Title: The association between partner bereavement and melanoma: cohort studies in the UK and Denmark

Short title: The association between partner bereavement and melanoma

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What's known

- Psychological stress has been proposed as a risk factor for the development and progression of cancer, including melanoma but evidence is conflicting.
- Clinical evidence is limited by small sample sizes, potential recall bias associated with self-report, and heterogeneous stress definitions.

What's new

- We found a decreased risk of melanoma diagnosis, but an increased mortality associated with partner bereavement.
- While stress might play a role in the progression of melanoma, an alternative explanation is that bereaved people no longer have a close person to help notice skin changes leading to delayed melanoma detection.

Abstract (<=250 words)

Background: Psychological stress is commonly cited as a risk factor for melanoma but clinical evidence is limited.

Objectives: This study aimed to evaluate the association between partner bereavement and: 1) first-time melanoma diagnosis; and 2) mortality in patients with melanoma.

Methods: We conducted two cohort studies using data from the UK Clinical Practice Research Datalink (1997-2017) and Danish nationwide registries (1997-2016). Study 1: We compared risk of first melanoma diagnosis in bereaved with matched non-bereaved people using stratified Cox regression. Study 2: We estimated HRs for death from melanoma in bereaved compared with non-bereaved individuals with melanoma using Cox regression. We estimated HRs separately for the UK and for Denmark, and then pooled the data to perform a random-effects meta-analysis.

Results: In Study 1, the pooled adjusted HRs for the association between partner bereavement and melanoma diagnosis were 0.88 [95% confidence interval (CI),0.84–0.92] across the entire follow-up period. In Study 2, we observed increased melanoma-specific mortality in people experiencing partner bereavement across the entire follow-up period (HR,1.17; 95% CI,1.06–1.30), with the peak occurring during the first year of follow-up (HR,1.31; 95% CI,1.07–1.60).

Conclusions: We found decreased risk of melanoma diagnosis, but increased mortality associated with partner bereavement. These findings may be partly explained by delayed detection resulting from the loss of a partner who could notice skin changes. Stress may play a role in melanoma progression. Our findings indicate

a need for low threshold for skin examination in individuals whose partners have died.

INTRODUCTION

Melanoma is a skin cancer characterised by abnormal growth of melanocytes in an existing mole (nevus-associated melanoma) or on normal skin (*de novo* melanoma). Intense sun exposure, pigmentary traits and family history of skin cancer are known risk factors of melanoma [1-3]. It is estimated that 197,000 new cases of melanoma are diagnosed globally each year, accounting for 1.6% of all incident cancers [4]. In the United Kingdom (UK) and Denmark, new melanoma cases account for 5-6% of all cancer cases, with approximately 16,000 incident cases diagnosed each year in the UK and 2,330 in Denmark [5, 6]. Early melanoma detection and treatment can improve survival. In Denmark, 5-year survival of melanoma is 90-94% [5]. In England, the 5-year survival rate is 92% in patients with thin tumours (Breslow thickness <1.5 mm) but only 42% in those with thick tumours (Breslow thickness >4.0 mm) [7].

Partner bereavement is perceived as one of the most stressful life events [8-10]. Psychological stress has been proposed as a risk factor for the development and progression of cancer, including melanoma but evidence is conflicting [11-16]. Several physiological pathways have been proposed that implicate stress hormones in carcinogenesis through effects on immune surveillance [11, 13, 17-19]. However, clinical evidence for such association is limited by small sample sizes, potential recall bias associated with self-report, and heterogeneous stress definitions [20-25]. Aside from stress, recent studies suggest that having a partner can enhance early detection of melanoma [26-28]. However, we do not know if partner loss negatively affects the incidence and prognosis of melanoma.

We used UK and Danish routinely-collected data to conduct population-based cohort studies to evaluate associations between partner bereavement and: 1) diagnosis of incident melanoma; and 2) melanoma-specific mortality. We also investigated whether the associations differed by time since bereavement and whether partner loss was expected.

