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The forthcoming inexorable decline of cutaneous melanoma mortality in light-skinned populations

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Abstract

Background: Reasons underlying time changes in cutaneous melanoma mortality in light-skinned populations are not well understood. An analysis of long-term time trends in melanoma mortality was carried out after regrouping countries in homogeneous regions.

Methods: Using the WHO mortality database, age-period-cohort models were fitted for seven regions where the majority of population is light-skinned. Cohort effects are denoted as changes in rates occurring at different time in steadily older age groups. Period effects are denoted as changes in rates occurring simultaneously in several age groups.

Findings: Cohort effects better explained changes in melanoma mortality over time than period effects. Lifetime risk to die from melanoma increased in successive generations from 1875 until a peak year. Peak years were for subjects born in 1936-40 in Oceania, 1937-43 in North America, 1941-42 in Northern Europe, 1945-53 in UK and Ireland, 1948 in Western Europe, and 1957 in Central Europe. After peak years, lifetime risk of melanoma death gradually decreased in successive generations and risks of subjects born in 1990-95 were back to risk levels observed for subjects born before 1900-05. In Southern Europe, birth years with highest lifetime risk of melanoma death have not yet been attained. As time passes, melanoma deaths will steadily rarefy in younger age groups and concentrate in older age groups, for ultimately fade away after 2043-54.

Interpretation: Independently from screening or treatment, over next decades, death from melanoma is likely to become an increasingly rare event. ~~The temporary epidemic of fatal melanoma was most probably due to the medically backed practice of exposing unclothed children to intense natural and artificial sources of ultraviolet radiation that prevailed in 1900-1960.~~ The temporary epidemic of fatal melanoma was most probably due to excessive UV-exposure of children that prevailed in 1900-1960, and recent mortality decreases would be due to progressive reductions in UV-exposure of children over the last decades.

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Introduction

The cutaneous malignant melanoma (hereafter termed melanoma) is the deadliest form of skin cancer. From 1955 to around 1985, melanoma death rates have more than doubled in all light-skinned populations. After 1985-1990, less steep increases or stabilizations, and even decreases in melanoma mortality rates have been observed in Australia,¹ in the USA² and in several European countries³⁻⁸ after that changes in the age distribution of populations over time had been controlled for in statistical analyses. However, understanding reasons possibly underlying time variations in the death toll due to melanoma is quite challenging when one looks more closely at the age at which these deaths occurred. For instance, in Northern Europe (i.e., Denmark, Finland, Iceland, Norway, Sweden), before 1970, a minority of melanoma deaths occurred in subjects aged 70 or more while after 1995 in men and 1985 in women, melanoma deaths were more numerous in this age group (Figure 1ab). Numbers of melanoma deaths in subjects less than 50 increased until around 1975, then stabilized and slowly decreased. Numbers of deaths in subjects aged 50 to 69 raised steeply until 1985-90, after which increases slowed down in men and death numbers plateaued in women. Comparable epidemiological features have been observed in all light-skinned populations (Figure S1). The contrasting time variations in melanoma death across age groups indicate that the influence of risk factors involved in the occurrence of deadly melanoma had varied over time and is independent from population ageing. Factors independent of ageing that influence disease burden over time are defined as period or cohort effects or a combination of both.⁹ Period effects are characterized by changes in mortality rates taking place at about the same time in several age groups, for instance after the offering of efficient screening program or treatment to subjects of different ages. Cohort effects are characterized by changes in mortality rates taking place in successive generations, for instance after introduction of prevention policies targeting children whose effect on mortality will be first observed in younger age groups and then progressively extend to older age groups.

In order to better understand reasons underlying divergences in age-specific trends in melanoma mortality, we carried out an analysis of long-term time trends in melanoma mortality in countries where the majority of the population is light-skinned. The objective of our study was to disentangle the respective contributions of age at which melanoma death occurred, of population aging, of cohort effects, and of period effects. To this end, we regrouped countries by homogeneous geographical regions so that sufficient statistical power could be secured.

Methods

Mortality data

Mortality data on melanoma were retrieved from the WHO mortality database (09/07/2012 release). Data were extracted for countries mainly populated with light-skinned subjects. Annual data were obtained for each sex by 5-years age groups (from 0-4 years to 85 and more). Melanoma mortality codes from the international classifications of diseases (ICD) were 190 for ICD7, 172 for ICD8, 172 for ICD9, C43 for ICD10. Data were available from 1955 to 2010 in most countries. France was excluded of the analysis because of misclassification in melanoma/Non Melanoma Skin Cancer codes in the 1960s owing to problems in transition from ICD7 to ICD8 lists. In the USA, melanoma mortality data were not available for the 1968-1978 period and we just estimated missing data by interpolation of data before 1968 and data after 1978.

Grouping countries into regions

In order to increase the statistical power of the analysis, countries were grouped into main regions of the world. Within each region, deaths and population by age group and sex were added. Countries were grouped as follows:

- Oceania: Australia and New-Zealand
- North America: Canada and the United States of America (USA)
- Northern Europe: Denmark, Finland, Iceland, Norway, Sweden
- United Kingdom and Ireland
- Western Europe: Austria, Belgium, Germany (former German Democratic Republic and former Federal Republic of Germany 1980-1989; Reunified Germany since 1990), the Netherlands and Switzerland
- Central Europe: Bulgaria, the Czech Republic, Estonia, Hungary, Latvia, Poland, Romania, Slovakia and Slovenia
- Southern Europe: Greece, Italy, Portugal and Spain

Statistical analysis

Age standardisation

Mortality rates were age-standardized by the direct method using Segi World standard population¹⁰ as reference.

Joinpoint Modelling

Time changes in the age-standardized rates were modeled using joinpoint version 3.5.0 (Joinpoint Regression Program, Version 3.5 - April 2011; Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program National Cancer Institute). Joinpoint enables to model several regression lines connected by joinpoints at which significant inflexion could be detected; the program reports the simplest model that the data allow. Log-linear models were used in the analysis of trends and the identification of 0 to 3 joinpoints to either end of the data were allowed. The minimum number of allowed datapoints between joinpoints was 4.

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This time-trend modeling approach enables to provide an evaluation of trends that is not user dependent as finding of joinpoints is data driven and identified through a series of permutation tests. Analyses were carried out for each region by sex and by age group (less than 50; 50 to 69 and more than 70).

Age-period-cohort modelling

Age-period-cohort (APC) models were fitted to mortality data using R 3.0.1. More precisely, the function `apc.fit` from the Epi 1.1.67 package¹¹ was used. To solve the problem of identifiability in such models,⁹ a penalty function was applied to period effects which constrained the average period effect to be null with a null slope. The analysis was repeated applying the same penalty function to the cohort effect. The two ways to parameterize data led to similar results (data not shown).

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The analysis was repeated applying the same penalty function to the cohort effect. Applying the penalty function to the period effect or to the cohort effect resulted in similar changes in deviance (data not shown).

Subjects less than 15 were excluded from analyses. In results, cohorts were identified by their middle-year. Because first and last years of available data on causes of death could vary between countries, or because of missing years, study periods were restricted to 5-year groups for which complete data were available. The reference cohort, noted 1935, corresponds to people born between the 1st of January 1933 and the 31st of December 1937. The year 1935 was selected because in all regions, it was approximately the median birth cohort of subjects who died from melanoma. Results from APC models included age-specific effects, cohorts and period effects reported as relative risk with a reference cohort set to 1935 (RR=1.0).

Results

Detailed results for Northern Europe are presented first after which main results for all regions are provided with complete results displayed in the supplementary materials.

Northern European countries

Mortality rates in Figure 1cd are the numbers of melanoma deaths displayed in Figure 1ab divided by numbers of men or women of each age group in given year, followed by age standardization on the Segi World Standard Population.¹⁰ Hence trends in Figures 1cd are independent of population aging. Time trends were derived from join point analyses that quantified percent changes in mortality rates during a specific time period and detected years during which statistically significant changes in trends were noticeable (Table S1).

Overall, melanoma mortality was still rising in the 2000s with annual percent changes of 2.47% (95% CI: 0.91; 4.05) in 2002-10 in men and of 1.53% (95% CI: 0.73; 2.34) in 1996-2010 in women. However, in men and women less than 50, an abrupt reversal in trends took place in 1970-71, while in men and women 50-69, trends stabilized after 1983-84, while in men and women aged 70 and more, trends have risen without interruption from 1955 to 2010.

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A more refined examination of trends specific to each 10-year age group show that the younger the men and women, the earlier the stabilization or start of declines in trends (Figure 1ef). For each increment in 10-year age group, there was a 6 to 8 years shift of the year from which rates started to stabilize. Downward trends in years after the stabilization were observed for men and women less than 50, but not yet for the 50-59 and 60-69 age groups. Above 69 years of age, melanoma mortality rates continued to rise. A subject aged 70 in 2010 was born in 1940. Hence the risk of melanoma death has leveled off in successive generations of subjects born after 1940, which is the hallmark of cohort effects. Because in 2010, subjects born after 1940 have not yet reached 70 years of age, stabilization of mortality rates are not yet visible in subjects aged 70 and more.

Instead of examining trends according to calendar years, one can examine trends according to years of birth (Figure 1gh). Each curve reflects changes in mortality rates specific to 10-year age groups whose subjects were born at different epochs. The vertical dashed line indicates that trends in melanoma mortality stabilized and then declined in successive cohorts of men born after 1940-45. Rates will continue to decline in cohorts of subjects less than 70 born after 1940. It is highly likely that in coming years, rates in subjects aged 70 or more born after 1940-45 will progressively stabilize and then decline.

From age-period-cohort analyses, we could quantify the influence of cohort and period effects on time trends of melanoma death through an examination of the residual deviance of models that is the amount of variation in mortality data not explained by a model. Analysis of deviance comparing the five classical models (Age, age-drift, age-cohort, age-period and age-period-cohort) are reported in Table S2. The residual deviance was smaller for age-cohort models than for age-period models, indicating that changes in melanoma mortality over time were better explained by cohort effects than by period effects. Therefore, the remaining of the text will focus on results from age-period-cohort models with penalty function applied to the period effect.

Birth cohort effects can be summarized as the risk to die from melanoma when born at a certain year relative to a reference year (1935) for which the risk is arbitrarily set to 1.0 (Figure 1ij). Peak years for highest risk of melanoma death were observed in men born around 1942 and in women born around 1941. The relative risk of melanoma death of men born before 1885 was less than 0.25, i.e., less than 25% the risk of melanoma death of men born around 1935. The relative risk of women born before 1885 was 30% the risk of melanoma death of women born around 1935. After 1941-42, risks declined without interruption. The risk of melanoma death of men and women born around 1990 was similar to the risk of men and women born around 1900.

Because of cohort effects, as time passes, melanoma deaths concentrate in older age groups and become steadily rarer in younger age groups (Figure 1kl). Independently from population aging, in 1955-59, 30% of melanoma deaths in men occurred before age 50, 40% of deaths occurred between 50 and 69, and 30% occurred after 69. From 2005 to 2010, 10% of melanoma deaths in men occurred before age 50, 40% of deaths occurred between 50 and 69, and 50% occurred after 69. Comparable changes were observed in women.

Results for other regions

Similarly to Northern Europe, age-adjusted melanoma mortality rates stabilized and then declined in subjects less than 50, raising trends slowed down or stabilized in subjects 50 to 69, and kept increasing in subjects 70 years or more (Figure S2). If from 2000 to 2010 annual percent changes for all age groups still indicated still raising melanoma mortality, principally in Europe (Table S1), this was largely due to the demographic weight of older subjects who experienced unabated raising trends in melanoma mortality. Hence, trends were mainly explained by cohort effects, and with few exceptions, the residual deviance of age-cohort models was smaller than that of age-period models (Table S2).

Figure 2 shows the lifetime risk of melanoma death for each birth year in a region relative to rates in that region observed in the birth cohort centered around 1935. Relative risks are to be interpreted for each region, and not between regions. Contrasts in trends between regions are the consequence of variations in peak birth years associated with highest risk of melanoma death. In all regions, the risk of melanoma death in men was minimal for men born before 1880. Then risks sharply increased, reaching a peak for men born in 1940 in Oceania, 1943 in North America, 1942 in Northern Europe, 1948 in Western Europe. After the peak years, the lifetime risk of dying from melanoma has gradually decreased among successive birth years. In Central Europe, a similar birth cohort pattern was observed, but it was delayed by 10-15 years. Of note, age-specific levels and changes in melanoma mortality rates in Western and in Central Europe are practically superimposable.

In general, lifetime risk patterns in women resembled to those seen in men, with closeness between sexes of birth years for which the risk of melanoma death was highest. In the Ireland and United Kingdom region, it took until 1995 before the lifetime risk of melanoma death in men came back to risk levels of men born around 1935. In Southern Europe, in both sexes, the birth years after which the risk to die from melanoma would decrease have not yet been reached, although in women less than 50, first signs of decreases are noticeable in recent years (Figure S3).

As a consequence of cohort effects, in most regions, stabilization and then declines in mortality rates progressively extended from younger to older age groups (Figure S3). This process is most advanced in Oceania and in North America, where first signs of leveling off and declines of rates in subjects more than 69 years of age are perceptible. In these two regions, trend in all ages have stabilized (men in Oceania) or are declining (women in Oceania and men and women in North America). In Western and Central Europe, mortality rates in all age groups have constantly risen but stabilization and declines in subjects less than 60 are discernible. In Southern Europe, stabilization of trends is perceptible over the recent past among subjects less than 50. In Ireland and United Kingdom, declines similar to those observed in women less than 50 were not yet visible in men of same age, which explains the persistence of a high risk of melanoma death in Irish and UK men born after 1953.

In all regions, independently of aging, melanoma deaths are progressively rarer in younger age groups and concentrates in subjects 50 years or more (Figures S4).

