

# The association of smoking and socioeconomic status on cutaneous melanoma: a population-based, data-linkage, case–control study\*

J.A.G. Gibson<sup>1,2</sup>, T.D. Dobbs<sup>1,2</sup>, R. Griffiths<sup>3</sup>, J. Song<sup>3</sup>, A. Akbari<sup>3,4,5</sup>, S. Whitaker<sup>6</sup>, A. Watkins<sup>3,4</sup>, S.M. Langan<sup>7,8</sup>, H.A. Hutchings<sup>4</sup>, R.A. Lyons<sup>3,4,5</sup> and I.S. Whitaker<sup>1,2</sup>

<sup>1</sup>Reconstructive Surgery & Regenerative Medicine Research Group, Institute of Life Science, <sup>4</sup>Patient and Population Health and Informatics Research and

<sup>5</sup>Administrative Data Research Centre Wales, Swansea University Medical School, Swansea, U.K.

<sup>2</sup>The Welsh Centre for Burns and Plastic Surgery, Morriston Hospital, Swansea, U.K.

<sup>3</sup>Health Data Research UK, Swansea University, Swansea, U.K.

<sup>6</sup>Department of Dermatology, Singleton Hospital, Swansea, U.K.

<sup>7</sup>Health Data Research UK, London, U.K.

<sup>8</sup>London School of Hygiene & Tropical Medicine, London, U.K.

**Linked Comment:** Thompson and Friedman. *Br J Dermatol* 2020; **182**:1080.

## Summary

### Correspondence

John Gibson.

E-mail: johnagibson@hotmail.com

### Accepted for publication

8 September 2019

### Funding sources

This work was supported by an iGrant from Tenovus Cancer Care. The ReconRegen research group is supported by the Royal College of Surgeons of England, the British Association of Plastic, Reconstructive and Aesthetic Surgeons and the Swansea Bay University Health Board. Health Data Research UK, which receives its funding from HDR UK Ltd (grant ref: NIWA1) funded by the U.K. Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation and the Wellcome Trust. This work was also supported by an ESRC award establishing the Administrative Data Research Centre Wales (ES/L007444/1). S.M.L. reports grants from Wellcome Senior Clinical Fellowship in Science (205039/Z/16/Z) during the conduct of the study. Funders played no role in the study design, methods, data collection, data analysis, manuscript preparation or publication.

### Conflicts of interest

None to declare.

\*Plain language summary available online

DOI 10.1111/bjd.18526

**Background** Previous studies have identified an inverse association between melanoma and smoking; however, data from population-based studies are scarce.

**Objectives** To determine the association between smoking and socioeconomic (SES) on the risk of development of melanoma. Furthermore, we sought to determine the implications of smoking and SES on survival.

**Methods** We conducted a population-based case–control study. Cases were identified from the Welsh Cancer Intelligence and Surveillance Unit (WCISU) during 2000–2015 and controls from the general population. Smoking and SES were obtained from data linkage with other national databases. The association of smoking status and SES on the incidence of melanoma were assessed using binary logistic regression. Multivariate survival analysis was performed on a melanoma cohort using a Cox proportional hazard model using survival as the outcome.

**Results** During 2000–2015, 9636 patients developed melanoma. Smoking data were obtained for 7124 (73.9%) of these patients. There were 26 408 controls identified from the general population. Smoking was inversely associated with melanoma incidence [odds ratio (OR) 0.70, 95% confidence interval (CI) 0.65–0.76]. Smoking was associated with an increased overall mortality [hazard ratio (HR) 1.30, 95% CI 1.09–1.55], but not associated with melanoma-specific mortality. Patients with higher SES had an increased association with melanoma incidence (OR 1.58, 95% CI 1.44–1.73). Higher SES was associated with an increased chance of both overall (HR 0.67, 95% CI 0.56–0.81) and disease-specific survival (HR 0.69, 95% CI 0.53–0.90).

**Conclusions** Our study has demonstrated that smoking appeared to be associated with reduced incidence of melanoma. Although smoking increases overall mortality, no association was observed with melanoma-specific mortality. Further work is required to determine if there is a biological mechanism underlying this relationship or an alternative explanation, such as survival bias.

### What's already known about this topic?

- Previous studies have been contradictory with both negative and positive associations between smoking and the incidence of melanoma reported.
- Previous studies have either been limited by publication bias because of selective reporting or underpowered.

**What does this study add?**

- Our large study identified an inverse association between smoking status and melanoma incidence.
- Although smoking status was negatively associated with overall disease survival, no significant association was noted in melanoma-specific survival.
- Socioeconomic status remains closely associated with melanoma. Although higher socioeconomic populations are more likely to develop the disease, patients with lower socioeconomic status continue to have a worse prognosis.

Although there is a wealth of knowledge on the association of melanoma with risk factors such as ultraviolet light exposure, skin type and genetics,<sup>1</sup> the relationship between tobacco smoke and melanoma is less clear. Tobacco smoke is a type 1 carcinogen, associated with 18 types of cancer.<sup>2</sup> Song *et al.*<sup>3</sup> reported a moderate inverse association between melanoma and smoking in a meta-analysis of two cohort studies. This association was observed in both ex-smokers and current smokers in men, but not women. A larger meta-analysis, including 23 studies, reported a similar inverse association.<sup>4</sup> Both papers reported significant limitations, notably publication bias because of selective reporting in the published studies. Furthermore, confounding variables were not included in the analysis.

A recent, prospective cohort study has further explored the association. After adjusting for potential confounding factors, no association was observed between current smoking and melanoma [odds ratio (OR) 1.01, 95% confidence interval (CI) 0.64–1.61].<sup>5</sup> Although the study addressed the aforementioned limitations by adjusting for confounding factors, the study was significantly underpowered; only a small proportion of the cohort developed melanoma and the average follow-up duration was short (3.5 years).

The relationship between socioeconomic status and melanoma, on the other hand, is well established in the literature, with research dating back to the 1980s.<sup>6,7</sup> Those in higher income or higher educational groups are at an increased risk of developing melanoma, attributed to greater exposure to lifestyle factors, such as sun holidays and tanning bed use.<sup>8</sup> However, once diagnosed, those with a lower socioeconomic status have a worse prognosis, a finding seen across multiple jurisdictions with different healthcare systems.<sup>8</sup> Understanding and addressing this worsened prognosis is therefore a clear public health priority.<sup>9–11</sup>

In this paper we describe the largest study investigating the association of smoking and melanoma published to date. We have used the power of routinely collected data to overcome limitations of previous studies and investigate the prognostic implications of smoking in this patient cohort. Furthermore, we sought to investigate the association of socioeconomic status on the incidence and survival of melanoma.

