficient (< 20), suboptimal 20-60 (reference), and sufficient (> 60) (Newton-Bishop et al., 2015). The Townsend score was grouped into approximate tertiles, as were the HLOC scores. BMI was a continuous measure. To calculate units (8 g alcohol) per week, the 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 of task values to activities (Ainsworth et al., 1993). Metabolic equivalent of task hours per week were summed for each participant and grouped: 0 (reference), 0–10, 10–20 and > 20.

An unadjusted linear regression was used to assess the predictors of Breslow thickness. A 100 x natural log was taken, so the coefficients were interpreted as percentage change. The clinicopathological variables and variables related to financial and home environment stressors were taken into multivariable models. Diabetes was not included, as it was colinear with BMI.

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

Univariable and multivariable linear regression models were performed to assess predictors of the 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. release 12.1 was used for analyses (Stata Corp LP, College Station, TX).

Data availability statement

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

ORCIDs

C. M. Hardie: https://orcid.org/0000-0002-1271-6159
F. Elliott: https://orcid.org/0000-0002-3239-6914
M. Chan: https://orcid.org/0000-0002-3073-5935
Z. Rogers: https://orcid.org/0000-0001-6189-2696
D.T. Bishop: https://orcid.org/0000-0002-8752-8785
J.A. Newton-Bishop: https://orcid.org/0000-0001-9147-6802

CONFLICT OF INTEREST

The authors state no conflicts of interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the participants who gave of their time and their very blood. We also thank the research nurses and technicians who collected the data over many years: Susan Leake, Susan Haynes, Birute Karpačiūnas, Paul Affleck, Kairen Kukalizch, Linda Whitaker, Sharon Jackson, Edwina Gerry, Elaine Fitzgibbon, Clarissa Nolan, Saila Waseem, Yvonne Taylor, Pauline Brunyee, Paul King, Tracy Lee, Samira Lobo and Minnlu Polso. We also thank To Jo Gascoyne and May Chan who provided critical support in managing the complex data set. This work was funded by Cancer Research UK through grants C588/A19167, C8216/A6129 and C588/A10721 and the NIH via CA83115, and the EU via Framework 6 LSH-2004-22.2-0-4.

AUTHOR CONTRIBUTIONS

Conceptualization: CMH, FE, ZR, DTB, JNB; Data curation: MC; Formal analysis: CMH, FE, ZR, DTB; Funding acquisition: DTB, JNB; Investigation: CMH, FE, ZR, DTB, JNB; Methodology: CMH, FE, MC, DTB, JNB; Project administration: DTB, JNB; Resources: DTB, JNB; Software: CMH, FE, MC, ZR, DTB, JNB; Supervision: DTB, JNB; Validation: FE, DTB, JNB; Visualization: CMH, DTB, JNB; Writing - original draft preparation: CMH, FE, JNB; Writing - review and editing: MC, ZE, and DTB.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2019.05.033.

REFERENCES

Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exer 1993; 25:71–80.
Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer Melanoma Staging system. J Clin Oncol 2001; 19:3622–34.
Fang S, Sui D, Wang Y, Liu H, Chiang YJ, Ross MI, et al. Association of vitamin Down  

Ellerhorst JA, Greene VR, Ekmekcioglu S, Warneke CL, Johnson MM, Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2008;5:466—75.

Cao Y. Angiogenesis modulates adipogenesis and obesity. J Clin Invest 2007;117:2362—8.

Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol 2008:5:466—75.

Rachet B, Quinn MJ, Cooper N, Coleman MP. Survival from melanoma of the skin in England and Wales up to 2001. Br J Cancer 2008;99:S47—9.

Socio-demographic inequalities in stage of cancer diagnosis: evidence from patients with female breast, lung, colon, rectal, prostate, renal, bladder, melanoma, ovarian and endometrial cancer. Ann Oncol 2013;24:843—50.

MacKie RM, Hole DJ. Incidence and thickness of primary tumours and survival of patients with cutaneous malignant melanoma in relation to socioeconomic status. BMJ 1996;312:1125—8.

Mateo-Pascual C, Julián-Viñals R, Alarcón-Alarcón T, Castell-Alcalá MV, Iturzaeta-Sánchez JM, Otero-Piáu A. Vitamin D deficiency in a cohort over 65 years: prevalence and association with sociodemographic and health factors. Rev Esp Geriatr Gerontol 2014;49:210—6.

McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. Ann N Y Acad Sci 2010;1186:190—222.

McLaren L. Socioeconomic status and obesity. Epidemiol Rev 2007;29:29—48.

Milen AE, Tucker MA, Hartge P, Halpern A, Elder DE, Guerry D, et al. Diet and melanoma in a case-control study. Cancer Epidemiol Biomarkers Prev 2004;13:1042—14.

Montella M, Crispo A, Grimaldi M, De Marco MR, Ascierto PA, Parese R, et al. An assessment of factors related to tumor thickness and delay in diagnosis of melanoma in Southern Italy. Prev Med 2002;35:271—7.

Mostofsky E, Chahal HS, Mukamal KJ, Rimm EB, Mittleman MA. Alcohol and immediate risk of cardiovascular events: a systematic review and dose—response meta-analysis. Circulation 2016;133:979—87.

Muralidhar S, Nsengimana J, Pozniak J, O’Shea S, Laye J, Adams D, et al. Primary melanoma expression of the vitamin D receptor (VDR) is protective for melanoma survival and is associated with increased tumor immune response, decreased Wnt/b-catenin signaling and tumor proliferation[lab-stract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2018. Chicago, PA: Cancer Res 2018;78:5205.

Náfrádi L, Nakamoto K, Schulz PJ. Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. PLOS ONE 2017;12:e0186458.

Newton-Bishop JA, Beswick S, Randerson-Moor J, Chang YM, Affleck P, Elliott F, et al. Serum 25-hydroxyvitamin D3 levels are associated with breslow thickness at presentation and survival from melanoma. J Clin Oncol 2009;27:5439—44.

Newton-Bishop JA, Davies JR, Latheef F, Randerson-Moor J, Chan M, Gascogne J, et al. 25-Hydroxyvitamin D2/D3 levels and factors associated with systemic inflammation and melanoma survival in the Leeds Mela-noma Cohort. Int J Cancer 2015;136:2890—9.

Norbeck JS, Lindsay AM, Carrier VL. The development of an instrument to measure social support. Nurs Res 1981;30:264—9.

Oei TJ, Zwart FM. The assessment of life events: self-administered questionnaire versus interview. J Affect Disord 1986;10:185—90.

Palesh O, Butler LD, Koopman C, Giese-Davis J, Carlson R, Spiegel D. Stress history and breast cancer recurrence. J Psychosom Res 2007;63:233—9.

Rachet B, Quinn MJ, Cooper N, Coleman MP. Survival from melanoma of the skin in England and Wales up to 2001. Br J Cancer 2008;99:547—9.

Reiche EMV, Nunes SOV, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol 2004;5:617—25.

Risica PM, Weinstock MA, Rakowski W, Kirtania U, Martin RA, Smith KJ. Body satisfaction effect on thorough skin self-examination. Am J Prev Med 2008;35:68—72.

Lumpkin JR. The relationship between locus of control and age: new evidence. J Soc Behav Pers 1986;1:1245.

Luszczynska A, Schwarzer R. Multidimensional health locus of control: comments on the construct and its measurement. J Health Psychol 2005;10:633—42.

Lyratzopoulos G, Abel GA, Brown CH, Rous BA, Vernon SA, Roland M, et al. Socio-demographic inequalities in stage of cancer diagnosis: evidence from patients with female breast, lung, colon, rectal, prostate, renal, bladder, melanoma, ovarian and endometrial cancer. Ann Oncol 2013;24:843—50.

Saigat P, Aegerter P, Vitoux D, Lebbe C, Wolkenstein P, Dupin N, et al. Prognostic value of 25-hydroxyvitamin D3 levels at diagnosis and during follow-up in melanoma patients. J Natl Cancer Inst 2015;107:dxv264.
Shack LG, Rachet B, Brewster DH, Coleman MP. Socioeconomic inequalities in cancer survival in Scotland 1986–2000. Br J Cancer 2007;97:999–1004.

Shin KJ, Lee YJ, Yang YR, Park S, Suh PG, Follo MY, et al. Molecular mechanisms underlying psychological stress and cancer. Curr Pharm Des 2016;22:2389–402.