Discussion

Our study documented that variations in melanoma mortality rates over time were the result of substantial changes in the risk of melanoma death in successive generations. [If after 2000 melanoma mortality was still on the rise in some Regions, particularly in Europe, this was essentially the consequence of sustained rising trends in older age groups because in younger age groups, these trends had stabilized or had started to decline well before 1990.](#)

Because data on causes of death are available from 1955 onwards in the WHO mortality database, ~~birth~~ cohort effects could not be explored for subjects born before 1875.

However, probably that increasing lifetime risk of melanoma death was already present among subjects born before 1875.¹² Peak years of risk were reached for subjects born around 1936-43 in Oceania, North America and Northern Europe, around 1948 in Western Europe, 1945-53 in the United Kingdom and Ireland and around 1957 in Central Europe. After peak years, steady reductions in mortality risks took place in successive generations. Over next decades, generations with gradually lower risk of lifetime melanoma death will replace generations that had higher lifetime risk of melanoma death. We thus expect that over coming decades, melanoma mortality will stop rising, stabilize and then decline in all light skinned populations. First signs of declines should be observed in Oceania and in Northern America, and lastly in Southern Europe.

However, if dying from melanoma is deemed to become a steadily uncommon event in younger and middle-aged adults, population aging will keep numbers of patients diagnosed with potentially fatal melanoma at a high level over the next two decades because the risk of melanoma death in men and women born around 1940 to 1950 is still high. After 2030, numbers of melanoma deaths are likely to progressively vanish when subjects born from

1970 onwards who have a low risk of melanoma death will reach their six or seventh decade of life.

A number of studies already indicated long-term declines in melanoma mortality starting in youngest age groups and progressively extending to older age groups.^{1,12-14} The principal strengths of our study is were that we compared groups of countries populated with a majority of light-skinned subjects, and data we the used of data were collected over longer periods than in previous studies. Also, assembling data by region increased the statistical power, which contributed to greater accuracy in estimations of statistical parameters related to age, cohort and period effects. Limitations of our study were the absence of usable data for France and gaps in mortality data for some years like in the USA. Also, some countries brought corrections to their data, which might explain inconsistencies in trends like in Central Europe before 1970 (Figure S2f).

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~~Could changes in melanoma mortality trends reflect the effect of treatment and of skin screening (including occasional removal of brown spots to periodical full body skin examination)? The predominance of cohort effects over period effects we found in our study argues against screening and treatment effects. If effective screening or treatment had existed since the 1980s, their impact on melanoma mortality rates would have affected several age groups at about the same time (period effect). Effective treatment exist only since 2010 and are not yet associated with long-lasting disease remission. For screening, first effects should have been observed in women 30 to 50 because this gender and age group is more inclined to attend skin screening. In addition, the purpose of skin screening is to detect melanoma before they have become thick with the possibility of metastases in lymph nodes or in distant organs. If skin screening was effective, downward mortality trends should be preceded by decreases in the incidence of thick melanoma. However, stable or steady increase in the incidence of thick melanoma are observed in virtually all fair-skinned populations (Ambrosini Spaltro et al., 2014; Bordoni et al., 2013; Downing et al., 2006; Hollestein et al., 2012; Jemal et al., 2001; Lasithiotakis et al., 2006; Lipsker et al., 1999; Mackie et al., 2007; Marrett et al., 2001; Montella et al., 2009; Richardson et al., 2008; Tejera Vaquerizo et al., 2008; van der Rhee et al., 1999; Whiteman et al., 2014). In subjects less than 50, trends in thick melanoma are stabilizing or increase at a slower pace than in older subjects, but no data suggest declines in incidence of thick melanoma that would correlate with stabilization or declines in mortality trends in younger age groups (Baade et al., 2012; Jemal et al., 2011; Linos et al., 2009). Moreover, trends in thick melanoma remain stable or continue to increase in the USA and in Queensland (Australia) despite notable increases in the in the prevalence of skin examinations and excisions, and in the incidence of in situ melanoma, a marker of skin screening intensity (Carrière; Coory et al., 2006; Geller et al., 2013; Welch et al., 2005). The predominance of cohort effects points to the epidemiological and experimental evidence that UV exposure during early life would be the most critical period for the occurrence of sun-induced biological events implicated in the genesis of melanoma (IARC, 1992). For instance, migrant studies have documented that the risk of melanoma occurrence or of death is two to three times greater among light-skinned subjects born in Australia than among subjects of European descent who migrated to Australia after 15 years (Khat et al., 1992; Whiteman et al., 2001). Melanoma occurrence in adult life seems unlikely in the absence of sun exposure during childhood (Autier & Doré, IJG, 1998 (Autier et al., 1997)). Animal experiments have shown that susceptibility to UV-~~

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induction of melanoma is greatest just after birth (Noonan et al., 2001; Zaidi et al., 2008) (Handoko et al., 2013). According to these data, some parallelism should exist between age-specific changes in melanoma incidence and mortality. Over the last three decades, increases in the incidence of invasive melanoma have been more marked than increases in melanoma mortality. Nonetheless, some evidence has recently emerged for stabilisation or decreasing trends in more recently born cohorts in Australia, New Zealand, the U.S.A., Canada and Norway (Erdmann et al., 2013).

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Taken altogether, these facts indicate that the ultraviolet radiation would be capable to cause the occurrence of deadly melanoma in adult life when exposure takes place in early life.

We therefore formulate the hypothesis that trends in melanoma mortality would be due to dramatic changes in exposure of small children to ultraviolet radiation, when in the second part of the 19th century, beliefs in the healthiness virtues of the sun and of the ultraviolet radiation expanded among health professionals and large segments of the population (Albert et al., 2002; Albert et al., 2003; Hockberger, 2002; Holman et al., 1980). The popularity of exposing children to natural or artificial sources of UV would have been maximal around 1936 to 1957, depending on regions. The sun spectrum contained large amounts of UVA and UVB radiation and many artificial UV-emitting devices commercialized before 1960 emitted the full UV range, including the UVC, a wavelength present in the sunlight that is completely absorbed by the stratospheric ozone layer. At the time, there was complete ignorance about the deleterious effects of UV radiation. Starting in Oceania in the 1970-80s, sun protection of children has become increasingly common with the recognition that sun exposure and sunburn experience during childhood causes irreversible damages to the skin and are strong risk factors for skin cancer in adult life (MacKie et al., 2009; Marks, 1990). So, most probably that UV exposure patterns of children associated with occurrence of deadly melanoma in adults have progressively disappeared in successive generations after 1960. However, in Southern Europe, these exposure patterns seem to have appeared more recently.

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Long-term data on incidence of advanced melanoma going back to the 1970s and before are not available. However, the contrast between trends in the incidence of advanced melanoma and of melanoma mortality in younger age groups could be the sign of a progressive change in the disease biology, with melanoma being progressively less aggressive as one moves away from the peak birth years associated with highest risk of melanoma death. This hypothesis is supported by studies that examined the influence of year at diagnosis on risk of melanoma death over a fixed duration of follow-up (e.g., 5-year survival) and that took into consideration major predictors of melanoma patient survival.^{30,37,38} In these studies, the more recent the year of diagnosis, the better the survival. One study has suggested that vaccination against common infectious diseases in early life was associated with greater melanoma survival (Kolmel et al., 2005). One could speculate that increasing vaccination coverage after 1950 has induced immune-editing phenomena that have strengthened the capacity of the immune system to control potentially deadly melanoma.

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The role of UV exposure during adulthood on the risk of melanoma death remains unclear. One clue may proceed from Central European countries, where between 1945 and the 1990s, political and economic circumstances limited possibilities of holidays in sunny climates. However, levels and trends in melanoma mortality in Central and in Western Europe were quite similar, apart from a 10-year difference in the start of declines. These similarities may be an indication that recreational UV exposure during adult life has probably less influence on the risk of melanoma death. Recreational and cosmetic UV exposure in adult life, together with increasing skin screening and variability in the classification of histologically equivocal lesions, would contribute for most of the raising incidence of non-life-threatening in situ or in thin invasive melanoma (Autier et al., 2011; Levell et al., 2009) (Norgaard et al., 2011; van der Rhee et al., 2009).

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The strong association between aging and the risk of melanoma death suggests an interplay between accumulated sun exposure and the age-related decreasing capability of the immune system to control dormant cancer cells having considerable malignant potential (Shen et al., 2014). Probably that studies in adults should put the emphasis on factors altering the anti-cancer control functions of the immune system. In conclusion, over next decades, deaths due to melanoma in light-skinned populations will progressively concentrate in oldest subjects, and then progressively diminish for becoming an increasingly rare event.

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Conflict of interest

None to declare

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IARC. International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenicity to Humans. Sunlight. IARC, Lyon. 1992

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Figure captions

Figure 1 – Time trends in cutaneous melanoma mortality in Northern Europe, 1955-2010 (Denmark, Finland, Iceland, Norway, Sweden). Crude numbers of men (1a) and women (1b) who died from melanoma. Age-adjusted rates for men (1c) or women (1d) aged less than 50, 50 to 69, and 70 or more. Age-specific rates for men (1e) or women (1f) by 10-year age group. Thick vertical bars indicate years of rate stabilization. Age-specific melanoma mortality rate according to year of birth of men (1g) and women (1h). Cumulative lifetime risk of melanoma death according to year of birth relative to the risk in men (1i) and women (1j) born around 1935. Age-adjusted proportions of melanoma deaths in men (1k) or in women (1l) less than 50, 50 to 69, and 70 or more.

Figure 2 - Cumulative lifetime risk of melanoma death in regions according to year of birth relative to the risk in men and women born around 1935.

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The forthcoming inexorable decline of cutaneous melanoma mortality in light-skinned populations

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Abstract

Background: Reasons underlying time changes in cutaneous melanoma mortality in light-skinned populations are not well understood. An analysis of long-term time trends in melanoma mortality was carried out after regrouping countries in homogeneous regions.

Methods: Using the WHO mortality database, age-period-cohort models were fitted for seven regions where the majority of population is light-skinned. Cohort effects are denoted as changes in rates occurring at different time in steadily older age groups. Period effects are denoted as changes in rates occurring simultaneously in several age groups.

Results: Cohort effects better explained changes in melanoma mortality over time than period effects. Lifetime risk to die from melanoma increased in successive generations from 1875 until a peak year. Peak years were for subjects born in 1936-40 in Oceania, 1937-43 in North America, 1941-42 in Northern Europe, 1945-53 in UK and Ireland, 1948 in Western Europe, and 1957 in Central Europe. After peak years, lifetime risk of melanoma death gradually decreased in successive generations and risks of subjects born in 1990-95 were back to risk levels observed for subjects born before 1900-05. In Southern Europe, birth years with highest lifetime risk of melanoma death have not yet been attained. As time passes, melanoma deaths will steadily rarefy in younger age groups and concentrate in older age groups, for ultimately fade away after 2040-50.

Conclusion: Independently from screening or treatment, over next decades, death from melanoma is likely to become an increasingly rare event. The temporary epidemic of fatal melanoma was most probably due to excessive UV-exposure of children that prevailed in 1900-1960, and mortality decreases would be due to progressive reductions in UV-exposure of children over the last decades.

Key words: Melanoma, mortality, time trends, age-period-cohort, ultraviolet

Introduction

The cutaneous malignant melanoma (hereafter termed melanoma) is the deadliest form of skin cancer. From 1955 to around 1985, melanoma death rates have more than doubled in all light-skinned populations. After 1985-1990, less steep increases or stabilizations, and even decreases in melanoma mortality rates have been observed in Australia,[1] in the USA [2] and in several European countries [3-8]. However, understanding reasons possibly underlying time variations in the death toll due to melanoma is quite challenging when one looks more closely at the age at which these deaths occurred. For instance, in Northern Europe (i.e., Denmark, Finland, Iceland, Norway, Sweden), before 1970, a minority of melanoma deaths occurred in subjects aged 70 or more while after 1995 in men and 1985 in women, melanoma deaths were more numerous in this age group (Figure 1ab). Numbers of melanoma deaths in subjects less than 50 increased until around 1975, then stabilized and slowly decreased. Numbers of deaths in subjects aged 50 to 69 raised steeply until 1985-90, after which rates slowed down in men and plateaued in women. Comparable epidemiological features have been observed in all light-skinned populations (Figure S1). The contrasting time variations in melanoma death across age groups indicate that the influence of risk factors involved in the occurrence of deadly melanoma had varied over time and is independent from population ageing. Factors independent of ageing that influence disease burden over time are defined as period or cohort effects or a combination of both.[9] Period effects are characterized by changes in mortality rates taking place at about the same time in several age groups, for instance after the offering of efficient screening program or treatment to subjects of different ages. Cohort effects are characterized by changes in mortality rates taking place in successive generations, for instance after introduction of

prevention policies targeting children whose effect on mortality will be first observed in younger age groups and then progressively extend to older age groups.

In order to better understand reasons underlying divergences in age-specific trends in melanoma mortality, we carried out an analysis of long-term time trends in melanoma mortality in countries where the majority of the population is light-skinned. The objective of our study was to disentangle the respective contributions of age at which melanoma death occurred, of population aging, of cohort effects, and of period effects. To this end, we regrouped countries by homogeneous geographical regions so that sufficient statistical power could be secured.

Methods

Mortality data

Mortality data on melanoma were retrieved from the WHO mortality database (09/07/2012 release). Data were extracted for countries mainly populated with light-skinned subjects. Annual data were obtained for each sex by 5-years age groups (from 0-4 years to 85 and more). Melanoma mortality codes from the international classifications of diseases (ICD) were 190 for ICD7, 172 for ICD8, 172 for ICD9, C43 for ICD10. Data were available from 1955 to 2010 in most countries. France was excluded of the analysis because of misclassification in melanoma/Non Melanoma Skin Cancer codes in the 1960s owing to problems in transition from ICD7 to ICD8 lists. In the USA, melanoma mortality data were not available for the 1968-1978.