METHODS

Settings

Study data were from UK (January 1997 to July 2017) and Denmark (January 1997 to December 2016). Both countries provide universal health coverage from publicly funded healthcare systems [29, 30].

In the UK, we used Clinical Practice Research Datalink (CPRD) Gold [31] primary care with linked mortality (Office for National Statistics (ONS)), hospital admission (Hospital Episode Statistics (HES)), and deprivation data (Index of Multiple Deprivation (IMD)) (Supplementary material method 1).

We used Danish nationwide registries to obtain data on: 1) demographics, civil status, and vital status (Civil Registration System [32]); 2) incident melanoma (Danish Cancer Registry [33]); 3) causes of death (Danish Registry of Causes of Death [34]); 4) diagnoses (Danish National Patient Registry [35]); 5) dispensed prescriptions (Danish National Prescription Registry [36]); and 6) education duration (Danish Education Registries [37]). Data were linked using the unique personal identifier assigned to all Danish residents at birth or immigration. We endeavoured to make UK and Danish studies as similar as possible to ensure comparability (Supplementary material method 1).

Study 1: Melanoma incidence analysis

We examined the association between partner bereavement and diagnosis of incident melanoma using a matched cohort study comparing risk of melanoma diagnosis in bereaved individuals with matched non-bereaved individuals.

In the UK, we identified eligible couples aged 30 and over using a previously reported algorithm while [38-42] in Denmark, we used an algorithm provided by Statistics Denmark (Supplementary material method 2). Among eligible couples, we identified a partner as bereaved (exposed) when their partner died and bereavement date was the index date. In the UK, we obtained dates of death from ONS when available (59.8%) and from CPRD for persons not linked to ONS (40.2%). In Denmark, we used death dates from the Civil Registration System. For each bereaved person, we identified a matched comparison cohort who had not previously experienced partner bereavement by sampling (with replacement) up to 10 partners on age (within 1 year) and sex (both settings), county of residence (Denmark), and general practice (UK) on the index date. We excluded all individuals who died on the index date as they did not contribute person-time. We also excluded all individuals with a diagnosis of melanoma before the index date. We required study participants to have ≥1 year of healthcare registration history prior to the index date in the UK, to allow adequate time for recording covariates and history of melanoma.

The outcome was the first-ever recorded diagnosis of melanoma (https://datacompass.lshtm.ac.uk/1317/ for UK and Supplementary material method 3 for Denmark). We followed all cohort members from index date until the first of: a melanoma diagnosis, date of last data collection from a members' practice (UK), transfer out of the practice by either member of the couple (UK), emigration of either

member of the couple (Denmark), death, or the study end date. If a person in the comparison cohort experienced bereavement, he/she was censored one day before bereavement and subsequently included in the bereaved cohort (Supplementary material figure 1).

Study 2: Melanoma mortality analysis

To assess the association between partner bereavement and melanoma-specific mortality, we identified a cohort of people diagnosed with melanoma with partners. We started follow-up on the date of melanoma diagnosis (Supplementary material figure 2).

Our main outcome was melanoma-specific mortality (Supplementary material method 4). We included all-cause mortality as a secondary outcome. In this analysis, we started follow-up on the date of melanoma diagnosis and ended at the earliest of: the date of last data collection from the patients' practice (UK), transfer out of practice by either member of the couple (UK), emigration of either member of the couple (Denmark), death, or study end date.

Covariates

As possible confounders, we included comorbidities (original Charlson Comorbidity Index (CCI) score) [43], lifestyle covariates (smoking and alcohol consumption) and body mass index (BMI), and socioeconomic status (IMD status and education duration) (Supplementary material method 5). We hypothesised that the level of stress associated with bereavement may depend on whether a partner's death was unexpected. Therefore, we stratified the estimates by the degree to which the partner's death might be considered unexpected based on level of comorbidity (age-adjusted CCI score for the deceased partner). As an alternative measure, we

identified presence of terminal disease among partners recorded before the date of death.