Stenehjem JS, Veierød MB, Nilsen LT, Ghiassvand R, Johnsen B, Grimsrud TK, et al. Anthropometric factors and Breslow thickness: prospective data on 2570 cases of cutaneous melanoma in the population-based Janus Cohort. Br J Dermatol 2018;179:632–41.

Steptoe A, Feldman PJ. Neighborhood problems as sources of chronic stress: development of a measure of neighborhood problems, and associations with socioeconomic status and health. Ann Behav Med 2001;23:177–83.

Stringhini S, Carmeli C, Jokela M, Avendaño M, Muenning P, Guida F, et al. Socioeconomic status and the 25 x 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. Lancet 2017;389:1229–37.

Stringhini S, Polidoro S, Sacerdote C, Kelly RS, van Veldhoven K, Agnoli C, et al. Life-course socioeconomic status and DNA methylation of genes regulating inflammation. Int J Epidemiol 2015;44:1320–30.

Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the North. London: Routledge; 1988.

Tromp DM, Brouha XD, Hordijk GJ, Winnubst JA, Gebhardt WA, Van Der Doef MP, et al. Medical care-seeking and health-risk behavior in patients with head and neck cancer: the role of health value, control beliefs and psychological distress. Health Educ Res 2005;20:665–75.

UK Chief Medical Officer. Low Risk Drinking Guidelines. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/545937/UK_CMOs__report.pdf; 2016 (accessed 18 July 2018).

Wallston KA, Wallston BS, DeVellis R. Development of the multidimensional health locus of control (MHLC) scales. Health Educ Monogr 1978;6:160–70.

Wardle J, Steptoe A. Socioeconomic differences in attitudes and beliefs about healthy lifestyles. J Epidemiol Commun Health 2003;57:440–3.

World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva: WHO; 2013.

Wyatt C, Lucas RM, Hurst C, Kimlin MG. Vitamin D deficiency at melanoma diagnosis is associated with higher Breslow thickness. PLOS ONE 2015;10: e0126394.

This work is licensed under a Creative Commons Attribution 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/
Supplementary Table S1. Association of Variables of Interest with Stage (High versus Low) from Univariable and Multivariable Generalized Linear Models to Estimate Risk Ratios