Grouping countries into regions

In order to increase the statistical power of the analysis, countries were grouped into main regions of the world. Within each region, deaths and population by age group and sex were added. Countries were grouped as follows:

- Oceania: Australia and New-Zealand
- North America: Canada and the United States of America (USA)
- Northern Europe: Denmark, Finland, Iceland, Norway, Sweden
- United Kingdom and Ireland
- Western Europe: Austria, Belgium, Germany (former German Democratic Republic and former Federal Republic of Germany 1980-1989; Reunified Germany since 1990), the Netherlands and Switzerland
- Central Europe: Bulgaria, the Czech Republic, Estonia, Hungary, Latvia, Poland, Romania, Slovakia and Slovenia
- Southern Europe: Greece, Italy, Portugal and Spain

Statistical analysis

Age standardisation

Mortality rates were age-standardized by the direct method using Segi World standard population [10] as reference.

Joinpoint Modelling

Time changes in the age-standardized rates were modelled using joinpoint version 3.5.0 (Joinpoint Regression Program, Version 3.5 - April 2011; Statistical Methodology and Applications Branch and Data Modelling Branch, Surveillance Research Program National

Cancer Institute). Joinpoint enables to model several regression lines connected by joinpoints at which significant inflexion could be detected; the program reports the simplest model that the data allow. Log-linear models were used in the analysis of trends and the identification of 0 to 3 joinpoints to either end of the data were allowed. The minimum number of allowed data points between joinpoints was 4.

This time-trend modeling approach enables to provide an evaluation of trends that is not user dependent as finding of joinpoints is data driven and identified through a series of permutation tests. Analyses were carried out for each region by sex and by age group (less than 50; 50 to 69 and more than 70).

Age-period-cohort modelling

Age-period-cohort (APC) models were fitted to mortality data using R 3.0.1. More precisely, the function `apc.fit` from the `Epi 1.1.67` package [11] was used. To solve the problem of identifiability in such models[9], a penalty function was applied to period effects which constrained the average period effect to be null with a null slope.

The analysis was repeated applying the same penalty function to the cohort effect. Applying the penalty function to the period effect or to the cohort effect resulted in similar changes in deviance (data not shown).

Subjects less than 15 were excluded from analyses. In results, cohorts were identified by their middle-year. Because first and last years of available data on causes of death could vary between countries, or because of missing years, study periods were restricted to 5-year groups for which complete data were available. The reference cohort, noted 1935, corresponds to people born between the 1st of January 1933 and the 31st of December 1937. The year 1935 was selected because in all regions, it was approximately the median birth

cohort of subjects who died from melanoma. Results from APC models included age-specific effects, cohorts and period effects reported as relative risk with a reference cohort set to 1935 (RR=1.0).

Results

Detailed results for Northern Europe are presented first after which main results for all regions are provided with complete results displayed in the supplementary materials.

Northern European countries

Mortality rates in Figure 1cd are the numbers of melanoma deaths displayed in Figure 1ab divided by numbers of men or women of each age group in given year, followed by age standardization on the Segi World Standard Population[10]. Hence trends in Figures 1cd are independent of population aging. Time trends were derived from joinpoint analyses that quantified percent changes in mortality rates during a specific time period and detected years during which statistically significant changes in trends were noticeable (Table S1).

Overall, melanoma mortality was still rising in the 2000s with annual percent changes of 2.47% (95% CI: 0.91; 4.05) in 2002-10 in men and of 1.53% (95% CI: 0.73; 2.34) in 1996-2010 in women. However, in men and women less than 50, an abrupt reversal in trends took place in 1970-71, while in men and women 50-69, trends stabilized after 1983-84. In men and women aged 70 and more, trends have risen without interruption from 1955 to 2010.

A more refined examination of trends specific to each 10-year age group show that the younger the men and women, the earlier the stabilization or start of declines in trends (Figure 1ef). For each increment in 10-year age group, there was a 6 to 8 years shift of the year from which rates started to stabilize. Downward trends in years after the stabilization were observed for men and women less than 50, but not yet for the 50-59 and 60-69 age

groups. Above 69 years of age, melanoma mortality rates continued to rise. A subject aged 70 in 2010 was born in 1940. Hence the risk of melanoma death has leveled off in successive generations of subjects born after 1940, which is the hallmark of cohort effects. Because in 2010, subjects born after 1940 have not yet reached 70 years of age, stabilization of mortality rates are not yet visible in subjects aged 70 and more.

Instead of examining trends according to calendar years, one can examine trends according to years of birth (Figure 1gh). Each curve reflects changes in mortality rates specific to 10-year age groups whose subjects were born at different epochs. The vertical dashed line indicates that trends in melanoma mortality stabilized and then declined in successive cohorts of men born after 1940-45. Rates will continue to decline in cohorts of subjects less than 70 born after 1940. It is highly likely that in coming years, rates in subjects aged 70 or more born after 1940-45 will progressively stabilize and then decline.

From age-period-cohort analyses, we could quantify the influence of cohort and period effects on time trends of melanoma death through an examination of the residual deviance of models that is the amount of variation in mortality data not explained by a model.

Analysis of deviance comparing the five classical models (Age, age-drift, age-cohort, age-period and age-period-cohort) are reported in Table S2. The residual deviance was smaller for age-cohort models than for age-period models, indicating that changes in melanoma mortality over time were better explained by cohort effects than by period effects.

Therefore, the remaining of the text will focus on results from age-period-cohort models with penalty function applied to the period effect.

Birth cohort effects can be summarized as the risk to die from melanoma when born at a certain year relative to a reference year (1935) for which the risk is arbitrarily set to 1.0

(Figure 1ij). Peak years for highest risk of melanoma death were observed in men born around 1942 and in women born around 1941. The relative risk of melanoma death of men born before 1885 was less than 0.25, i.e., less than 25% the risk of melanoma death of men born around 1935. The relative risk of women born before 1885 was 30% the risk of melanoma death of women born around 1935. After 1941-42, risks declined without interruption. The risk of melanoma death of men and women born around 1990 was similar to the risk of men and women born around 1900.

Because of cohort effects, as time passes, melanoma deaths concentrate in older age groups and become steadily rarer in younger age groups (Figure 1kl). Independently from population aging, in 1955-59, 30% of melanoma deaths in men occurred before age 50, 40% of deaths occurred between 50 and 69, and 30% occurred after 69. From 2005 to 2010, 10% of melanoma deaths in men occurred before age 50, 40% of deaths occurred between 50 and 69, and 50% occurred after 69. Comparable changes were observed in women.

Results for other regions

Similarly to Northern Europe, age-adjusted melanoma mortality rates stabilized and then declined in subjects less than 50, slowed down or stabilized in subjects 50 to 69, and kept rising in subjects 70 years or more (Figure S2). If from 2000 to 2010 annual percent changes for all age groups indicated still raising melanoma mortality, principally in Europe (Table S1), this was largely due to the demographic weight of older subjects who experienced unabated raising trends in melanoma mortality. Hence, trends were mainly explained by cohort effects, and with few exceptions, the residual deviance of age-cohort models was smaller than that of age-period models (Table S2).

Figure 2 shows the lifetime risk of melanoma death for each birth year in a region relative to rates in that region observed in the birth cohort centered around 1935. Relative risks are to be interpreted for each region, and not between regions. Contrasts in trends between regions are the consequence of variations in peak birth years associated with highest risk of melanoma death. In all regions, the risk of melanoma death in men was minimal for men born before 1880. Then risks sharply increased, reaching a peak for men born in 1940 in Oceania, 1943 in North America, 1942 in Northern Europe, 1948 in Western Europe and 1957 in Central Europe. After peak years, the lifetime risk of dying from melanoma has gradually decreased among successive birth years. Of note, age-specific levels and changes in melanoma mortality rates in Western and in Central Europe are practically superimposable.

In general, lifetime risk patterns in women resembled to those seen in men, with closeness between sexes of birth years for which the risk of melanoma death was highest. In the Ireland and United Kingdom region, it took until 1995 before the lifetime risk of melanoma death in men came back to risk levels of men born around 1935. In Southern Europe, in both sexes, the birth years after which the risk to die from melanoma would decrease have not yet been reached, although in women less than 50, first signs of decreases are noticeable in recent years (Figure S3).

As a consequence of cohort effects, in most regions, stabilization and then declines in mortality rates progressively extended from younger to older age groups (Figure S3). This process is most advanced in Oceania and in North America, where first signs of leveling off and declines of rates in subjects more than 69 years of age are perceptible. In these two regions, rates have stabilized (men in Oceania) or are declining (women in Oceania and men

and women in North America) in all age groups. In Western and Central Europe, stabilization and declines in subjects less than 60 are discernible. In Southern Europe, stabilization of rates is perceptible over the recent past among subjects less than 50. In Ireland and United Kingdom, declines similar to those observed in women less than 50 were not yet visible in men of same age, which explains the persistence of a high risk of melanoma death in Irish and UK men born after 1953.

In all regions, independently of aging, melanoma deaths are progressively rarer in younger age groups and concentrates in subjects 50 years or more (Figures S4).

Discussion

Our study documents that variations in melanoma mortality rates over time were the result of substantial changes in the risk of melanoma death in successive generations. If after 2000 melanoma mortality was still on the rise in some Regions, particularly in Europe, this was essentially the consequence of sustained rising trends in older age groups because in younger age groups, these trends had stabilized or had started to decline before 1990. Data on causes of death are available from 1955 onwards in the WHO mortality database, and cohort effects could not be explored for subjects born before 1875. However, probably that increasing lifetime risk of melanoma death was already present among subjects born before 1875[12]. After years of highest risk of melanoma deaths, steady reductions in mortality risks took place in successive generations. Over next decades, generations with gradually lower risk of lifetime melanoma death will replace generations that had higher lifetime risk of melanoma death. We thus expect that in the near future, melanoma mortality will stabilize and then decline in all light skinned populations. First signs of declines should be observed in Oceania and in Northern America, and lastly in Southern Europe.

However, if dying from melanoma is deemed to become a steadily uncommon event in younger and middle-aged adults, population aging will keep numbers of patients diagnosed with potentially fatal melanoma at a high level over the next two decades because the risk of melanoma death in men and women born around 1940 to 1950 is still high. After 2030, numbers of melanoma deaths are likely to progressively vanish when subjects born from 1970 onwards who have a low risk of melanoma death will reach their six or seventh decade of life.

A number of studies already indicated long-term declines in melanoma mortality starting in youngest age groups and progressively extending to older age groups. [1, 12-14] The principal strengths of our study is the use of data collected over longer periods than in previous studies. Also, assembling data by region increased the statistical power, which contributed to greater accuracy in estimations of statistical parameters related to age, cohort and period effects. Limitations of our study were the absence of usable data for France and gaps in mortality data for some years like in the USA. Also, some countries brought corrections to their data, which might explain inconsistencies in trends like in Central Europe before 1970 (Figure S2f).

The predominance of cohort effects over period effects we found in our study argues against screening and treatment effects. If effective screening or treatment had existed since the 1980s, their impact on melanoma mortality rates would have affected several age groups at about the same time (period effect). Effective treatment exist only since 2010 and are not yet associated with long-lasting disease remission [15]. For screening, first effects should have been observed in women 30 to 50 because this sex and age group is more inclined to attend skin screening. In addition, the purpose of skin screening is to detect melanoma

before they have become thick with the possibility of metastases in lymph nodes or in distant organs. If skin screening was effective, downward mortality trends should be preceded by decreases in the incidence of thick melanoma. However, stable or steady increase in the incidence of thick melanoma are observed in virtually all fair-skinned populations [3, 7, 16-27]. In subjects less than 50, trends in thick melanoma are stabilizing or increase at a slower pace than in older subjects, but no data suggest declines in incidence of thick melanoma that would correlate with stabilization or declines in mortality trends in younger age groups [2, 28, 29].

The predominance of cohort effects points to the knowledge that early life would be the most critical period for the occurrence of UV-induced biological events implicated in the genesis of melanoma [30]. For instance, migrant studies have documented that the risk of melanoma occurrence or of death is two to three times greater among light-skinned subjects born in Australia than among subjects of European descent who migrated to Australia after 15 years [31, 32]. Melanoma risk in adult life seems to be low in the absence of sun exposure during childhood [33, 34]. Animal experiments have shown that susceptibility to UV-induction of melanoma is greatest just after birth [35-37]. According to these data, some parallelism should exist between age-specific changes in melanoma incidence and mortality. Over the last three decades, increases in the incidence of invasive melanoma have been more marked than increases in melanoma mortality. Nonetheless, some evidence has recently emerged for stabilisation or decreasing incidence in more recently-born cohorts in Australia, New Zealand, the U.S.A., Canada and Norway [38].

Taken altogether, these facts indicate that the ultraviolet radiation would be capable to cause the occurrence of deadly melanoma in adult life when exposure takes place in early

life. We therefore formulate the hypothesis that trends in melanoma mortality would be due to dramatic changes in exposure of small children to UV radiation, when in the second part of the 19th century, beliefs in the healthiness virtues of the sun and of the ultraviolet radiation expanded among health professionals and large segments of the population [12, 39-41]. The popularity of exposing children to natural or artificial sources of UV would have been maximal around 1930 to 1960, depending on regions. The sun spectrum contained large amounts of UVA and UVB radiation and many artificial UV-emitting devices commercialized before 1960 emitted the full UV range, including the UVC, a highly carcinogenic wavelength present in the sunlight but that is completely absorbed by the stratospheric ozone layer. At the time, there was complete ignorance about the carcinogenic effects of UV radiation. Starting in Oceania in the 1970-80s, sun protection of children has become increasingly common with the recognition that sun exposure and sunburn experience during childhood causes irreversible damages to the skin and are strong risk factors for skin cancer in adult life [42, 43]. So, most probably that UV-exposure patterns of children associated with occurrence of deadly melanoma in adults have progressively disappeared in successive generations after 1960. However, in Southern Europe, these exposure patterns seem to have appeared more recently.