**Patients and methods**

The described study has been reported in accordance with the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement (see Table S1 in the Supporting Information).<sup>12</sup> The study was conducted in two stages. In stage one, a case-control study was performed to assess the relationship between smoking and the development of melanoma. In stage two, a cohort study was conducted to determine the association between smoking and survival within the melanoma cohort (Fig. 1).

**Overview of methods**

Analyses of primary and secondary care National Health Service data and national administrative data for 2000–2015 in Wales, U.K. (population 3.1 million) were performed. In instances where relevant data were unavailable from a single source, multiple datasets were linked. Data were retrieved from six national databases (Table 1). In Wales, population-level de-identified person-based health and socioeconomic administrative datasets are collated and linked within the Secure Anonymised Information Linkage (SAIL) databank.<sup>13–15</sup> Robust policies, structures and controls are in place to protect privacy through a reliable matching and anonymization process, achieved in conjunction with the NHS Wales Informatics Service using a split-file multiple-encryption approach described in detail in previous published work.<sup>14</sup>

**Cases**

In Wales, all patients with a diagnosis of melanoma are recorded in the Welsh Cancer Intelligence and Surveillance Unit (WCISU) register. Cases were identified from WCISU using International Classification of Disease 10 (ICD-10) codes C43.0–C43.9 and morphology codes according to the International Classification of Diseases for Oncology (ICDO-3) 8720–8790.<sup>16</sup> Patients with melanoma *in situ* were not included in the study as either cases or controls. Demographic information was assessed at the date of diagnosis. Melanoma-specific variables (tumour location, stage and morphology) were assessed at the date of diagnosis.

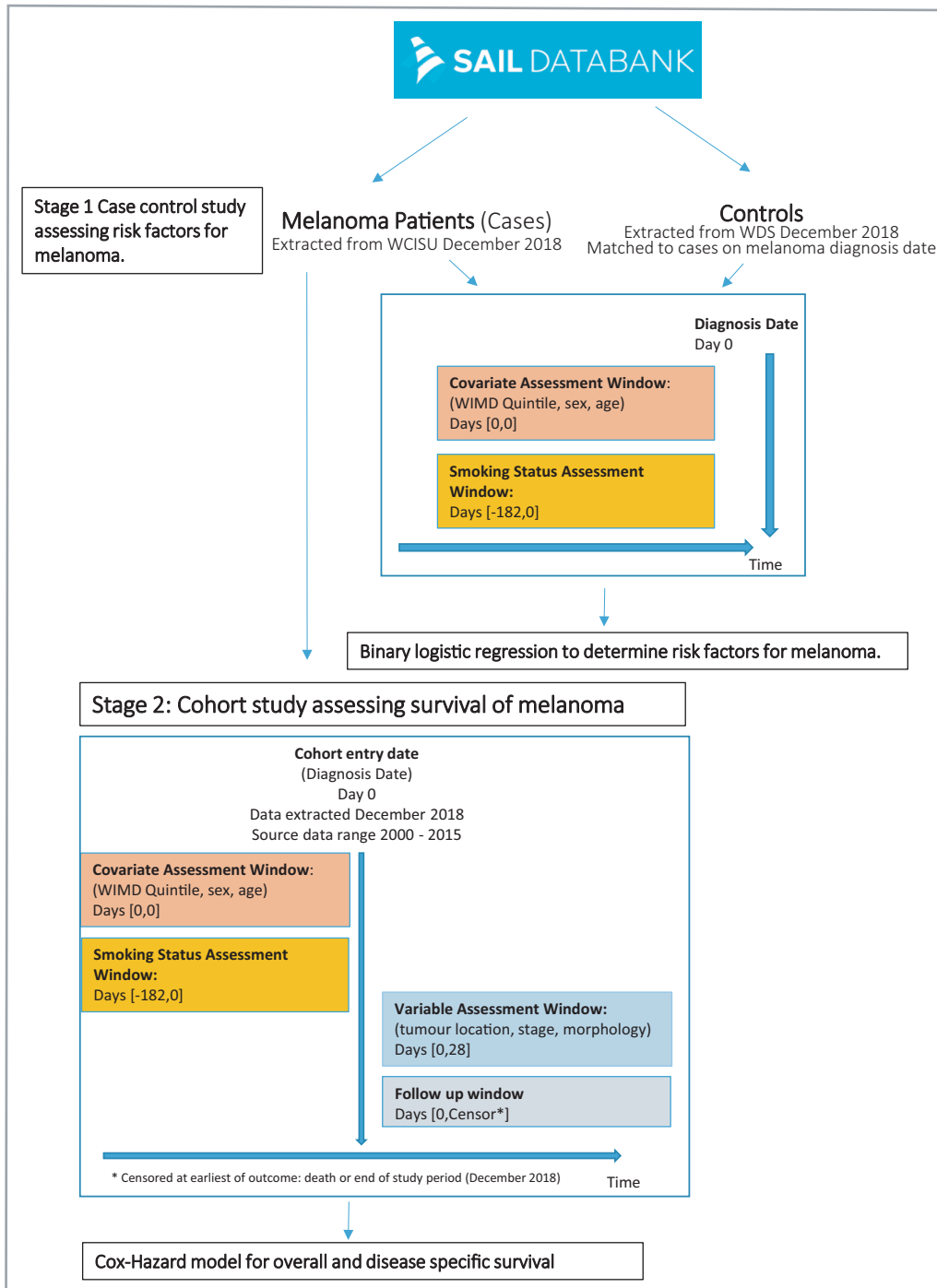


Fig 1. Study design. SAIL, Secure Anonymised Information Linkage; WCISU, Welsh Cancer Intelligence and Surveillance Unit; WDS, Welsh Demographic Service; WIMD, Welsh Index of Multiple Deprivation.

### Controls

Four sets of general population controls were randomly selected from the Welsh Demographic Service Dataset. Controls were not matched to cases. Both cases and controls needed to be alive and resident in Wales on the date of melanoma diagnosis. To increase the power of the study we aimed to have four controls for every case.<sup>17</sup>

### Smoking status

Self-reported smoking status, for cases and controls were obtained from the Welsh Longitudinal General Practice (WLGP) data, as recorded during patients' consultations with their general practitioner in primary care, using Read codes that have been previously validated<sup>18</sup> (Table S2; see Supporting Information). Patients were defined as either a nonsmoker

Table 1 List of databases used and their description

Database	Description
Annual District Death Extract	Collected from the Office for National Statistics, containing death registration information, relating to Welsh residents including those who died outside of Wales.
Outpatient Dataset for Wales	Administrative and clinical data obtained from outpatient appointments in Wales.
Patient Episode Database for Wales	Administrative and clinical data for all hospital admissions, including diagnosis and operations performed.
Welsh Cancer Intelligence and Surveillance Unit	The national cancer registry for Wales. Captures all Welsh patients with melanoma from a number of sources: multidisciplinary team data, pathology data, other routine data sources in Wales and the English cancer registry.
Welsh Longitudinal General Practice	Administrative and clinical data from all patient visits to a general practitioner.
Welsh Demographic Service Dataset	Administrative data about individuals resident or registered in Wales that have used National Health Service services.