| Factor                        | Statistic | Stage 0—II (n = 1,864) | Stage III-IV (n = 289) | Univariable Risk ratio (95% CI) | P     | Multivariable Risk ratio (95% CI) | P     |
|-------------------------------|-----------|-------------------------|------------------------|--------------------------------|-------|----------------------------------|-------|
| Age (years)                   | mean, SD  | 54.19 (13.68)           | 56.80 (13.09)          | 1 (1.00-1.02)                  | 0.002 | 1 (1.00-1.02)                    | 0.07  |
| Sex                           | n(%)      | 1,073 (89)              | 139 (11)               | 1                               |       | 1.23 (0.99-1.53)                | 0.07  |
| Male                          | 791 (84)  | 150 (16)                | 1.39 (1.12-1.72)       | 0.003                           |       | 1.39 (1.12-1.72)                | 0.003 |
| Site                          | n(%)      | 905 (90)                | 103 (10)               | 1                               |       | 1                               |       |
| Back                          | 457 (84)  | 85 (16)                 | 1.53 (1.17-2.01)       | 0.002                           |       | 1.52 (1.06-2.16)                | 0.02  |
| Trunk                         | 189 (89)  | 23 (11)                 | 1.06 (0.69-1.63)       | 0.78                            |       | 1.19 (0.71-2.00)                | 0.50  |
| Head/neck                     | 191 (92)  | 16 (8)                  | 0.76 (0.46-1.25)       | 0.28                            |       | 0.80 (0.45-1.42)                | 0.44  |
| Acral/sun protected           | 122 (66)  | 62 (34)                 | 3.30 (2.51-4.33)       | < 0.001                         |       | 3.23 (2.29-4.54)                | < 0.001|
| Vitamin D1 nM                 | 20-60 n(%)| 1,032 (87)              | 149 (13)               | 1                               |       | 1                               |       |
| < 20                          | 81 (76)   | 25 (24)                 | 1.87 (1.29-2.72)       | 0.001                           |       | 2.21 (1.61-3.02)                | < 0.001|
| > 60                          | 434 (91)  | 41 (9)                  | 0.68 (0.49-0.95)       | 0.02                            |       | 0.71 (0.50-1.02)                | 0.07  |
| Townsend score                | n(%)      | 607 (87)                | 88 (13)                | 1                               |       | 1                               |       |
| Least deprived                | 618 (87)  | 95 (13)                 | 1.05 (0.80-1.38)       | 0.71                            |       | 0.87 (0.64-1.19)                | 0.40  |
| Moderate                      | 606 (86)  | 97 (14)                 | 1.09 (0.83-1.43)       | 0.53                            |       | 1.04 (0.83-1.31)                | 0.73  |
| Smoking                       | n(%)      | 998 (87)                | 144 (13)               | 1                               |       | 1                               |       |
| Never                         | 587 (85)  | 103 (15)                | 1.18 (0.94-1.50)       | 0.16                            |       | 0.95 (0.73-1.25)                | 0.71  |
| Ex-smoker                     | 208 (87)  | 31 (13)                 | 1.03 (0.72-1.48)       | 0.88                            |       | 0.71 (0.43-1.18)                | 0.19  |
| Smoker                        | 208 (87)  | 31 (13)                 | 1.03 (0.72-1.48)       | 0.88                            |       | 0.71 (0.43-1.18)                | 0.19  |
| BMI Mean/SD                   | 26.79 (4.59) | 27.09 (3.97)  | 1.01 (0.99-1.04)       | 0.30                            |       | 1.01 (0.98-1.03)                | 0.50  |
| Alcohol units/week            | 0 n(%)    | 341 (85)                | 61 (15)                | 0.98 (0.72-1.32)                | 0.88  | 1.16 (0.83-1.61)                | 0.38  |
| > 0 < 7                      | 468 (84)  | 86 (16)                 | 1                      |       | 1                               |       |
| > 7 ≤14                      | 371 (87)  | 54 (13)                 | 0.82 (0.60-1.12)       | 0.21                            |       | 0.70 (0.47-1.06)                | 0.09  |
| > 14                         | 604 (89)  | 71 (11)                 | 0.68 (0.51-0.91)       | 0.009                           |       | 0.58 (0.40-0.85)                | 0.005 |
| Exercise MET hrs/week         | 0 n(%)    | 455 (86)                | 74 (14)                | 1                               |       | 1                               |       |
| 0.1—10                       | 415 (88)  | 59 (12)                 | 0.89 (0.65-1.22)       | 0.47                            |       | 0.94 (0.64-1.37)                | 0.74  |
| 10.1—20                      | 499 (87)  | 75 (13)                 | 0.93 (0.69-1.26)       | 0.65                            |       | 1.09 (0.80-1.48)                | 0.61  |
| > 20                         | 408 (86)  | 65 (14)                 | 0.98 (0.72-1.34)       | 0.91                            |       | 1.17 (0.80-1.71)                | 0.41  |
| Financial hardship            | 0 n(%)    | 181 (92)                | 15 (8)                 | 1                               |       | 1                               |       |
| 1                            | 386 (88)  | 53 (12)                 | 1.58 (0.91-2.33)       | 0.10                            |       | 1.35 (0.72-2.55)                | 0.35  |
| > 1                          | 1124 (86) | 189 (14)                | 1.88 (1.14-3.11)       | 0.01                            |       | 1.66 (0.92-2.98)                | 0.09  |
| Chance HLOC                   | Low n(%)  | 562 (87)                | 81 (13)                | 1                               |       | 1                               |       |
| Moderate                      | 569 (87)  | 82 (13)                 | 1.00 (0.75-1.33)       | 0.99                            |       | 0.92 (0.66-1.28)                | 0.64  |
| High                         | 642 (86)  | 106 (14)                | 1.12 (0.86-1.47)       | 0.39                            |       | 0.99 (0.72-1.35)                | 0.93  |

Abbreviations: BMI, body mass index; CI, confidence interval; HLOC, health locus of control; MET, metabolic equivalence of task; SD, standard deviation. Boldface indicates \( P < 0.05 \)