Long-term data on incidence of advanced melanoma going back to the 1970s and before are not available. However, the contrast between trends in the incidence of advanced melanoma and of melanoma mortality in younger age groups could be the sign of a gradual change in the disease biology, with melanoma being progressively less aggressive as one moves away from the peak birth years associated with highest risk of melanoma death. This hypothesis is supported by studies that examined the influence of year at diagnosis on risk of melanoma death over a fixed duration of follow-up (e.g., 5-year survival) and that took into

consideration major predictors of melanoma patient survival. [16, 44, 45] In these studies, the more recent the year of diagnosis, the better the survival. One study has suggested that vaccination against common infectious diseases in early life was associated with greater melanoma survival [46]. One could speculate that increasing vaccination coverage of small children after 1950 could have strengthened the immune surveillance of potentially deadly melanoma initiated by UV exposures during early life.

How UV exposure during adulthood affects the risk of melanoma death remains unclear. One clue may proceed from Central European countries, where between 1945 and 1989, political and economic circumstances have limited possibilities of holidays in sunny climates. However, levels and trends in melanoma mortality in Central and in Western Europe were quite similar, apart from a 10-year difference in birth cohorts with highest risk of melanoma death. These similarities may be an indication that recreational UV exposure during adult life has probably little influence on the risk of melanoma death. In contrast, recreational and cosmetic UV exposure in adult life, together with increasing skin screening and variability in the classification of histologically equivocal lesions would have contributed to most of the rising incidence of non-life-threatening in situ or thin invasive melanoma [47-50].

The strong association between aging and the risk of melanoma death suggests an interplay between accumulated sun exposure and the age-related decreasing capability of the immune system to control dormant cancer cells having considerable malignant potential [51]. Probably that studies in adults should put the emphasis on factors altering the anti-cancer control functions of the immune system like for instance the UV-induced inflammation [52].

In conclusion, over next decades, deaths due to melanoma in light-skinned populations will progressively concentrate in oldest subjects, and then progressively diminish for becoming an increasingly rare event.

Conflict of interest

None to declare

Figure captions

Figure 1 – Time trends in cutaneous melanoma mortality in Northern Europe, 1955-2010 (Denmark, Finland, Iceland, Norway, Sweden). Crude numbers of men (1a) and women (1b) who died from melanoma. Age-adjusted rates for men (1c) or women (1d) aged less than 50, 50 to 69, and 70 or more. Age-specific rates for men (1e) or women (1f) by 10-year age group. Thick vertical bars indicate years of rate stabilization. Age-specific melanoma mortality rate according to year of birth of men (1g) and women (1h). Cumulative lifetime risk of melanoma death according to year of birth relative to the risk in men (1i) and women (1j) born around 1935. Age-adjusted proportions of melanoma deaths in men (1k) or in women (1l) less than 50, 50 to 69, and 70 or more.

Figure 2 - Cumulative lifetime risk of melanoma death in regions according to year of birth relative to the risk in men and women born around 1935.