(for lifelong nonsmokers), ex-smoker (for those that had previously smoked) or current smokers. The smoking assessment window extended from the melanoma diagnosis date to 6 months prior. Where serial assessments were available, the smoking record most recent to the diagnosis was selected. Where 'nonsmoker' was recorded, the WLGPD dataset was explored to establish whether the individual had previously been classified as a smoker. In such circumstances, the individual was classed as an ex-smoker.

### Socioeconomic status

Socioeconomic status was measured using the Welsh Index of Multiple Deprivation (WIMD) version 2001, a measure based on the Index of Multiple Deprivation and used as the official measure of socioeconomic status for the Welsh Government.<sup>19</sup> Individual scores are based upon a person's postal address. Wales is divided into 1896 lower-layer super-output areas (LSOAs) following the 2001 Census, each consisting of approximately 1600 people. The WIMD scores for each LSOA are calculated from weighted scores from eight domains of socioeconomic status (income, employment, health, education, access to services, community safety, physical environment and housing socioeconomic status). Each LSOA in Wales has been ranked according to its WIMD score and grouped into quintiles, with quintile five being the highest socioeconomic status and one being the lowest.

### Mortality data

Data relating to mortality, including cause of death for the melanoma cohort were obtained from the Annual District Death Extract dataset, which contains the diagnostic codes listed on patient's death certificates, held within the SAIL Databank.

### Charlson Comorbidity Index

The Charlson Comorbidity Index is a widely used measure of comorbidity. An overall score is calculated from a list of conditions, each of which has been allocated a weight of between

one and six based upon its adjusted relative risk of 1-year mortality.<sup>20</sup>

### Ethical approval

Study approval was granted by the SAIL Databank independent Information Governance Review Panel (project 0593). Data held within the SAIL Databank are made available to researchers in an anonymized format and are therefore not subject to data protection legislation. SAIL follows all relevant legislative and regulatory frameworks in using population data for research.

### Statistical analysis

#### Case-control (stage one)

Descriptive statistics were used to characterize the melanoma cases and controls by smoking status and stage at diagnosis (cases only). An unconditional binary logistic regression model was used to calculate ORs with 95% CIs for the association with melanoma. Sex, socioeconomic status and age at the time of diagnosis (as a continuous variable) were incorporated into the statistical model as confounders.

#### Cohort study (patients with melanoma only) (stage two)

In this stage of the study only those with a diagnosis of melanoma were included (Fig. 1). Overall survival was calculated as the time from melanoma diagnosis to the time of death (outcome) or the end of the study (December 2018). Melanoma-specific survival was calculated as the time from melanoma diagnosis to the date of death from melanoma, or the end of the study for patients still alive (December 2018). Cases with missing variables were excluded from this aspect of the study.

Kaplan–Meier curves were generated for smoking status and socioeconomic status, with curves compared using the log-rank test. A Cox hazard proportional regression model was used to determine the association between smoking and mortality in the melanoma cohort. Sex, socioeconomic status,

melanoma stage at diagnosis and age at diagnosis as a continuous variable were incorporated into the model as confounders. Both overall survival (deaths from any cause) and melanoma-specific survival (defined on their death registration held within the Annual District Death Extract) were analysed in the melanoma cohort. All data were analysed using IBM SPSS Statistics for Windows (Released 2017, version 25.0, IBM Corp, Armonk, NY, U.S.A.). Statistical significance was assumed with a  $P < 0.05$ .

## Results

Between 2000 and 2015, 9636 patients were diagnosed with melanoma in Wales.

### Stage one: case-control study

Patient demographics and clinical characteristics of the cases and controls are outlined in Table 2. Data relating to smoking status were available for 7124 (73.9%) of the melanoma cohort; 1460 current smokers (20.5%), 3065 (43.0%) ex-smokers and 2599 (36.5%) nonsmokers.

### Smoking

After adjusting for sex, age and socioeconomic status, current smokers had 30% reduced odds for developing melanoma compared with nonsmokers, (OR 0.70, 95% CI 0.65–0.76) (Table 3). There was no association between being an ex-smoker or nonsmokers and melanoma (OR 1.05, 95% CI 0.98–1.12).

### Socioeconomic status

We observed an inverse relationship between socioeconomic status and melanoma, whereby patients from higher socioeconomic WIMD quintiles were more likely to develop melanoma. Those in the highest socioeconomic quintile (WIMD 5) were 1.58 times more likely to develop melanoma as opposed to the lowest (HR 1.58, 95% CI 1.44–1.73) (Table 3).

### Stage two: survival analysis of the melanoma cohort

#### Demographic data

Table 4 displays the demographics of the melanoma cohort. The median age at diagnosis was higher in nonsmokers (66.7 years) and ex-smokers (64.5 years) than in current smokers (62.4 years). Socioeconomic status had significant variation among groups, with the current and ex-smokers being more likely to have lower socioeconomic status WIMD quintiles. Stage at diagnosis was not significantly different between smoking groups or socioeconomic status. No differences between the mean Charlson Comorbidity Index scores were noted between the smoking groups or between WIMD quintiles (Table 4).

**Table 2** Demographic and clinical characteristics of the case and control participants

Parameter	Cases (n = 7124)	Controls (n = 26 408)	P-value
Age, median (IQR)	63.0 (50.0–74.0)	43.0 (26.0–60.0)	
Age group			
< 20	46 (0.7)	3980 (16.2)	$\leq 0.001$
20–29	262 (3.7)	3866 (15.7)	
30–39	488 (6.9)	3898 (15.8)	
40–49	833 (11.7)	4230 (17.2)	
50–59	1312 (18.4)	3801 (15.5)	
60–69	1582 (22.2)	3180 (12.9)	
70–79	1654 (23.2)	2230 (9.1)	
80–89	974 (13.7)	1030 (4.2)	
> 90	144 (2.0)	193 (0.8)	
Sex			
Male	3489 (49.0)	12 735 (51.8)	0.26
Female	3635 (51.0)	13 673 (55.6)	
WIMD quintile			
1	1010 (14.18)	5502 (22.4)	$\leq 0.001$
2	1202 (16.87)	5329 (21.7)	
3	1464 (20.6)	5333 (21.7)	
4	1446 (20.3)	4797 (19.5)	
5	1996 (28.0)	5447 (22.1)	
Unspecified	6 (0.1)	0 (0.0)	
Smoking status			
Nonsmoker	2599 (36.5)	10 128 (41.2)	$\leq 0.001$
Ex-smoker	3065 (43.0)	7326 (29.8)	
Current smoker	1460 (20.5)	8954 (36.4)	

Data are n (%) unless otherwise indicated. IQR, interquartile range; WIMD, Welsh Index of Multiple Deprivation.