\(^1\)Vitamin D adjusted for season and batch.
### Supplementary Table S2. Association of Variables of Interest with Townsend Deprivation Score from Univariable and Multivariable Linear Regression Models

| Factor                | Univariable |          | Multivariable |          |
|-----------------------|-------------|----------|--------------|----------|
|                       | Coefficient | (95% CI) | p            | Coefficient | (95% CI) | p          |
| Vitamin D \(^1\) nM   |             |          |              |           |          |            |
| 20-60                 | Reference   | —        | —            | Reference  | —        | —          |
| < 20                  | 0.38 (0.1, 0.65) | 0.21    | Reference    | 0.05 (0.68) | 0.87  |
| > 60                  | -0.40 (-0.72, -0.08) | 0.02    | -0.30 (-0.63, 0.03) | 0.07 |
| Smoking               |             |          |              |           |          |            |
| Never                 | Reference   | —        | —            | Reference  | —        | —          |
| Ex-smoker             | 0.38 (0.1, 0.65) | 0.09    | 0.17 (-0.50) | 0.28 |
| Smoker                | 1.25 (0.84, 1.66) | < 0.001 | 1.05 (0.57, 1.52) | < 0.001 |
| BMI                   | 0.06 (0.03, 0.09) | < 0.001 | 0.06 (0.03, 0.09) | < 0.001 |
| Alcohol units/week    |             |          |              |           |          |            |
| 0                     | 0.28 (0.10, 0.66) | 0.14    | 0.12 (-0.56) | 0.60 |
| > 0 ≤7               | Reference   | —        | Reference    | —        | —        | —          |
| > 7 ≤14              | -0.33 (-0.71, 0.04) | 0.08    | -0.44 (-0.87, -0.01) | 0.05 |
| > 14                 | -0.19 (-0.52, 0.15) | 0.27    | -0.32 (-0.71, 0.06) | 0.10 |
| Financial hardship    |             |          |              |           |          |            |
| 0                     | Reference   | —        | Reference    | —        | —        | —          |
| 1                     | -0.40 (-0.89, 0.10) | 0.11    | -0.52 (-1.06, 0.01) | 0.06 |
| > 1                  | 0.29 (-0.15, 0.73) | 0.20    | 0.01 (-0.38, 0.58) | 0.68 |
| Chance HLOC           |             |          |              |           |          |            |
| Low                   | Reference   | —        | Reference    | —        | —        | —          |
| Moderate              | 0.009 (-0.32, 0.34) | 0.96    | 0.01 (-0.38, 0.35) | 0.94 |
| High                  | -0.008 (-0.32, 0.31) | 0.96    | -0.11 (-0.46, 0.25) | 0.56 |

Abbreviations: BMI, body mass index; CI, confidence interval; HLOC, health locus of control.
Boldface indicates \( P < 0.05 \).
\(^1\)Vitamin D adjusted for season and batch.

### Supplementary Table S3. Questions Used to Create Psychosocial Variables

| Variable                                                                 | Financial hardship                                                                 | Housing problems                                                                 | Negative life events (within the past 2 years)                                                                 |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Have you ever been forced to give up work owing to redundancy,             | Is there objective overcrowding? (calculated by person per room)                   | Have you or a loved one ever been seriously ill?                                  |
| enforced early retirement, or illness?                                   |                                                                                   |                                                                                   |                                                                                                             |
| Do you feel that your income now is enough to support you and your family? | Is your housing adequate in terms of space for you and your family?                | Has a loved one or yourself been in a serious accident?                            |
| Have you earned more in the past?                                        | Is your housing too cold in the winter?                                            | Have you or your partner miscarried or had an abortion or damp?                    |
| Do you have any unpaid credit card bills?                                | Do you feel safe in your neighborhood?                                             | Have you been separated or divorced?                                              |
| Do you have any difficulty paying your mortgage?                         | Do you have good neighbors overall?                                                | Have you been worried about any important relationship with someone?               |
| Do you feel financially secure?                                          |                                                                                    |                                                                                    |                                                                                                             |
| Can you afford to run a car?                                             |                                                                                    |                                                                                    |                                                                                                             |
| Can you take holidays where and when you want to?                        |                                                                                    |                                                                                    |                                                                                                             |
| Have you or someone very close to you had major money problems?          |                                                                                    |                                                                                    |                                                                                                             |
| Have you or someone very close to you been convicted of any offense or    |                                                                                    |                                                                                    |                                                                                                             |
| given a prison sentence?                                                 |                                                                                    |                                                                                    |                                                                                                             |
| Have you been burgled or suffered serious loss or damage to any property? |                                                                                    |                                                                                    |                                                                                                             |
| Has anyone close to you died?                                            |                                                                                    |                                                                                    |                                                                                                             |