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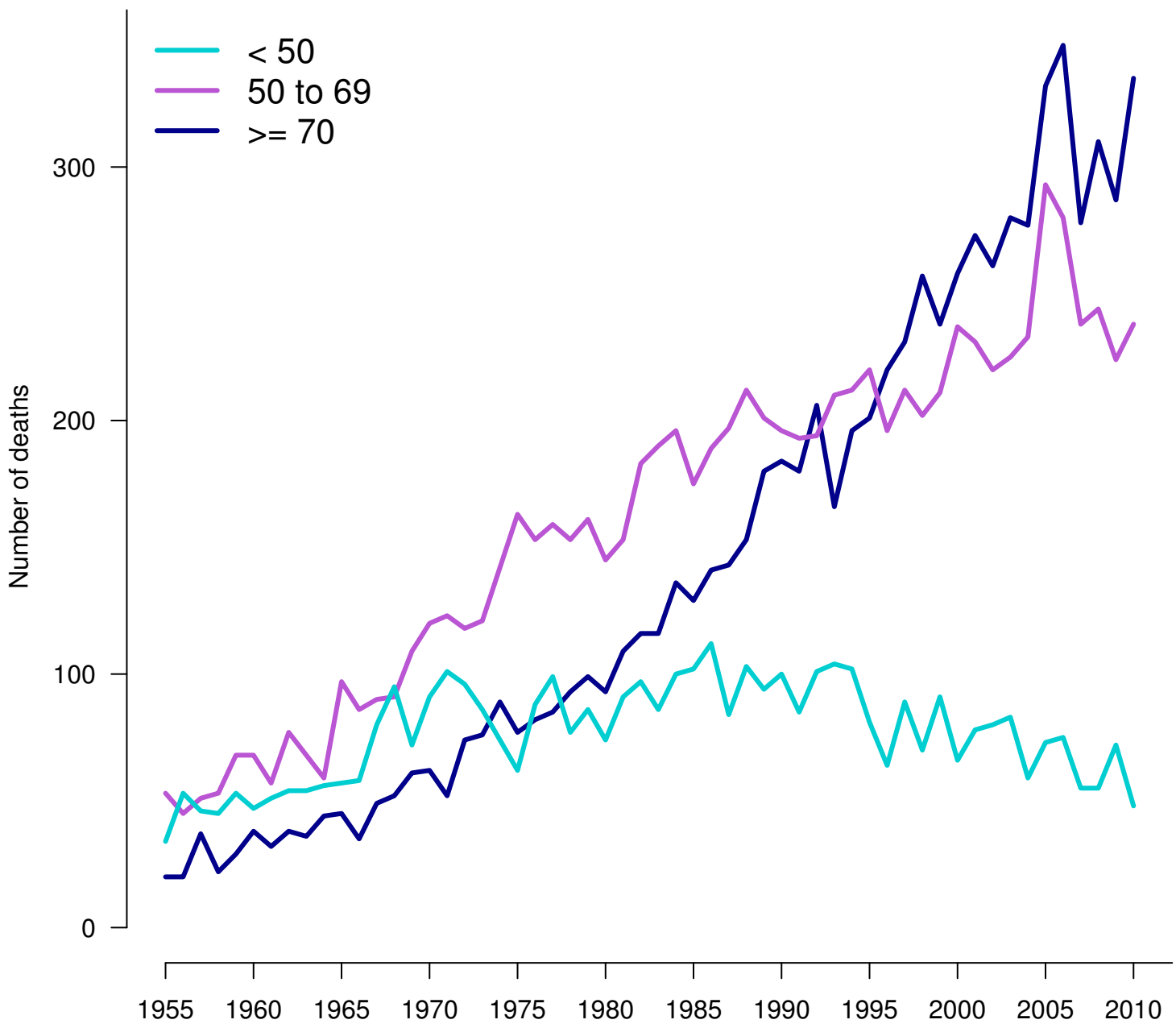
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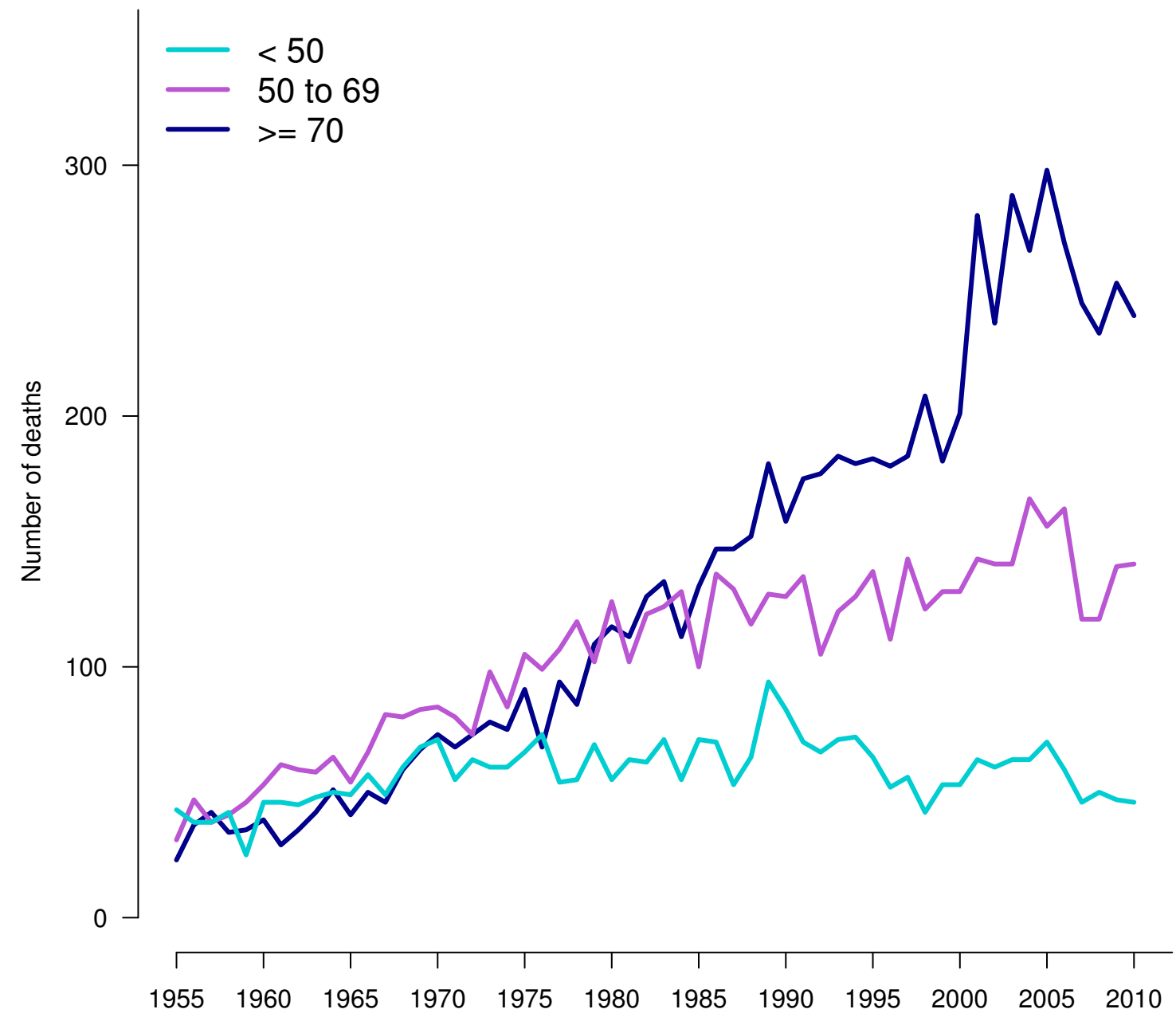
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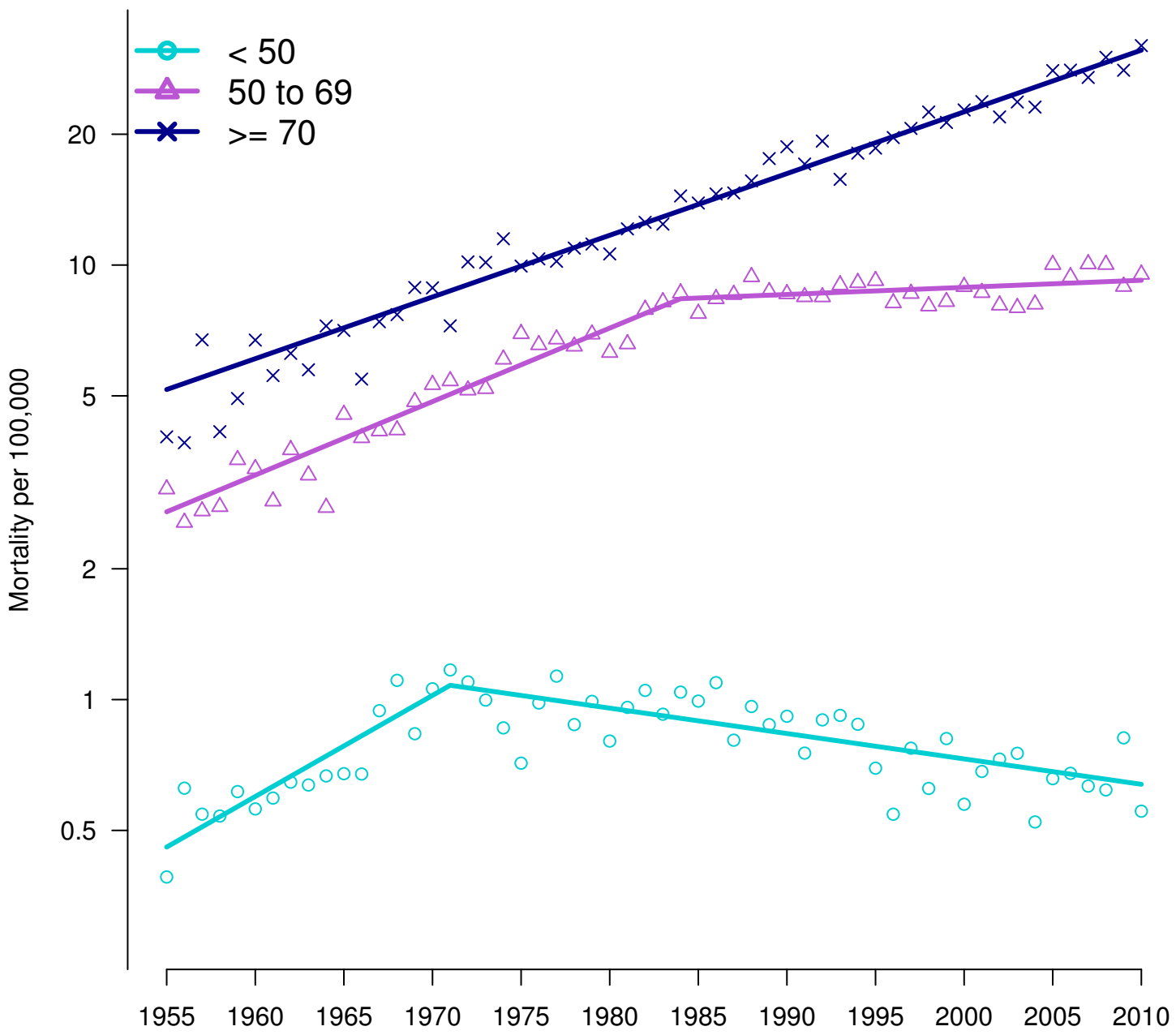
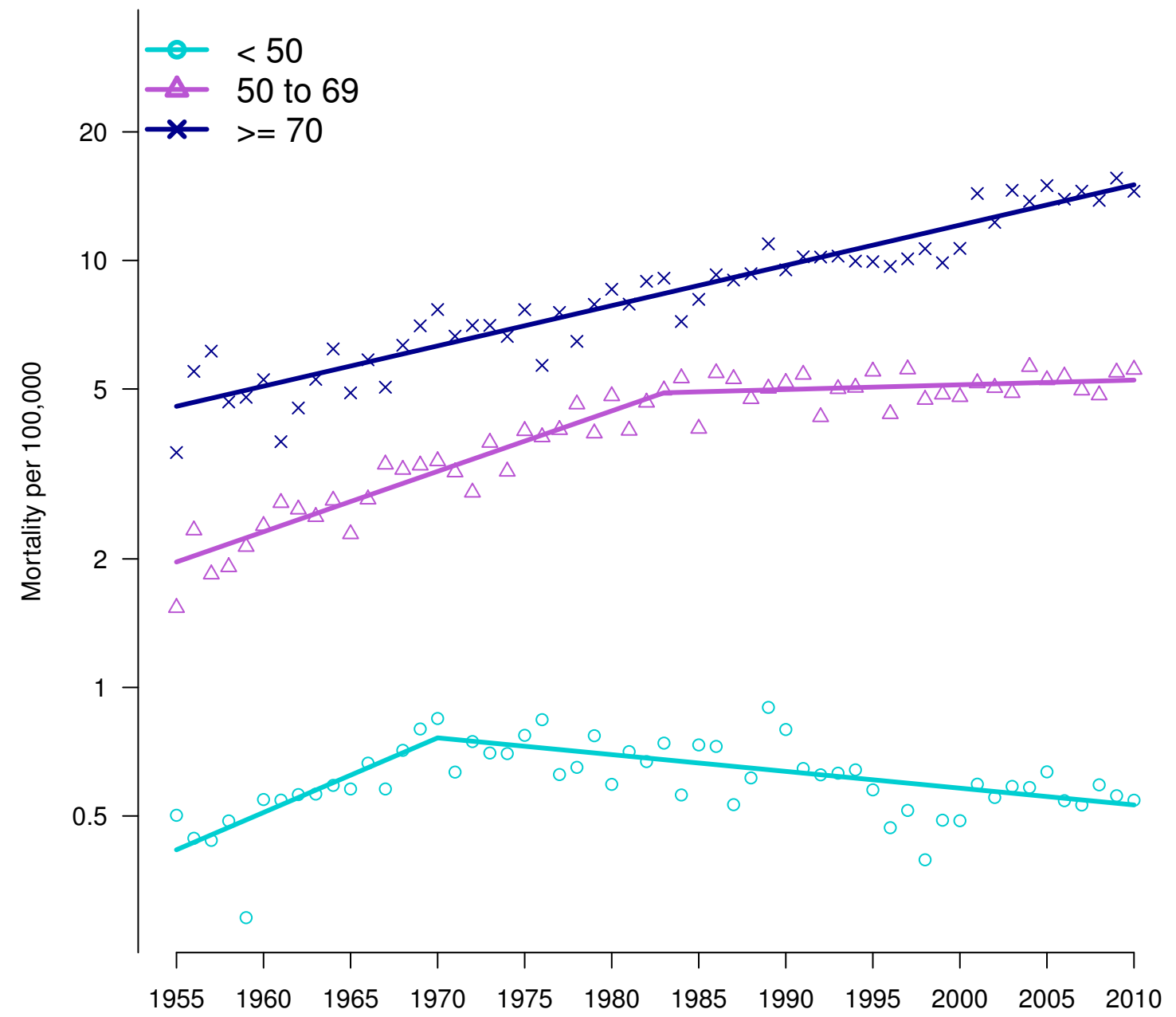
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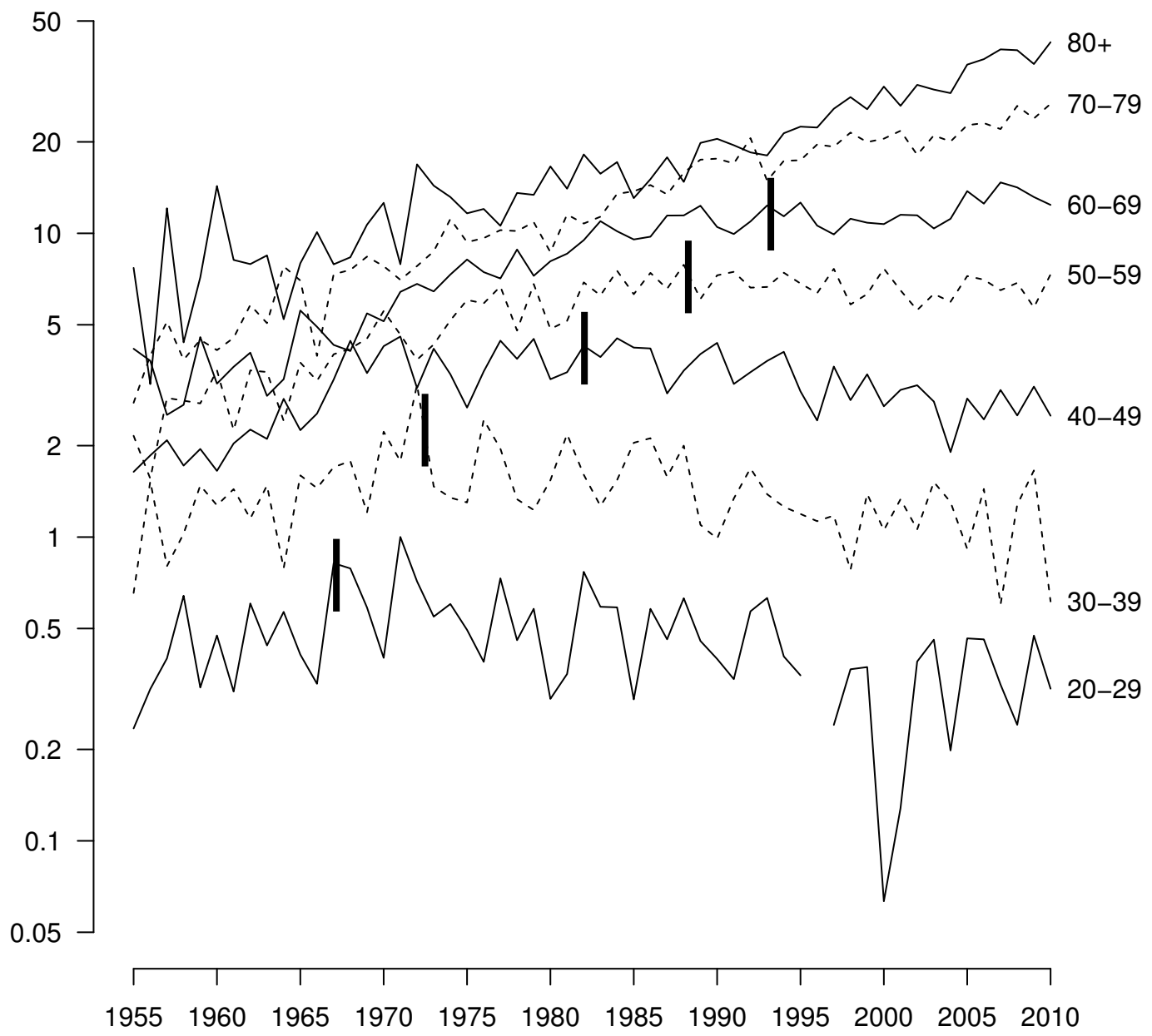
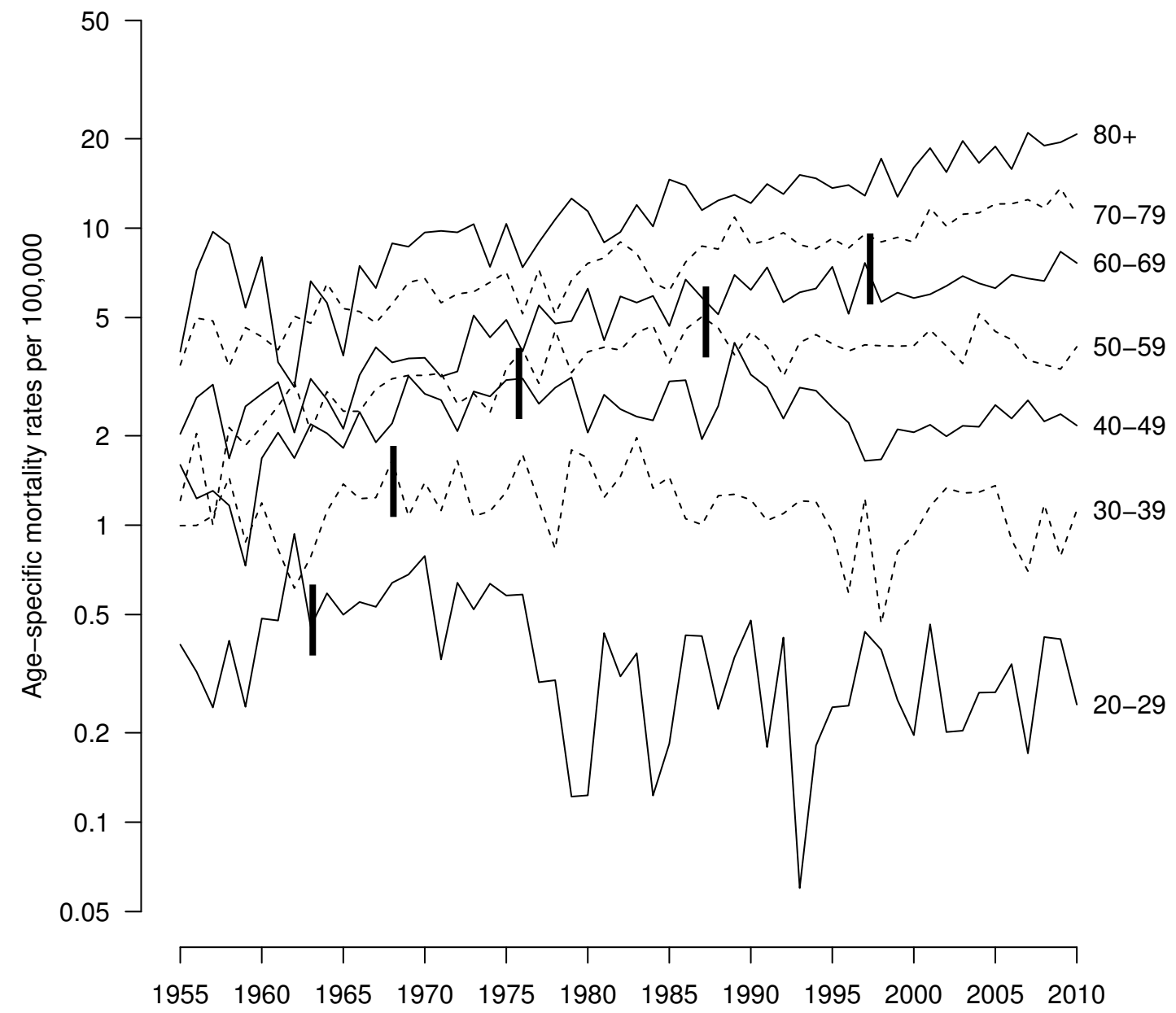
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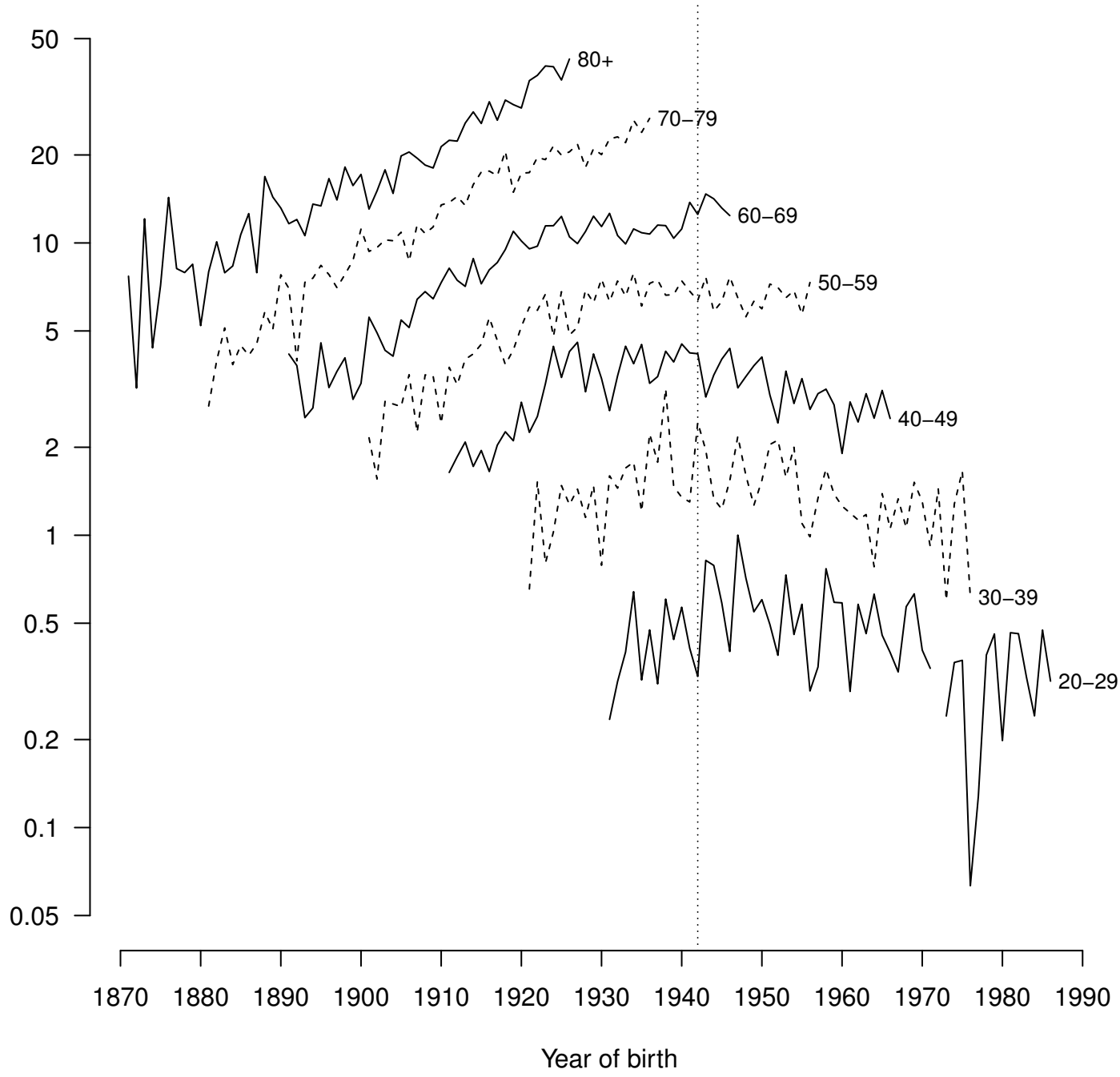
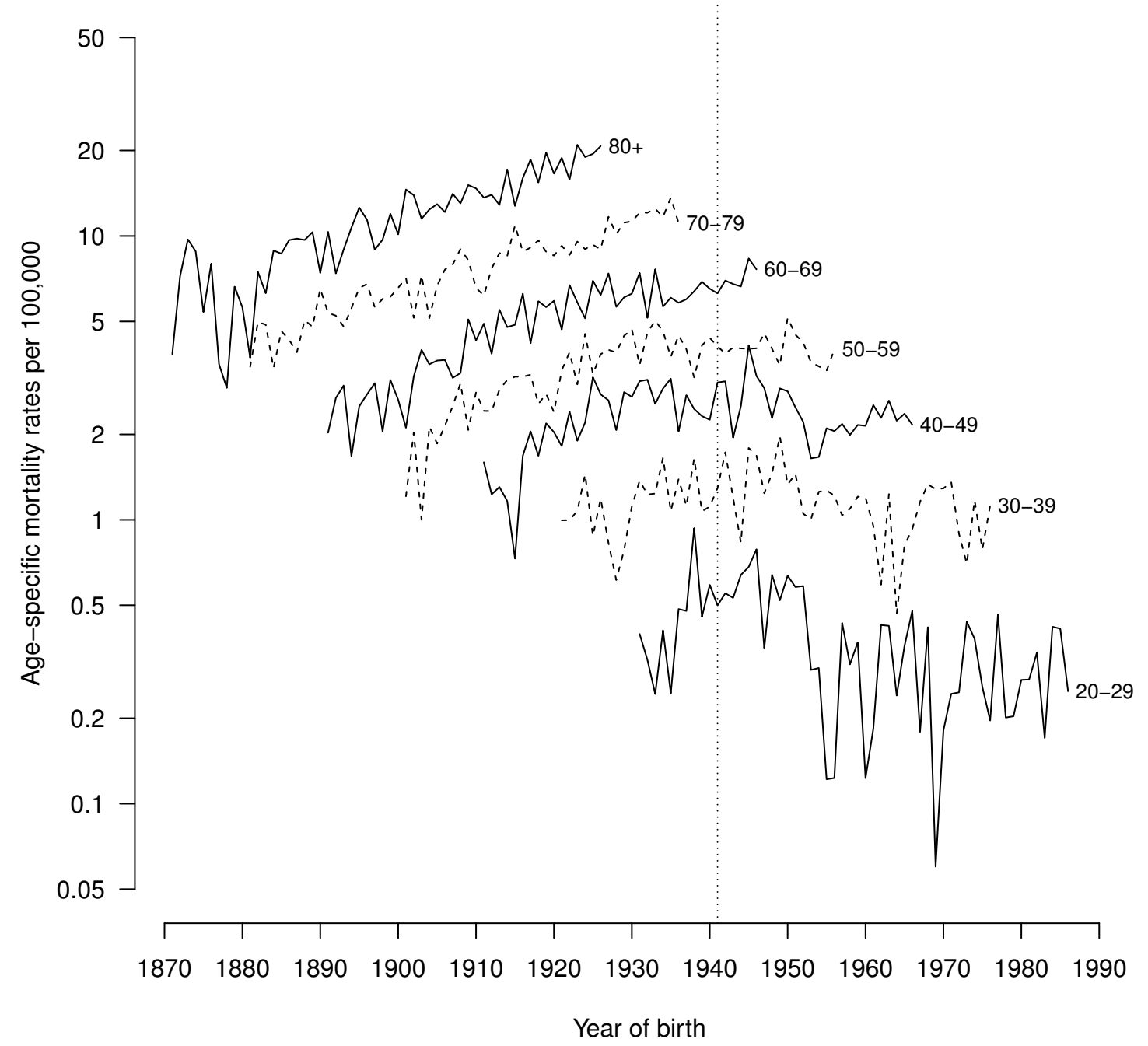