### Mortality

A total of 3103 (32.2%) patients with melanoma died during the study period. Of these, 1688 (54.4%) died from melanoma (melanoma listed as the primary cause of death on their death certificate) and 1415 (45.6%) deaths were unrelated to melanoma. For patients who died from any cause, median time to death was 2.36 years. For patients who died of melanoma, median time to death was 1.73 years.

### Univariate survival analysis

Median follow-up duration of the entire cohort was 5.22 years (range: 0–18 years). Overall survival rates were different across the three smoking status groups, with ex-smokers having lower survival than current or nonsmokers ( $P \leq 0.001$ ). In contrast, no difference was observed across the three smoking status groups for disease-specific mortality ( $P = 0.88$ ). Overall and melanoma-specific survival rates by smoking status are shown in Table S3 (see Supporting Information). Figures 2 and 3 shows the overall and disease-specific survival curves, respectively, by smoking status. Overall and disease-specific survival rates differed significantly across the WIMD quintiles (Table S4; see Supporting Information). Figures 4

**Table 3** Univariable logistic regression assessing risk factors for melanoma

Variable	P-value	Odds ratio (95% CI)
Age	≤ 0.001	1.04 (1.04–1.05)
Smoking status		
Nonsmokers	Reference	
Ex-smokers	0.17	1.05 (0.98–1.12)
Smokers	≤ 0.001	0.70 (0.65–0.76)
Men	0.26	0.97 (0.92–1.02)
WIMD		
Q1 (lowest socioeconomic status)	Reference	
Q2	0.09	1.09 (0.97–1.20)
Q3	≤ 0.001	1.20 (1.09–1.32)
Q4	≤ 0.001	1.30 (1.18–1.43)
Q5 (highest socioeconomic status)	≤ 0.001	1.58 (1.44–1.73)

CI, confidence interval; WIMD, Welsh Index of Multiple Deprivation; Q, quintile.

and 5 show the overall and disease-specific survival curves, respectively, by socioeconomic status.

### Multivariable survival analysis

After adjusting for the aforementioned factors, current smokers had an increased overall risk of death as compared with nonsmokers (HR 1.30, 95% CI 1.09–1.55) (Table 5). There was no association between current smoking and melanoma-specific mortality. Increased odds of survival was noted in the highest socioeconomic WIMD quintile (quintile 5), compared with the lowest (quintile 1) (HR 0.67, 95% CI 0.56–0.81). A similar trend was observed with disease-specific mortality (HR 0.69, 95% CI 0.53–0.90).

Men had an increased risk of overall and melanoma-specific death compared with women (overall HR 1.28, 95% CI 1.13–1.46; disease-specific HR 1.35, 95% CI 1.12–1.62). Tumour location was an important predictor of survival. For overall survival, tumours located on the upper limb were associated with increased survival compared with those on the trunk (HR 0.73, 95% CI 0.61–0.88), with no association between tumours on the head and neck, and lower limbs. With regards to melanoma-specific mortality, tumours located on the trunk were associated with an increased risk of mortality when compared with those in other locations.

Age was associated with a small increased risk of overall and melanoma-specific mortality (overall HR 1.06, 95% CI 1.05–1.06,  $P \leq 0.001$ ; disease-specific HR 1.02, 95% CI 1.01–1.03,  $P \leq 0.001$ ). Melanoma morphology was not associated with overall survival, however, melanoma-specific mortality was increased in those with nodular melanoma (HR 1.23, 95% CI 0.98–1.54) whereas those with lentigo maligna melanoma had improved survival (HR 0.43, 95% CI 0.21–0.89). The Charlson Comorbidity Index was not associated

with overall (HR 1.01, 95% CI 1.00–1.02) or melanoma-specific survival (HR 1.00, 95% CI 0.99–1.02).

### Discussion

We found that smokers were less likely to develop melanoma in this population-based, case-control study, but that their overall survival was reduced. After controlling for age, sex, socioeconomic status, tumour location, morphology and stage, the smoking group had an increased risk of death from all causes as compared with the nonsmoking group. However, when investigating melanoma-specific mortality, no association was observed.

The mechanism responsible for the observed protective association of smoking on the risk of developing melanoma is not yet known, but several plausible hypotheses exist. Some authors hypothesize that the accumulation of nicotine in cells containing melanin suppresses the inflammatory response to ultraviolet B.<sup>21–23</sup> Additionally, as smoking increases elastosis, it has been hypothesized that elastosis formation is protective of melanoma.<sup>24</sup> Alternative explanations include earlier deaths in current and ex-smokers leading to survival bias, whereby those exposed to smoking die before being at risk of developing melanoma.

Melanoma is not the only condition where smoking has been shown to have a favourable association, others include Parkinson disease and ulcerative colitis.<sup>25,26</sup> The protective association in Parkinson disease has been attributed to nicotine's ability to prevent brain damage and dopamine depletion. The depletion of dopamine occurs in the substantia nigra, an area of the brain populated by melanocytes. It is therefore plausible that Parkinson disease and melanoma share similar pathogenesis.<sup>27</sup> Numerous studies have demonstrated an increased risk of melanoma in patients with Parkinson disease and vice versa.<sup>28</sup> The inverse association of smoking and the risk of developing ulcerative colitis is well reported in the literature; however, the pathogenesis is less well understood.<sup>29</sup>

The relationship with smoking status has been investigated for nonmelanoma skin cancers. In a prospective cohort study of over one million participants, current smokers were found to have a reduced risk of developing basal cell carcinoma (BCC). Similar to our study, this 'protective' association was not observed in ex-smokers. Squamous cell carcinoma (SCC) is conversely more common in smokers.<sup>30</sup> The Notch pathway, which functions broadly in specifying cell fates during embryogenesis and adult life, has a key role in linking the control of epidermal differentiation and proliferation.<sup>31</sup> Aberrant Notch signalling leads to skin cancer, although with different associations with different skin cancer types.<sup>31</sup> For melanoma, nodular and superficial BCC, Merkel carcinoma and SCC in sun-protected sites increased Notched signalling has an oncogenic effect. However, for basosquamous BCC and SCC on sun-exposed sites increased signalling has an oncosuppressive effect. The Notch pathway has been found to be downregulated in smokers, which could provide a further explanation on the protective association of smoking on