Statistical analysis

We examined descriptive characteristics for different study cohorts on the follow-up start date. We used Cox regression (with time-since cohort entry as the underlying timescale) to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between partner bereavement and (1) melanoma incidence and (2) melanoma-specific mortality. We examined associations for the entire follow-up period, and by time since start of follow-up (0–1 year, 0–2 years, 0–3 years, 0–4 years and 0–5 years) to detect any variation due to time lag in the effect of bereavement on outcome for the *incidence analysis* and to explore the time effect of bereavement since melanoma diagnosis for the *mortality analysis*. For the *incidence analysis*, we stratified regression models by matched set; thus, unadjusted HRs accounted for matching factors. In sequential models, we estimated HRs adjusted for participants' CCI level (adjusted model) and then added lifestyle variables and deprivation status (UK), and education duration (Denmark) (fully-adjusted model).

We assessed the assumption of proportional hazards by visual inspection of log-log plots (Supplementary material figure 3). Additionally, we examined HRs over time by stratifying the follow-up period since bereavement (0–1 year, 1–2 years, 2–3 years, 3–4 years and 4–5 years, 5+ years) (Supplementary material table 1).

We also examined variation by age at index date, sex and risk of partner death (deceased partner's age-adjusted CCI score and terminal disease) and performed likelihood ratio tests to explore possible effect modification by these characteristics.

For the *mortality analysis*, we included time-varying bereavement as the exposure in the unadjusted model. In the adjusted model, we also adjusted for age, sex, and CCI score; and in the fully adjusted model we additionally adjusted for lifestyle and socioeconomic variables. We also examined the association between bereavement and melanoma-specific mortality in categories of cancer stage at diagnosis (localised, regional, distant) among patients with this information recorded in the Danish Cancer Registry. Finally, we assessed the association between bereavement and mortality according to age at melanoma diagnosis and sex and performed likelihood ratio tests to analyse effect modification.

In both analyses, we undertook complete-case analyses in the fully-adjusted models, which would be unbiased assuming that missingness was not associated with the outcome conditional on the other variables. As lifestyle data (used in UK analyses only) are unlikely to be missing at random and we lacked data on probable predictors of missingness, imputation techniques were not appropriate for correcting potential biases [44]. For the *incidence analysis*, we further investigated patterns of missing data using conditional logistic regression. We conducted several sensitivity analyses to test the robustness of the results in both *incidence* and *mortality analyses* (Supplementary material table 2). All study analyses were pre-planned unless otherwise stated.

We conducted all analyses separately for the UK (using Stata/MP 15.1) and Denmark (using SAS 9.4). We combined the main results (from the adjusted models) in Stata using DerSimonian and Lairds' random-effects model [45].

RESULTS

Study 1: Melanoma incidence analysis

The study included 170,002 bereaved and 1,599,260 matched non-bereaved individuals in the UK; and 345,915 bereaved and 3,319,788 matched non-bereaved individuals in Denmark (Figure 1). Median age was 74 years in the UK and 71 years in Denmark. Approximately two-third of both cohorts were women (Table 1). Bereaved people were more likely to have higher CCI scores, to be more deprived, to have a shorter education, and to have slightly longer median follow-up than people in the comparison cohort.

The pooled HR (adjusted for study participants' CCI scores) comparing melanoma diagnosis rates in bereaved to non-bereaved individuals was 0.88 (95% CI, 0.84–0.92) (Figure 2). We did not find evidence of lower HRs for melanoma within 0–1 year (0.97; 95% CI,0.86–1.09) and 0–2 years (0.94; 95% CI,0.83–1.05). However, we found evidence of a lower melanoma rate following partner bereavement within 0–3 years (0.89; 95% CI,0.83–0.96), 0–4 years (0.90; 95% CI,0.85–0.96) and 0–5 years (0.88; 95% CI,0.83–0.93) of follow-up. Estimates were similar in the fully adjusted models (Supplementary material table 3).