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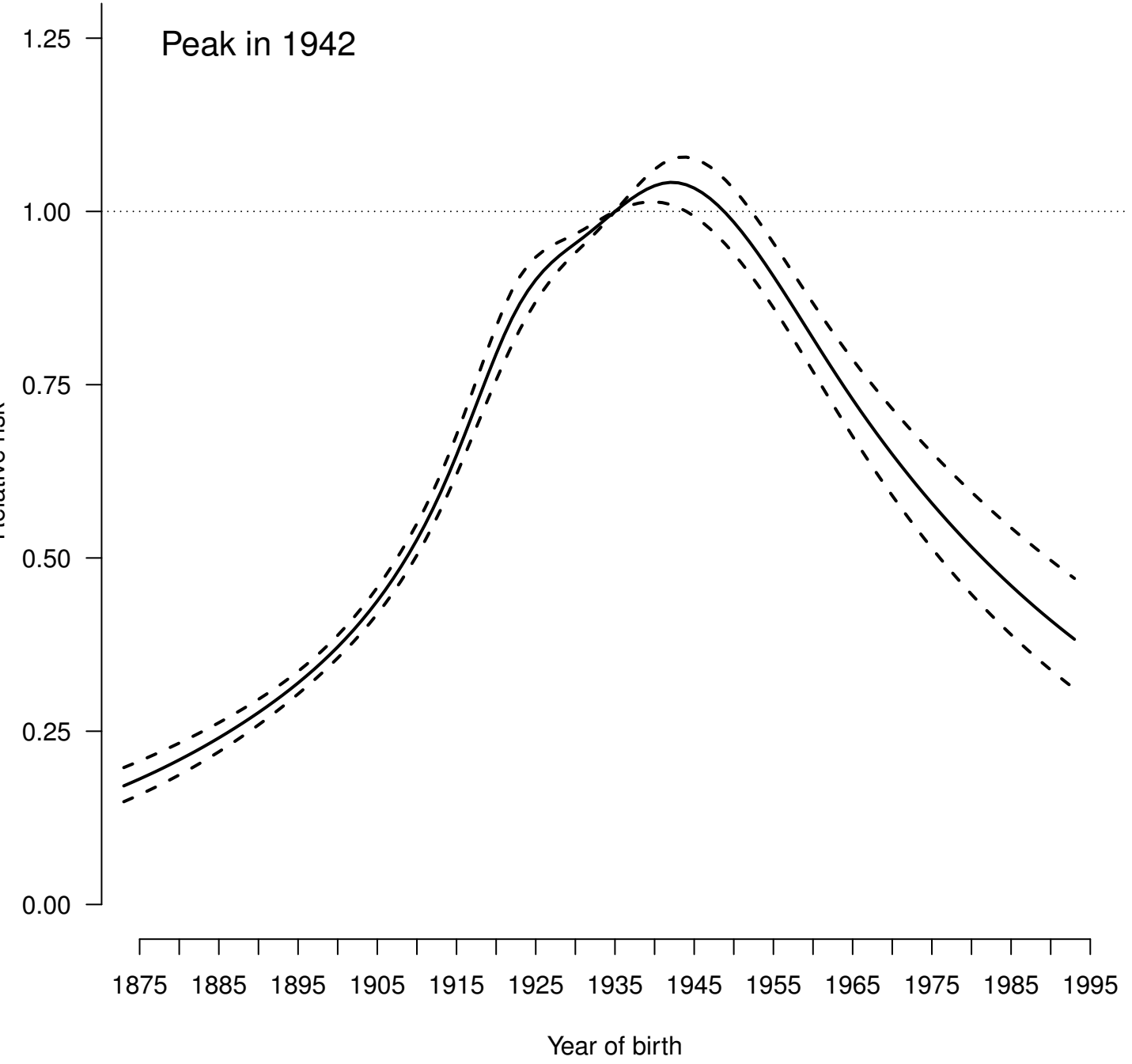