Table 4 Demographic characteristics of the melanoma cohort

Characteristic	Total (n = 9636)	Unknown (n = 2512)	Nonsmoker (n = 2599)	Ex-smoker (n = 3065)	Current smoker (n = 1460)	$\chi^2$ P-value
Age, median (IQR)	64.3 (50.5–75.5)	62.6 (48.9–75.0)	66.7 (51.9–77.0)	64.5 (51.4–75.4)	62.4 (48.5–73.37)	
Age group						
0–9	< 5 (0.1) <sup>a</sup>	< 5 (0.2) <sup>a</sup>	0 (0)	0 (0)	0 (0)	
10–19	46 (0.5)	13 (0.5)	20 (0.8)	< 5 (0.2) <sup>a</sup>	9 (0.6)	
20–29	327 (3.4)	82 (3.3)	97 (3.7)	57 (1.9)	91 (6.2)	
30–39	726 (7.5)	180 (7.2)	221 (8.5)	154 (5.0)	171 (11.7)	
40–49	1242 (12.9)	291 (11.6)	406 (15.6)	266 (8.7)	279 (19.1)	
50–59	1615 (16.8)	385 (15.3)	480 (18.5)	417 (13.6)	333 (22.8)	
60–69	2103 (21.8)	536 (21.3)	552 (21.2)	716 (23.4)	299 (20.5)	
70–79	2085 (21.6)	571 (22.7)	471 (18.1)	850 (27.7)	193 (13.2)	
80–89	1257 (13.0)	368 (14.6)	294 (11.3)	515 (16.8)	80 (5.5)	
90–99	230 (2.4)	82 (3.3)	57 (2.2)	86 (2.8)	5 (0.3)	
> 100	< 5 (0.1) <sup>a</sup>	0 (0)	< 5 (0.2) <sup>a</sup>	0 (0)	0 (0)	
Sex						
Men	4750 (49.3)	1261 (50.2)	1161 (44.7)	1661 (54.2)	667 (45.7)	≤ 0.001
Women	4886 (50.7)	1251 (49.8)	1438 (55.3)	1404 (45.8)	793 (54.3)	
WIMD quintile						
1 (lowest socioeconomic status)	1300 (13.5)	290 (11.5)	269 (10.4)	450 (14.7)	291 (19.9)	≤ 0.001
2	1662 (17.2)	460 (18.3)	382 (14.7)	508 (16.6)	312 (21.4)	
3	1951 (20.2)	487 (19.3)	507 (19.5)	669 (21.8)	288 (19.7)	
4	2169 (22.5)	723 (28.8)	558 (21.5)	606 (19.8)	282 (19.3)	
5 (highest socioeconomic status)	2547 (26.4)	551 (21.9)	881 (33.9)	828 (27.0)	287 (19.7)	
Unspecified	7 (0.1)	0 (0)	< 5 (0.1) <sup>a</sup>	< 5 (0.2) <sup>a</sup>	< 5 <sup>a</sup>	
Charlson Comorbidity score, mean	4.27	4.62	4.06	4.18	4.21	0.69
Location						
Head and neck	1836 (19.1)	521 (20.7)	451 (17.4)	649 (21.2)	216 (14.8)	≤ 0.001
Upper limb	2071 (21.5)	497 (19.8)	758 (29.2)	662 (21.6)	466 (31.9)	
Lower limb	2370 (24.6)	593 (23.6)	593 (22.8)	685 (22.3)	319 (21.8)	
Trunk	2884 (29.9)	706 (28.1)	698 (26.9)	956 (31.2)	395 (27.1)	
Unspecified	476 (4.9)	195 (7.8)	99 (3.8)	113 (3.7)	64 (4.4)	
Stage						
1	4216 (43.8)	900 (35.8)	1220 (46.9)	1484 (48.4)	612 (41.9)	0.06
2	1837 (19.1)	488 (19.4)	473 (18.2)	676 (22.1)	200 (13.7)	
3	319 (3.3)	100 (4.0)	82 (3.2)	95 (3.1)	42 (2.9)	
4	125 (1.3)	30 (1.2)	39 (1.5)	35 (1.1)	21 (1.4)	
Unspecified	3139 (32.6)	994 (39.6)	785 (30.2)	775 (25.3)	585 (40.1)	
Morphology						
Melanoma – not otherwise specified	3122 (32.4)	954 (38.0)	798 (30.7)	844 (27.5)	526 (36.0)	≤ 0.001
Superficial spreading melanoma	4129 (42.8)	887 (35.3)	1221 (47.0)	1367 (44.6)	654 (44.8)	
Nodular melanoma	1578 (16.4)	436 (17.4)	387 (14.9)	561 (18.3)	194 (13.3)	
Melanoma in lentigo maligna	466 (4.8)	124 (4.9)	109 (4.2)	187 (6.1)	46 (3.2)	
Other <sup>b</sup>	347 (3.6)	111 (4.4)	84 (3.2)	106 (3.5)	40 (2.7)	

Data are n (%) unless otherwise indicated. IQR, interquartile range; WIMD, Welsh Index of Multiple Deprivation. <sup>a</sup>Results under five are not released from Secure Anonymised Information Linkage via disclosure control policies, to ensure privacy protection adherence. <sup>b</sup>Balloon cell melanoma, regressing melanoma, amelanotic melanoma, melanoma in junctional naevus, acral lentiginous melanoma, desmoplastic melanoma, melanoma in giant pigment naevus, mixed epithelial and spindle cell, epithelioid cell, spindle cell – not otherwise specified, spindle cell type A.

melanoma and nodular BCC and the higher risk of SCC on sun-exposed sites.<sup>31–34</sup>

Although we observed that smokers appeared to be at reduced risk of melanoma, their overall survival was reduced. This finding is not surprising given the strong relationship between smoking and other life-limiting conditions, such as the majority of cancers and cardiorespiratory disease.

However, consistent with the potential protective influence of smoking on melanoma development, the risk of death from melanoma was not different between the smokers and non-smokers after adjusting for age, sex, stage of disease, morphology, socioeconomic status and tumour location. This might imply that smoking does not affect the disease progression of melanoma. This is however, not consistent with the

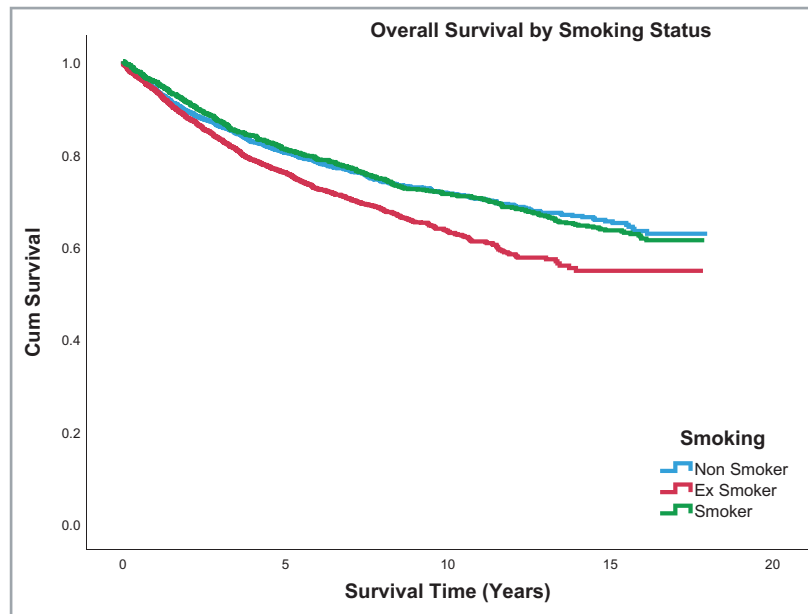


Fig 2. Overall survival by smoking status.