We found evidence of effect modification by age in the UK but not in Denmark (Supplementary material table 4). We observed no substantial variation by sex or whether partner's death was forseen in both countries.

In the UK, missing lifestyle data was dependent on incident melanoma, conditional on bereavement status and other covariates (Supplementary material table 5). However, HRs for the whole cohort and the complete-case cohort were similar in the unadjusted and adjusted models in both countries (Supplementary material table 6). The results of sensitivity analyses were broadly similar to those of the main analyses (Supplementary material tables 7–12).

Study 2: Melanoma mortality analysis

We followed 3597 patients with melanoma in the UK and 24,911 people with melanoma in Denmark (Figure 1). Median follow-up time was 3.5 years in the UK and 5.0 years in Denmark (Table 2). More people who were under age 50 and had fewer comorbidities were included in Denmark compared with the UK. In Denmark, most individuals had localised cancer at diagnosis (74.6%). Among 2162 individuals who experienced bereavement on/prior to melanoma diagnosis, 1,485 (68.7%) had localised melanoma, 135 (6.2%) had regional melanoma, 24 (1.1%) individuals had distant cancer at diagnosis.

After adjusting for age, sex and study participants' CCI score, we observed an increased melanoma-specific mortality in those with partner bereavement (pooled HR,1.17; 95% CI,1.06–1.30) compared with those without (Figure 3). The analysis by time-since melanoma diagnosis showed that the increased HR for melanoma-specific mortality in the bereaved compared with the non bereaved peaked within 0–1 year (1.31; 95% CI,1.07–1.60) of follow-up and remained stable during 0–2 years (1.19; 95% CI,1.02–1.38), 0–3 years (1.21; 95% CI,1.06–1.38), 0–4 years (1.21; 95% CI,1.07–1.36), and 0–5 years (1.20; 95% CI,1.07–1.35) of follow-up. Similar HRs were observed in the fully adjusted models (Supplementary material table 13). HRs generated by unadjusted and adjusted models for the whole cohort and the complete-case cohort were similar in both countries (Supplementary material table 14). Additionally, we observed approximately 20-30% increased hazard of all-cause mortality associated with partner bereavement during the entire follow-up period in both countries (Supplementary material table 15).

Wide CIs were observed for all subgroups due to small sample size (Supplementary material table 16). In Denmark, we did not find evidence of effect modification by cancer stage (Supplementary material table 17). Results of all other sensitivity analyses were similar to the main analysis (Supplementary material tables 18–24).

DISCUSSION

This study showed that partner bereavement was associated with a 12% decreased risk of being diagnosed with incident melanoma in two large population-based studies. We observed an increase in melanoma-specific mortality associated with partner bereavement, which peaked during the first year following melanoma diagnosis.

Comparison with other studies

Several studies have examined the role of other stressors in melanoma incidence, but no studies have focused on partner bereavement and melanoma [12, 20, 21]. A meta-analysis showed no association between risk of skin cancers, including melanoma, and stress-related psychosocial factors such as stressful life events, severe chronic stress and daily stress [12]. However, the review did not assess studies focusing on melanoma only. In contrast, a case-control study assessing self-reported loss of a relative or friend in the past year reported an increased risk of melanoma in bereaved individuals [20]. Our observed lower rate of melanoma diagnosis in bereaved people may reflect delayed melanoma detection after partner loss. Supporting this theory, a recent randomised controlled trial reported that providing structured skin self-examination education intervention to patients with prior melanoma and their partners resulted in identification of more melanomas compared with customary care, including identification of more *in situ* melanomas [26]. Another study reported that people married at melanoma diagnosis, were 2 to 3 times more likely to have a thinner tumour than non-married individuals [28]. A cohort study based on data from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results database also showed that widowed

people were less likely to undergo sentinel lymph node biopsy and more likely to present with a higher stage of melanoma compared with married people [27]. These studies suggest the partner loss could decrease early diagnosis of melanoma, which is consistent with our findings. Social isolation, residual socioeconomic confounding, reduced self-care and reduced likelihood of seeking medical attention following bereavement may also have contributed to the lower incidence of diagnosed melanoma we observed. Our study highlights the importance of encouraging family members or caregivers to perform skin examinations for bereaved persons.