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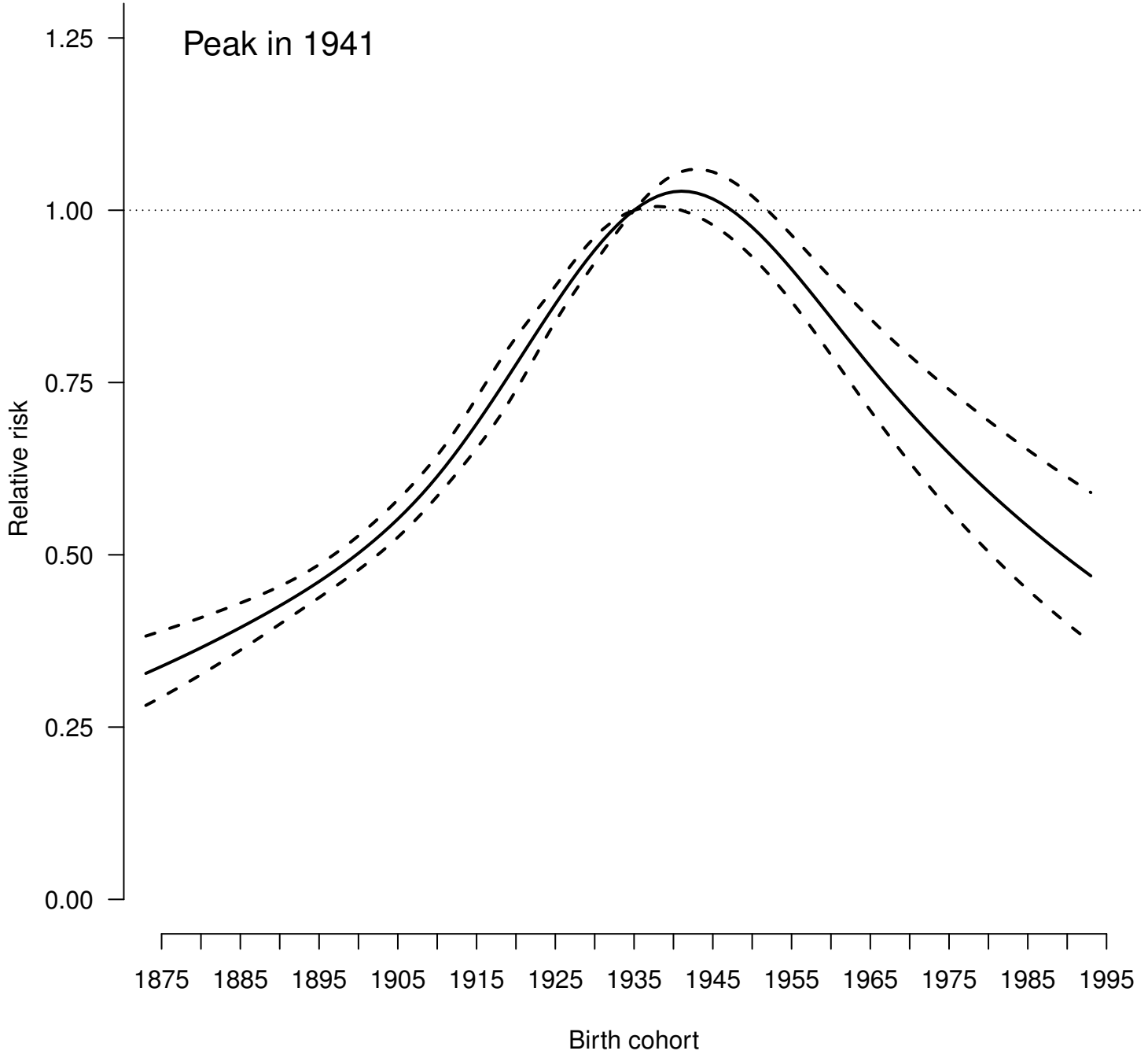
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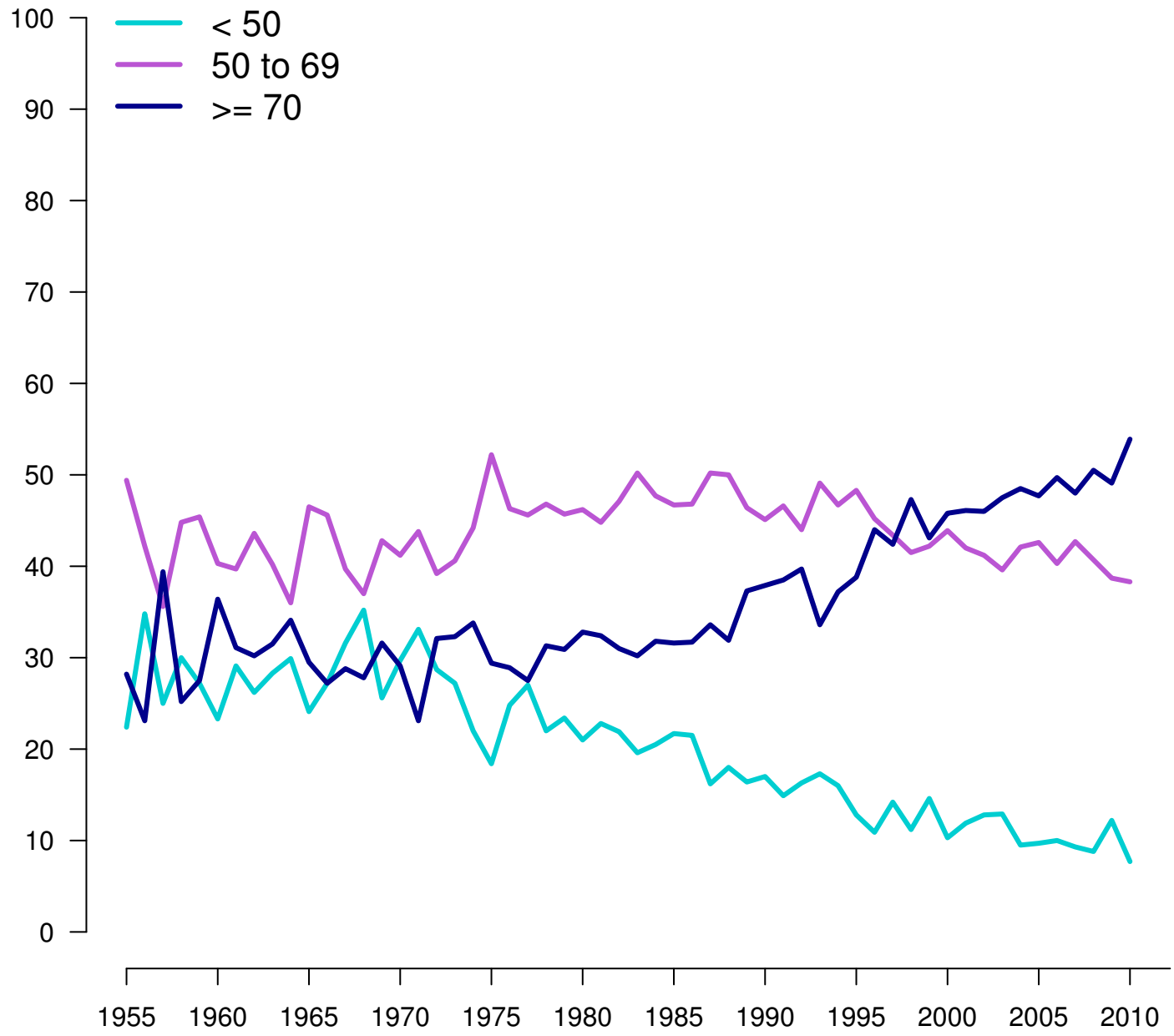
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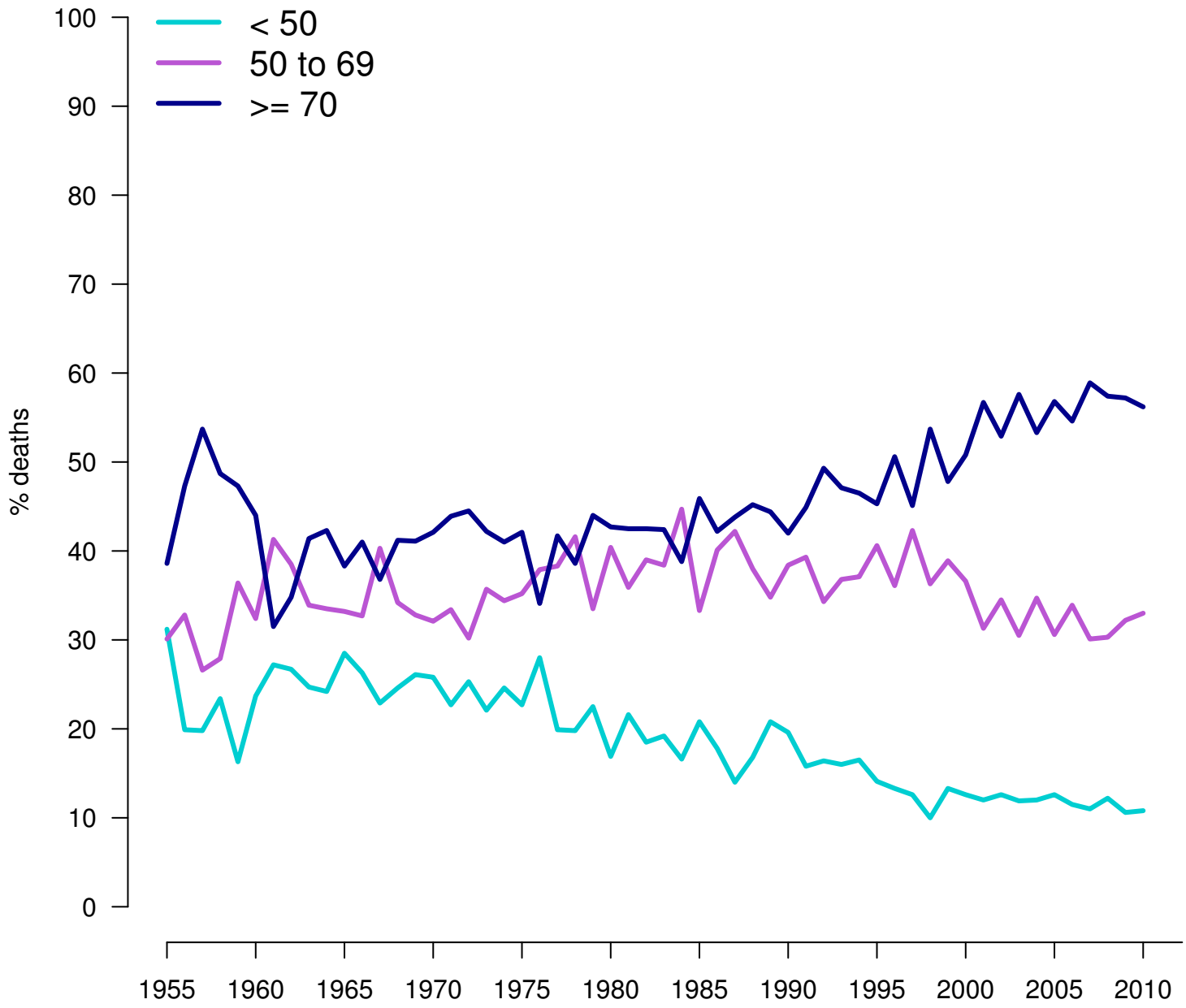
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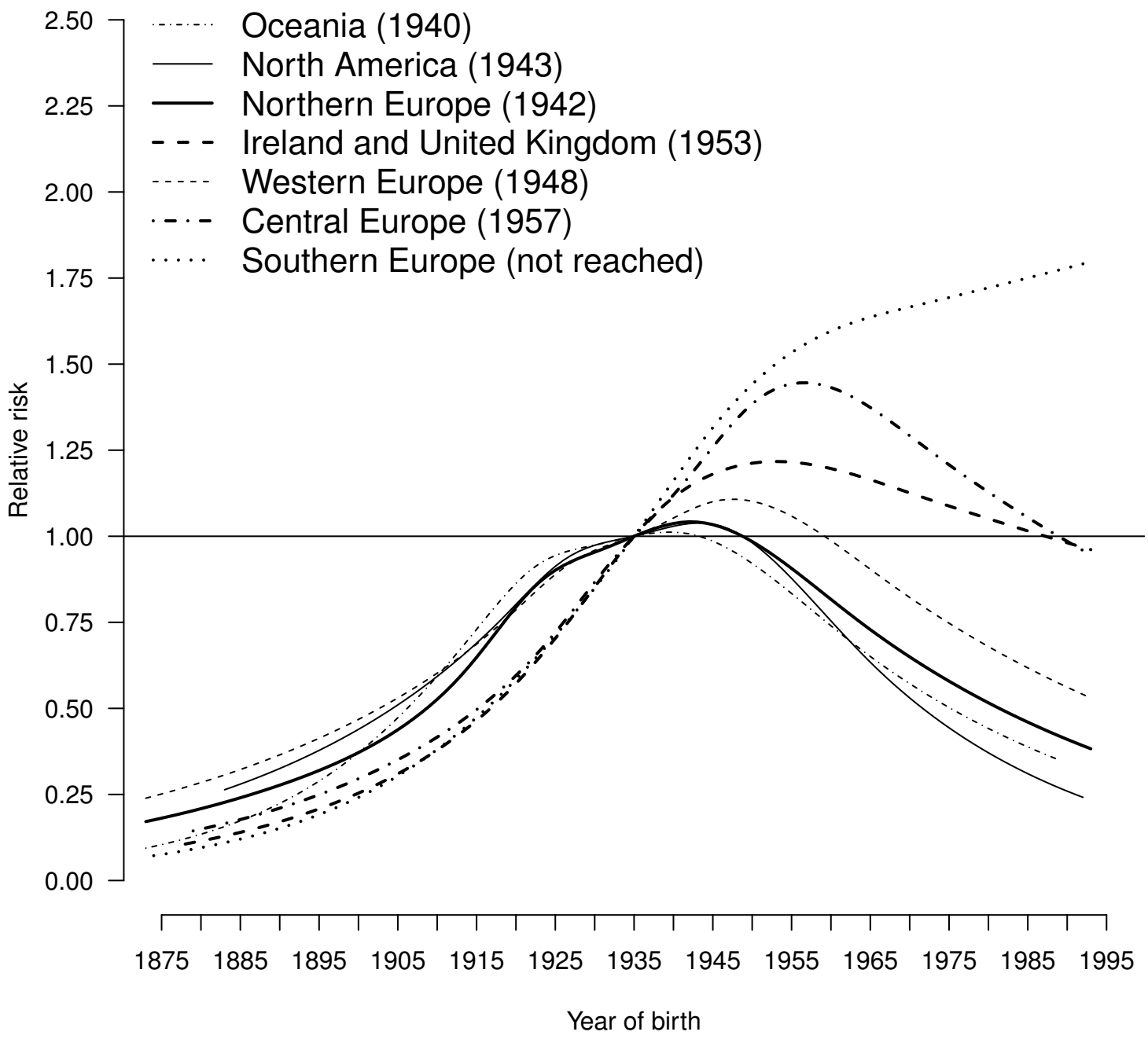


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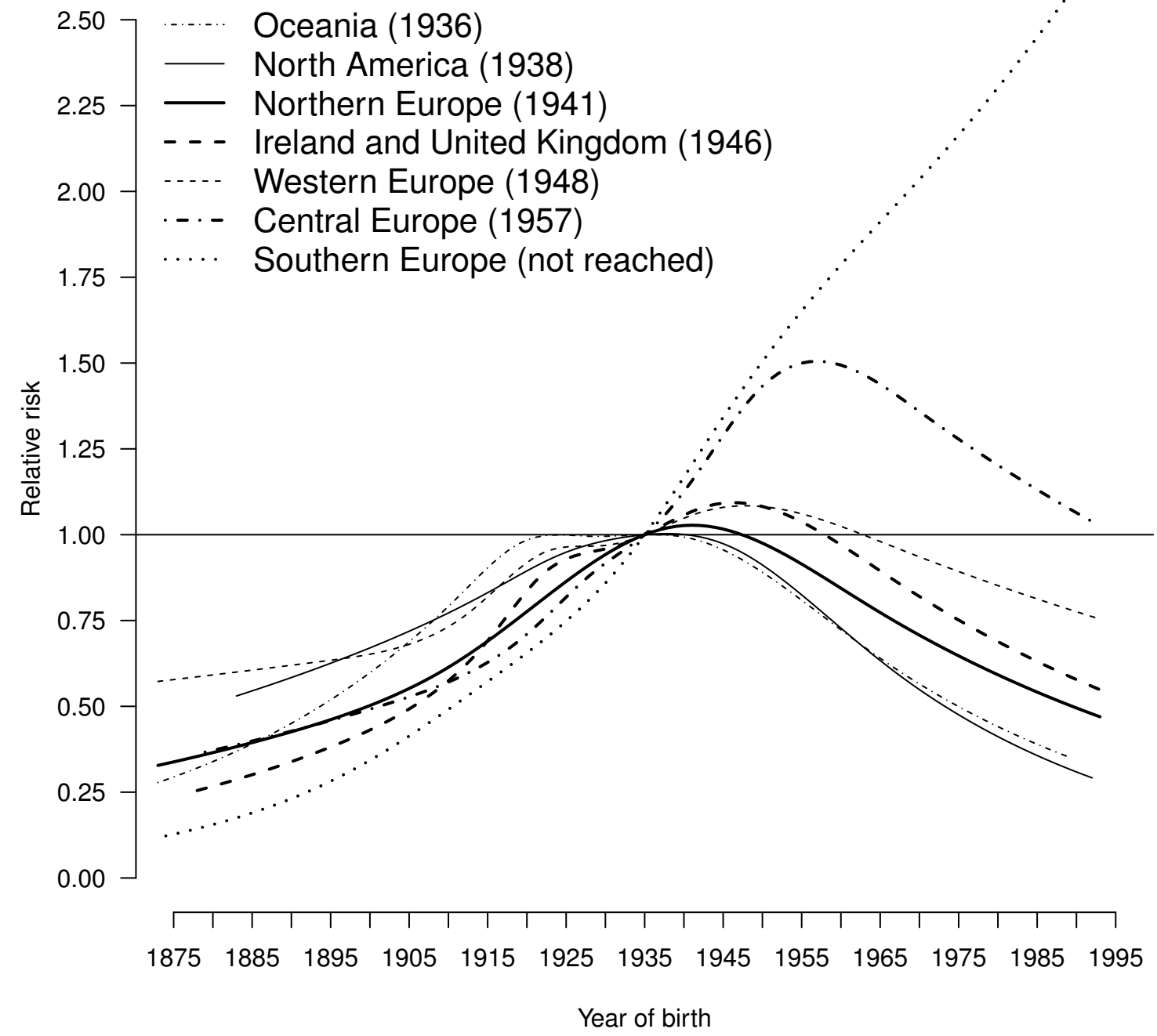


Figure

a



b



Conflict of Interest

Authors declare no conflict of interest

Supplementary materials to the article:

The forthcoming inexorable decline of cutaneous melanoma mortality in light-skinned populations

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Table S1 Joinpoint regression analysis of time trends of melanoma death after adjustment for age (World standard population).