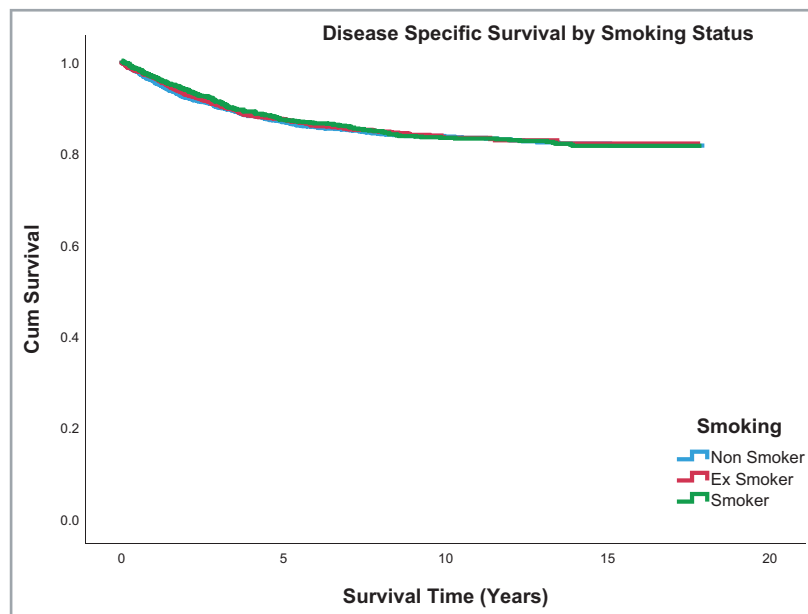


Fig 3. Disease-specific survival rates by smoking status.

work of Jones *et al.*, who identified that at presentation, smokers had an increased risk of lymph node metastasis.<sup>35</sup> The discrepancy may be explained by the fact that their study did not control for socioeconomic status. In addition, Jones *et al.* reported an association between smoking status and Breslow thickness at presentation. In our study we did not have data on Breslow thickness; however, smoking status was not associated with stage at presentation.

Consistent with the published literature we found that the risk of developing melanoma was positively associated with socioeconomic status in our study.<sup>1</sup> The underlying

explanation is poorly understood and likely to be complex and multifactorial. Socioeconomic status is closely linked with lifestyle factors such as travel, sunbed use and hobbies that are also associated with sunlight exposure, with the literature supporting the notion that those that are more affluent have greater exposure to lifestyle factors that increase melanoma incidence.<sup>1,8</sup> Our study also demonstrated that those in the highest socioeconomic status group were less likely to smoke.

Despite higher socioeconomic status being associated with an increased risk of melanoma development, lower socioeconomic status is associated with poorer survival once



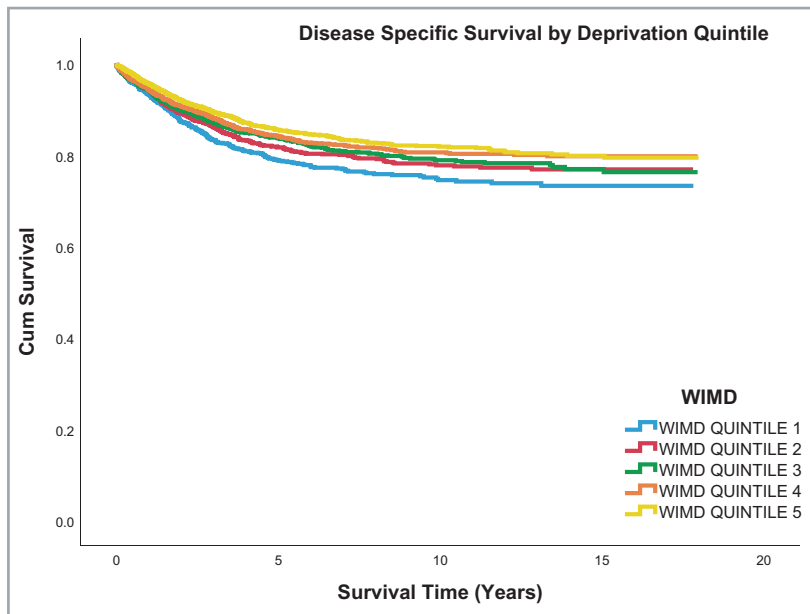


Fig 4. Overall survival by socioeconomic status. WIMD, Welsh Index of Multiple Deprivation.

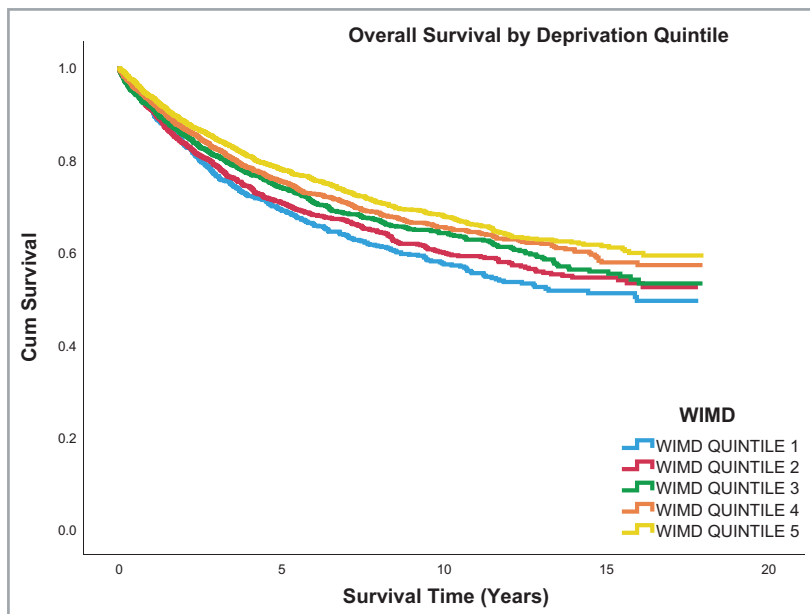


Fig 5. Disease-specific survival by socioeconomic status. WIMD, Welsh Index of Multiple Deprivation.

diagnosed. This relationship was observed in both overall and disease-specific survival rates. This is consistent with the broader health literature where it has been shown that lower socioeconomic status is associated with premature mortality from a number of conditions such as cardiovascular disease, respiratory disease and some malignancies.<sup>36</sup> In previous studies, low socioeconomic status has been associated with later stage of melanoma diagnosis; however, this was not observed in this study. Our results may be explained by the measure used to classify socioeconomic status, the WIMD score. One of the seven domains used to determine the WIMD quintile is

health, which is determined by the number of limiting long-term illnesses, the all-cause death rate, cancer incidence and birthweight. Patients within the low socioeconomic status group may therefore have other attributable factors influencing survival.