It has been suggested that stress hormones can accelerate growth and migration of tumour cells, worsening melanoma prognosis, as immunologic surveillance is important in melanoma outcomes [13, 17, 18]. Consistent with our findings, two small studies reported that a range of positive psychosocial factors (including marriage) predicted longer survival following melanoma [22, 25], while another found no association with time to relapse among 155 patients with melanoma or breast cancer [23, 24]. A meta-analysis showed no significant effects of stress-related psychosocial factors on skin cancer survival (melanoma and non-melanoma) [12]. All of these prior studies suffered from limitations including inadequate power, inclusion of a wide range of psychological constructs, and lack of control for other risk factors [22-25, 46], but the results were similar to our study. A previous study [38] reported a short-term increased risk of cardiovascular events within 90 days after partner bereavement, suggesting that cardiovascular events may partly explain our observation of increased all-cause mortality up to 5 years following bereavement, although some of these deaths may represent misclassified melanoma-specific mortality.

Apart from stress, delayed detection of recurrence or a secondary melanoma due to lack of an available partner to notice skin changes might also account for our findings. Unfortunately, our stage-specific analyses in Denmark were associated with large statistical imprecision precluding firm conclusions. Previous studies have shown that those without a partner experienced higher death rates [47], shorter survival [48-52], and advanced stage of melanoma at time of diagnosis [50, 53, 54]. However, most studies have focused on women only [47, 48] or lacked adjustment for lifestyle factors [51, 52] or socioeconomic status [49, 50].

Strengths and weaknesses

Combining population-based data from two countries (UK and Denmark), provides credibility to our findings by demonstrating replicability, attaining a greater sample size, exploring various sources of bias (e.g., confounding by lifestyle factors), and the use of validated outcomes. Validation studies have shown high positive predictive values (≥83%) of identifying melanoma cases based on data both in the CPRD and the Danish Cancer Registry [55, 56].

To control for potential confounding, we adjusted our analyses for socioeconomic status and lifestyle variables. However, we did not have information on some risk factors of melanoma including sun exposure, pigmentary traits and family history of skin cancer. Residual confounding is a possibility. We matched our cohort with replacement in the main analysis in both settings, which might have led to narrower confidence intervals. Excluding people with missing lifestyle information in the UK had minimal effects on estimates, implying that this missing data was unlikely to have affected our interpretation of results. Misclassification of partnership also could have occurred including changes in partner status over time. Particularly in the UK

where direct data on partnership status were not available may have led to non-differential misclassification and underestimation of any association. However, we used relatively strict criteria (*e.g.*, age difference of members of the couples) to identify partners in the UK, to minimise such misclassification [38-41]. Importantly, longitudinal data on partnership were available in the Danish study, and findings were broadly similar to those of the UK study.

CONCLUSIONS

We observed a lower risk of a melanoma diagnosis following partner bereavement. This finding might be explained by delayed detection in the absence of partner help with skin examinations among the bereaved. This mechanism could also explain the increase in melanoma mortality associated with partner bereavement, although stress might promote melanoma progression. Our findings highlight the need for raising public awareness of the association to perform self-skin examination, as well as encouraging clinicians to have a lower threshold for undertaking skin examinations in bereaved people.