Limitations of this study included missing data, the lack of information available on ethnicity and ultraviolet light exposure. As with any population-based study, missing data prevented analysis on the total cohort. Data were missing for some of the cohort on smoking status and stage of disease. Smoking status was obtained from the WLGP, as recorded

Table 5 Cox model for overall and disease-specific survival

Variable	Overall mortality			Disease-specific mortality		
	P-value	Hazard ratio (95% CI)		P-value	Hazard ratio (95% CI)	
<b>Sex</b>						
Men	Reference			Reference		
Women	≤ 0.001	1.28	(1.13–1.46)	0.01	1.35	(1.12–1.62)
<b>Smoking status</b>						
Nonsmoker	Reference			Reference		
Ex-Smoker	0.93	1.00	(0.87–1.14)	0.20	0.88	(0.73–1.07)
Smoker	0.03	1.30	(1.09–1.55)	0.25	1.15	(0.91–1.45)
<b>WIMD quintile</b>						
1 (Lowest socioeconomic status)	Reference			Reference		
2	0.75	0.97	(0.80–1.18)	0.93	0.99	(0.75–1.30)
3	0.01	0.78	(0.65–0.95)	0.09	0.79	(0.60–1.04)
4	0.04	0.75	(0.62–0.91)	0.08	0.78	(0.59–1.03)
5 (highest socioeconomic status)	≤ 0.001	0.67	(0.56–0.81)	0.01	0.69	(0.53–0.90)
Charlson Comorbidity Index	0.08	1.01	(1.00–1.02)	0.517	1.00	(0.99–1.02)
<b>Location</b>						
Trunk	Reference			Reference		
Lower limb	0.10	0.86	(0.72–1.02)	≤ 0.001	0.79	(0.63–1.01)
Upper limb	0.01	0.73	(0.61–0.88)	≤ 0.001	0.62	(0.48–0.79)
Head and neck	0.48	0.94	(0.80–1.11)	0.06	0.80	(0.63–1.01)
Unspecified	0.28	1.21	(0.86–1.70)	0.83	1.05	(0.67–1.64)
<b>Stage</b>						
1	Reference			Reference		
2	≤ 0.001	2.48	(2.15–2.86)	≤ 0.001	6.24	(4.95–7.88)
3	≤ 0.001	3.65	(2.96–4.59)	≤ 0.001	11.48	(8.52–15.48)
4	≤ 0.001	11.78	(8.76–15.53)	≤ 0.001	32.55	(22.73–46.61)
Age <sup>a</sup>	≤ 0.001	1.06	(1.05–1.06)	≤ 0.001	1.02	(1.02–1.03)
<b>Morphology</b>						
Superficial spreading melanoma	Reference			Reference		
Nodular melanoma	0.96	1.15	(0.98–1.35)	0.08	1.23	(0.98–1.54)
Melanoma in lentigo maligna	0.70	1.05	(0.81–1.37)	0.02	0.43	(0.21–0.89)
Other <sup>b</sup>	0.12	1.25	(0.95–1.67)	0.50	1.16	(0.76–1.74)
Unspecified	0.01	1.24	(1.05–1.47)	0.04	1.28	(1.01–1.62)

CI, confidence interval; WIMD, Welsh Index of Multiple Deprivation. <sup>a</sup>Age was included as a continuous variable in the model; <sup>b</sup>Balloon cell melanoma, regressing melanoma, amelanotic melanoma, melanoma in junctional naevus, acral lentiginous melanoma, desmoplastic melanoma, melanoma in giant pigment naevus, mixed epithelial and spindle cell, epithelioid cell, spindle cell – not otherwise specified, spindle cell type A.

during patient's consultations with their general practitioner. To date, the WLGP covers 80% of general practices across Wales. Of the 2512 patients for whom smoking data were absent, 2431 (96.8%) belonged to general practices not contributing data to the SAIL Databank. It is therefore assumed that data for this variable were missing at random and would not bias the results.

Additionally, information was not available on the quantity of tobacco smoked by participants. The Read codes listed in the Table S2 (see Supporting Information) do capture some information on the amount of smoking. In practice, these codes were rarely utilized by general practitioners, with the majority simply recording 137R (current smoker) and therefore we were unable to provide meaningful results. This is a substantial limitation as the cumulative exposure to tobacco was not assessed, thus it was not possible to calculate a dose–response relationship.

When stage of melanoma was not recorded in the WCISU data, and could not be obtained from other linked data, these data were missing. To assess the effect of this missingness, a sensitivity analysis was performed. Missing data were incorporated into the regression model as a separate category for stage. This was found not to affect the statistical significances outlined in the results section.

A further limitation of population-based studies using routinely collected data is incomplete control of confounding, that of data that are not specified, incompletely captured or misclassified, namely tumour location (relating to ICD-10 Code C43.9 melanoma unspecified) and tumour morphology [M7203 – MM NOS (melanoma – not otherwise specified)]. The classification codes used to extract smoking status from general practitioner data have shown to classify 8.6% ex-smokers as never smokers. Any misclassification would not significantly bias the results.

Ethnicity is only available on special request within the SAIL Databank and was therefore not incorporated into the statistical model. In Wales, population statistics reveal that 95% of the population are white and therefore the significance of ethnicity on the results would be minimal.<sup>37</sup>

In conclusion, this is the largest study to date indicating that smoking has an inverse relationship on the risk of developing melanoma. While the detrimental repercussions of smoking are well documented, further work is required to uncover the mechanism underlying this relationship, including further assessment about survival bias. If a biological association seems likely, this could lead to the development of novel prevention and treatment options, opening up a new wave of medical therapy for melanoma. Furthermore, this work reinforces the ongoing association between melanoma and socioeconomic status. Despite numerous public health strategies, higher socioeconomic groups continue to have a higher incidence of melanoma, however, lower socioeconomic status is related to poor survival once melanoma is diagnosed. The implications of these results, in a country such as the U.K. where health care is free to all, are significant. Further work is required to investigate the barriers to care that may exist for the lowest socioeconomic status group so that policies can be implemented to prevent healthcare inequality and improve melanoma outcomes for all.

## Acknowledgments

This study makes use of the Secure Anonymised Information Linkage (SAIL) Databank. We would like to acknowledge all the data providers who make anonymized data available for research.

## References

- Jiang AJ, Rambhatla PV, Eide MJ. Socioeconomic and lifestyle factors and melanoma: a systematic review. *Br J Dermatol* 2015; **172**:885–915.
- Secretan B, Straif K, Baan R *et al.* A review of human carcinogens; Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009; **10**:1033–4.
- Song F, Qureshi AA, Gao X *et al.* Smoking and risk of skin cancer: a prospective analysis and a meta-analysis. *Int J Epidemiol* 2012; **41**:1694–705.
- Li Z, Wang Z, Yu Y *et al.* Smoking is inversely related to cutaneous malignant melanoma: results of a meta-analysis. *Br J Dermatol* 2015; **173**:1540–3.
- Dusingize JC, Olsen CM, Pandeya N *et al.* Smoking and cutaneous melanoma: findings from the QSkin Sun and Health Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2018; **27**:874–81.
- Graham S, Marshall J, Haughey B *et al.* An inquiry into the epidemiology of melanoma. *Am J Epidemiol* 1985; **122**:606–19.
- Vagero D, Persson G. Risks, survival and trends of malignant melanoma among white and blue collar workers in Sweden. *Soc Sci Med* 1984; **19**:475–8.
- Idorn LW, Wulf HC. Socioeconomic status and cutaneous malignant melanoma in Northern Europe. *Br J Dermatol* 2013; **170**:787–93.
- Buchanan L. Slip, slop, slap, seek, slide – is the message really getting across? *Dermatol Online J* 2013; **19**:19258.
- Makin JK, Warne CD, Dobbins SJ *et al.* Population and age-group trends in weekend sun protection and sunburn over two decades of the SunSmart programme in Melbourne, Australia. *Br J Dermatol* 2013; **168**:154–61.
- Cancer Research UK. *Be Clear on Cancer: Skin Cancer Campaign*. London: Cancer Research UK, 2014.
- Benchimol EI, Smeeth L, Guttmann A *et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLOS Med* 2015; **12**:e1001885.
- Ford DV, Jones KH, Verplancke JP *et al.* The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res* 2009; **9**:157.
- Jones KH, Ford DV, Jones C *et al.* A case study of the Secure Anonymous Information Linkage (SAIL) Gateway: a privacy-protecting remote access system for health-related research and evaluation. *J Biomed Inform* 2014; **50**:196–204.
- Lyons RA, Jones KH, John G *et al.* The SAIL databank: linking multiple health and social care datasets. *BMC Med Inform Decis Mak* 2009; **9**:3.
- Fritz A, Percy C, Jack A *et al.* *International Classification of Diseases for Oncology*, 3rd edn. Geneva: World Health Organization, 2003.
- Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. *Lancet* 2005; **365**:1429–33.
- Atkinson MD, Kennedy JI, John A *et al.* Development of an algorithm for determining smoking status and behaviour over the life course from UK electronic primary care records. *BMC Med Inform Decis Mak* 2017; **17**:2.
- Welsh Government. *What is the Welsh Index of Multiple Deprivation and How Should it be Used?* Cardiff: Welsh Government, 2014.
- Charlson ME, Pompei P, Ales KL *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987; **40**:373–83.
- Yerger VB, Malone RE. Melanin and nicotine: a review of the literature. *Nicotine Tob Res* 2006; **8**:487–98.
- Mills CM, Hill SA, Marks R. Transdermal nicotine suppresses cutaneous inflammation. *Arch Dermatol* 1997; **133**:823–5.
- Mills CM, Hill SA, Marks R. Altered inflammatory responses in smokers. *BMJ* 1993; **307**:911.
- Grant WB. Skin aging from ultraviolet irradiance and smoking reduces risk of melanoma: epidemiological evidence. *Anticancer Res* 2008; **28**:4003–8.
- Hernan MA, Takkouche B, Caamano-Isorna F *et al.* A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* 2002; **52**:276–84.
- Thomas GAO, Rhodes J, Green JT *et al.* Role of smoking in inflammatory bowel disease: implications for therapy. *Postgrad Med J* 2000; **76**:273.
- Pan T, Li X, Jankovic J. The association between Parkinson's disease and melanoma. *Int J Cancer* 2011; **128**:2251–6.
- Huang P, Yang X-D, Chen S-D *et al.* The association between Parkinson's disease and melanoma: a systematic review and meta-analysis. *Transl Neurodegener* 2015; **4**:21.
- Parkes GC, Whelan K, Lindsay JO. Smoking in inflammatory bowel disease: impact on disease course and insights into the aetiology of its effect. *J Crohn Colitis* 2014; **8**:717–25.
- Pirie K, Beral V, Heath AK *et al.* Heterogeneous relationships of squamous and basal cell carcinomas of the skin with smoking: the UK Million Women Study and meta-analysis of prospective studies. *Br J Cancer* 2018; **119**:114–20.
- Panelos J, Massi D. Emerging role of Notch signaling in epidermal differentiation and skin cancer. *Cancer Biol Ther* 2009; **8**:1986–93.
- Balint K, Xiao M, Pinnix CC *et al.* Activation of Notch1 signaling is required for  $\beta$ -catenin-mediated human primary melanoma progression. *J Clin Invest* 2005; **115**:3166–76.

- 33 Nakayama K. Growth and progression of melanoma and non-melanoma skin cancers regulated by ubiquitination. *Pigment Cell Melanoma Res* 2010; **23**:338–51.
- 34 Zhang M, Biswas S, Qin X *et al.* Does Notch play a tumor suppressor role across diverse squamous cell carcinomas? *Cancer Med* 2016; **5**:2048–60.
- 35 Jones MS, Jones PC, Stern SL *et al.* The impact of smoking on sentinel node metastasis of primary cutaneous melanoma. *Ann Surg Oncol* 2017; **24**:2089–94.
- 36 Romeri E, Baker A, Griffiths C. Mortality by deprivation and cause of death in England and Wales, 1999–2003. *Health Stat Q* 2006; **32**:19–34.
- 37 Stats Wales. *Ethnicity by Year And Ethnic Group*. Cardiff: Welsh Government, 2018.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Table S1** The Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement.

**Table S2** List of Read codes used for smoking status in this study.

**Table S3** Overall and disease-specific survival rates by smoking status.

**Table S4** Overall and disease-specific survival rates by socioeconomic status.