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TABLES

Table 1. Study 1: Characteristics of the bereaved and matched comparison cohorts used in the melanoma incidence analysis

	UK, No. (%)		Denmark, No. (%)	
	Bereaved cohort	**Comparison cohort[a]**	**Bereaved cohort**	**Comparison cohort[a]**
Total	170,002 (9.6)	1,599,260 (90.4)	345,915 (9.4)	3,319,788 (90.6)
Age at index date, years				
Range	31.9-101.4	31.4-100.4	16.5-100.0	16.1-99.9
Median (IQR)	74.5 (66.8-80.8)	73.8 (66.3-79.8)	71.3 (62.4-78.8)	70.8 (62.0-78.0)
Groups				
<50	3081 (1.8)	30,096 (1.9)	23,956 (6.9)	238,640 (7.2)
50–59	15,843 (9.3)	158,537 (9.9)	45,143 (13.1)	449,727 (13.5)
60–69	39,239 (23.1)	391,003 (24.5)	89,214 (25.8)	887,777 (26.7)
70–79	64,000 (37.7)	630,668 (39.4)	114,708 (33.2)	1,123,948 (33.9)
≥80	47,839 (28.1)	388,956 (24.3)	72,894 (21.1)	619,696 (18.7)
Sex				
Women	111,427 (65.5)	1,048,995 (65.6)	231,022 (66.8)	2,214,531 (66.7)
Comorbidity burden[b]				
Low	78,347 (46.1)	773,297 (48.4)	249,026 (72.0)	2,458,135 (74.0)
Intermediate	62,126 (36.5)	571,089 (35.7)	81,430 (23.5)	728,846 (22.0)
High	29,529 (17.4)	254,874 (15.9)	15,459 (4.5)	132,807 (4.0)
Smoking status[c]				
Non-smoker	61,330 (36.1)	624,987 (39.1)	NA	NA
Ex-smoker	69,069 (40.6)	666,389 (41.7)	NA	NA
Current smoker	36,862 (21.7)	286,561 (17.9)	NA	NA
Missing	2741 (1.6)	21,323 (1.3)	NA	NA
Alcohol consumption[c]				
Non-drinker	19,913 (11.7)	169,930 (10.6)	NA	NA
Ex-drinker	22,128 (13.0)	185,976 (11.6)	NA	NA
Current drinker	114,823 (67.5)	1,134,558 (70.9)	NA	NA
Missing	13,138 (7.7)	108,796 (6.8)	NA	NA
Body Mass Index[c]				
<18.5 kg/m^2	4216 (2.5)	28,321 (1.8)	NA	NA
18.5-24.9 kg/m^2	57,830 (34.0)	544,495 (34.1)	NA	NA
25-29.9 kg/m^2	58,967 (34.7)	590,334 (36.9)	NA	NA
≥30 kg/m^2	35,856 (21.1)	333,589 (20.9)	NA	NA
Missing	13,133 (7.7)	102,521 (6.4)	NA	NA
Index of multiple deprivation[c]				
1 (least deprived)	39,713 (23.4)	400,092 (25.0)	NA	NA
2	35,361 (20.8)	345,884 (21.6)	NA	NA
3	36,653 (21.6)	344,956 (21.6)	NA	NA
4	33,049 (19.4)	292,864 (18.3)	NA	NA
5 (most deprived)	25,226 (14.8)	215,464 (13.5)	NA	NA

Education duration[d]				
Short (7-10 years)	NA	NA	157,611 (45.6)	1,370,756 (41.3)
Medium (11-12 years)	NA	NA	103,144 (29.8)	1,058,069 (31.9)
Long (≥13 years)	NA	NA	40,506 (11.7)	526,196 (15.9)
Missing	NA	NA	44,654 (12.9)	364,767 (11.0)
Follow-up (years)				
Total	905,281	8,137,952	2,552,711	22,027,622
Median (IQR)	4.3 (1.8-8.1)	4.1 (1.8-7.5)	6.6 (3.0-11.2)	5.6 (2.5-10.0)

Abbreviations: IQR, interquartile range, NA, not applicable

[a]In the UK comparison cohort, 18.7% (15.1% of unique subjects) experienced bereavement after the end of follow-up. In the Danish comparison cohort, 22.7% (17.0% of unique subjects) experienced bereavement after the end of follow-up.

[b]Comorbidity burden was measured using the Charlson Comorbidity Index. Comorbidity burden was determined on the index date based on the Charlson Comorbidity Index score, categorised as low (0 point), intermediate (1-2 points), and high (≥3 points).

[c]Information on smoking status, alcohol consumption, body mass index and index of multiple deprivation was not available in Denmark.

[d]Information on education duration was not available in the United Kingdom.

Table 2. Study 2: Characteristics of patients with melanoma among couples in the mortality analysis

	UK, No. (%)	**Denmark, No. (%)**
Total	3597	24,911
Age, years		
Range	32.8-99.0	18.3-99.5
Median (IQR)	67.2 (58.2-75.5)	58.7 (45.3-69.8)
Groups		
<50	283 (7.9)	8,276 (33.2)
50–59	782 (21.7)	4,888 (19.6)
60–69	1092 (30.4)	5,633 (22.6)
70–79	958 (26.6)	4,051 (16.3)
80+	482 (13.4)	2,063 (8.3)
Sex		
Women	1606 (44.7)	13,035 (52.3)
Men	1991 (55.4)	11,876 (47.7)
Comorbidity burden[a]		
Low	1858 (51.7)	20,254 (81.3)
Intermediate	1117 (31.1)	3,847 (15.4)
High	622 (17.3)	810 (3.3)
Smoking status[b]		
Non-smoker	1415 (39.3)	NA
Ex-smoker	1559 (43.3)	NA
Current smoker	595 (16.5)	NA
Missing	28 (0.8)	NA
Alcohol consumption[b]		
Non-drinker	236 (6.6)	NA
Ex-drinker	266 (7.4)	NA
Current drinker	2832 (78.7)	NA
Missing	263 (7.3)	NA
Body Mass Index[b]		
<18.5 kg/m^2	43 (1.2)	NA
18.5-24.9 kg/m^2	1172 (32.6)	NA
25-29.9 kg/m^2	1405 (39.1)	NA
≥30 kg/m^2	754 (21.0)	NA
Missing	223 (6.2)	NA
Index of multiple deprivation[b]		
1 (least deprived)	1099 (30.6)	NA
2	1019 (28.3)	NA
3	788 (21.9)	NA
4	522 (14.5)	NA
5 (most deprived)	169 (4.7)	NA
Education duration[c]		
Short (7-10 years)	NA	5,909 (23.7)
Medium (11-12 years)	NA	10,410 (41.8)
Long (≥13 years)	NA	7,563 (30.4)
Missing	NA	1,029 (4.1)
Melanoma stage at diagnosis[c]		
Localised	NA	18,575 (74.6)
Regional	NA	1,500 (6.0)
Distant	NA	254 (1.0)
Unknown	NA	4,582 (18.4)

Follow-up (years)		
Total	17,625	154,189
Median (IQR)	3.5 (1.4-6.8)	5.0 (2.2-9.3)

Abbreviations: IQR, interquartile range; NA, not applicable

[a]Comorbidity burden was measured using the Charlson Comorbidity Index. Comorbidity burden was determined on the index date using the Charlson Comorbidity Index score, categorised as low (0 point), intermediate (1-2 points), and high (≥3 points).

[b]Information on smoking status, alcohol consumption, body mass index and index of multiple deprivation was not available in Denmark.

[c]Information on education duration and melanoma stage at diagnosis was not available in the United Kingdom.

FIGURE CAPTIONS

Figure 1. Flowcharts for inclusion in the UK and Denmark cohorts. Figure 1a: the incidence analysis in the UK; Figure 1b: the incidence analysis in Denmark; Figure1c: the mortality analysis in the UK; Figure 1d: the mortality analysis in Denmark

Figure 2. Pooled adjusted hazard ratios for the association between partner bereavement and diagnosis of incident melanoma in the UK and Denmark. Hazard ratios were adjusted for Charlson Comorbidity Index scores.

Figure 3. Pooled adjusted hazard ratios for the association between partner bereavement and melanoma-specific mortality among patients with melanoma in the UK and Denmark. Hazard ratios were adjusted for age, sex, and Charlson Comorbidity Index scores.