APC: annual percent change

Region	Sex	Age	Trend 1		Trend 2 (if any)		Trend 3 (if any)		Trend 4 (if any)	
			Period	APC (95% CI)	Period	APC (95% CI)	Period	APC(95% CI)	Period	APC(95% CI)
Oceania	M	All	1955-1985	3.07 [2.77; 3.38]	1985-2006	0.24 [-0.10; 0.59]				
Oceania	M	<50	1955-1981	1.51 [0.98; 2.05]	1981-2006	-2.23 [-2.75; -1.72]				
Oceania	M	50-69	1955-1984	4.03 [3.45; 4.62]	1984-2006	-0.26 [-0.79; 0.27]				
Oceania	M	≥70	1955-1989	5.39 [4.86; 5.92]	1989-2006	2.70 [2.09; 3.31]				
Oceania	F	All	1955-1984	1.72 [1.34; 2.11]	1984-2006	-0.50 [-0.94; -0.07]				
Oceania	F	<50	1955-1984	0.36 [-0.25; 0.98]	1984-2006	-2.42 [-3.30; -1.53]				
Oceania	F	50-69	1955-1977	3.53 [2.66; 4.41]	1977-2006	-0.20 [-0.58; 0.18]				
Oceania	F	≥70	1955-1992	3.35 [2.88; 3.82]	1992-1995	-4.96 [-24.61; 19.83]	1995-2006	3.38 [1.85; 4.94]		
North America	M	All	1960-1979	3.07 [2.06; 4.08]	1979-1991	1.50 [1.09; 1.92]	1991-2009	-0.29 [-0.48; -0.10]		
North America	M	<50	1960-1981	1.76 [1.39; 2.12]	1981-1991	-1.31 [-2.19; -0.42]	1991-2009	-2.90 [-3.27; -2.53]		
North America	M	50-69	1960-1979	3.87 [2.44; 5.33]	1979-1991	2.02 [1.47; 2.57]	1991-2009	-0.39 [-0.62; -0.15]		
North America	M	≥70	1960-1994	3.61 [3.39; 3.82]	1994-2009	1.42 [1.06; 1.98]				
North America	F	All	1960-1983	1.66 [1.47; 1.85]	1983-2009	-0.63 [-0.75; -0.50]				
North America	F	<50	1960-1984	0.71 [0.45; 0.97]	1984-2009	-2.38 [-2.62; -2.14]				
North America	F	50-69	1960-1982	2.28 [1.98; 2.59]	1982-2009	-0.26 [-0.42; -0.10]				
North America	F	≥70	1960-1994	2.01 [1.81; 2.21]	1994-2009	0.08 [-0.33; 0.49]				
Northern Europe	M	All	1955-1971	4.69 [3.83; 5.55]	1971-1988	1.97 [1.36; 2.59]	1988-2002	-0.03 [-0.77; 0.71]	2002-2010	2.47 [0.91; 4.05]

Region	Sex	Age	Trend 1		Trend 2 (if any)		Trend 3 (if any)		Trend 4 (if any)	
			Period	APC (95% CI)	Period	APC (95% CI)	Period	APC(95% CI)	Period	APC(95% CI)
Northern Europe	M	<50	1955-1971	5.50 [3.79; 7.25]	1971-2010	-1.34 [-1.73; -0.94]				
Northern Europe	M	50-69	1955-1984	3.97 [3.49; 4.46]	1984-2010	0.38 [0.01; 0.74]				
Northern Europe	M	≥70	1955-2010	3.32 [3.16; 3.48]						
Northern Europe	F	All	1955-1969	3.74 [2.63; 4.85]	1969-1990	1.40 [0.89; 1.89]	1990-1996	-2.06 [-5.56; 1.56]	1996-2010	1.53 [0.73; 2.34]
Northern Europe	F	<50	1955-1970	4.11 [2.32; 5.93]	1970-2010	-0.90 [-1.27; -0.52]				
Northern Europe	F	50-69	1955-1983	3.31 [2.80; 3.82]	1983-2010	0.25 [-0.13; 0.64]				
Northern Europe	F	≥70	1955-2010	2.20 [2.00; 2.39]						
UK & Ireland	M	All	1955-1993	3.13 [2.95; 3.32]	1993-2010	1.82 [1.48; 2.16]				
UK & Ireland	M	<50	1955-1985	2.79 [2.31; 3.28]	1985-2010	0.31 [0.73; 0.12]				
UK & Ireland	M	50-69	1955-1995	3.67 [3.42; 3.92]	1995-2010	1.43 [0.85; 2.01]				
UK & Ireland	M	≥70	1955-1976	2.08 [0.86; 3.32]	1976-2010	4.79 [4.53; 5.06]				
UK & Ireland	F	All	1955-1982	2.98 [2.56; 3.40]	1982-2010	0.50 [0.25; 0.76]				
UK & Ireland	F	<50	1955-1979	2.36 [1.58; 3.14]	1979-2010	-1.14 [-1.55; -0.73]				
UK & Ireland	F	50-69	1955-1981	4.20 [3.55; 4.85]	1981-2010	0.63 [0.30; 0.96]				
UK & Ireland	F	≥70	1955-1970	1.17 [-0.81; 3.18]	1970-1994	4.22 [3.63; 4.80]	1994-2010	1.62 [0.96; 2.29]		
Western Europe	M	All	1955-1971	5.73 [4.57; 6.89]	1971-1992	1.84 [1.46; 2.21]	1992-1996	-1.76 [-6.26; 2.95]	1996-2010	1.08 [0.63; 1.52]
Western Europe	M	<50	1955-1972	4.92 [3.73; 6.13]	1972-1987	0.39 [-0.40; 1.19]	1987-2010	-1.42 [-1.74; -1.09]		
Western Europe	M	50-69	1955-1978	5.13 [4.41; 5.86]	1978-1993	1.54 [0.96; 2.12]	1993-1996	-2.77 [-11.99; 7.42]	1996-2010	1.17 [0.70; 1.63]

Region	Sex	Age	Trend 1		Trend 2 (if any)		Trend 3 (if any)		Trend 4 (if any)	
			Period	APC (95% CI)	Period	APC (95% CI)	Period	APC(95% CI)	Period	APC(95% CI)
Western Europe	M	≥70	1955-1971	6.58 [4.41; 8.79]	1971-1976	-2.73 [-13.33; 9.16]	1976-1991	4.00 [2.98; 5.03]	1991-2010	1.94 [1.57; 2.31]
Western Europe	F	All	1955-1970	5.43 [4.10; 6.79]	1970-1991	1.35 [0.95; 1.75]	1991-1998	-1.29 [-3.01; 0.46]	1998-2010	0.83 [0.20; 1.47]
Western Europe	F	<50	1955-1970	5.30 [3.53; 7.10]	1970-1993	0.15 [-0.33; 0.64]	1993-1998	-4.58 [-9.54; 0.64]	1998-2010	0.78 [-0.31; 1.88]
Western Europe	F	50-69	1955-1972	5.76 [4.28; 7.26]	1972-1989	1.77 [1.06; 2.48]	1989-1999	-1.01 [-2.17; 0.16]	1999-2010	0.84 [-0.05; 1.73]
Western Europe	F	≥70	1955-1993	2.52 [2.14; 2.89]	1993-2010	1.06 [0.59; 1.52]				
Central Europe	M	All	1961-1970	11.44 [8.21; 14.78]	1970-1981	3.19 [1.59; 4.81]	1981-1987	7.39 [5.14; 9.69]	1987-2010	1.32 [1.16; 1.49]
Central Europe	M	<50	1961-1991	4.17 [3.51; 4.83]	1991-2010	-1.19 [-1.85; -0.54]				
Central Europe	M	50-69	1961-1970	13.00 [6.62; 19.77]	1970-1989	5.30 [4.24; 6.38]	1989-2010	1.47 [1.19; 1.75]		
Central Europe	M	≥70	1961-1988	5.35 [4.17; 6.54]	1988-2010	3.00 [2.53; 3.46]				
Central Europe	F	All	1961-1964	32.84 [5.68; 66.99]	1964-1987	4.17 [3.59; 4.75]	1987-1999	1.63 [0.56; 1.72]	1999-2010	-0.44 [-1.17; 0.30]
Central Europe	F	<50	1961-1994	3.53 [2.85; 4.22]	1994-2010	-2.19 [-3.32; -1.04]				
Central Europe	F	50-69	1961-1964	39.41 [-1.48; 97.27]	1964-1989	4.29 [3.57; 5.01]	1989-2010	1.07 [0.69; 1.46]		
Central Europe	F	≥70	1961-1990	4.31 [3.59; 5.02]	1990-2010	1.28 [0.88; 1.69]				
Southern Europe	M	All	1956-1982	6.28 [5.78; 6.79]	1982-1992	3.48 [2.17; 4.81]	1992-2009	0.91 [0.47; 1.35]		
Southern Europe	M	<50	1956-1986	4.83 [4.31; 5.34]	1986-2009	-0.09 [-0.59; 0.40]				
Southern Europe	M	50-69	1956-1982	6.99 [6.25; 7.74]	1982-1992	3.71 [1.96; 5.49]	1992-2009	0.98 [0.42; 1.53]		
Southern Europe	M	≥70	1956-1988	6.79 [6.06; 7.52]	1988-2009	2.50 [2.03; 2.96]				
Southern Europe	F	All	1956-1989	5.28 [4.88; 5.69]	1989-2009	0.35 [-0.12; 0.83]				

Region	Sex	Age	Trend 1		Trend 2 (if any)		Trend 3 (if any)		Trend 4 (if any)	
			Period	APC (95% CI)	Period	APC (95% CI)	Period	APC(95% CI)	Period	APC(95% CI)
Southern Europe	F	<50	1956-1959	25.01 [-6.18; 66.56]	1959-1993	3.78 [3.37; 4.20]	1993-2009	-1.17 [-2.05; -0.28]		
Southern Europe	F	50-69	1956-1975	4.78 [3.41; 6.16]	1975-1981	9.98 [3.97; 16.35]	1981-1992	2.62 [1.09; 4.18]	1992-2009	0.79 [0.18; 1.39]
Southern Europe	F	≥70	1956-1989	6.35 [5.62; 7.07]	1989-2009	0.72 [0.15; 1.28]				

Table S2 Analysis of deviance for Age-Period-Cohort models

Region	Sex	Model	Residual degrees of freedom	Residual Deviance
Oceania	Men	Age	724	3808.5
		Age-drift	723	2483.0
		Age-Cohort	719	892.6
		Age-Period-Cohort	715	864.0
		Age-Period	719	2296.0
		Age-drift	723	2483.0
	Women	Age	724	1526.69
		Age-drift	723	1338.10
		Age-Cohort	719	775.96
		Age-Period-Cohort	715	755.60
		Age-Period	719	1254.41
		Age-drift	723	1338.10
North America	Men	Age	560	11964.8
		Age-drift	559	7857.8
		Age-Cohort	555	1492.2
		Age-Period-Cohort	551	1237.1
		Age-Period	555	6567.3
		Age-drift	559	7857.8
	Women	Age	560	3320.9
		Age-drift	559	3032.0
		Age-Cohort	555	1128.9
		Age-Period-Cohort	551	966.1
		Age-Period	555	2511.1
		Age-drift	559	3032.0
Northern Europe	Men	Age	799	3698.8
		Age-drift	798	1992.5
		Age-Cohort	794	955.7
		Age-Period-Cohort	790	892.4
		Age-Period	794	1823.3
		Age-drift	798	1992.5

Region	Sex	Model	Residual degrees of freedom	Residual Deviance
	Women	Age	799	1909.03
		Age-drift	798	1278.15
		Age-Cohort	794	935.74
		Age-Period-Cohort	790	887.78
		Age-Period	794	1196.94
		Age-drift	798	1278.15
Ireland and the United Kingdom	Men	Age	700	6438.4
		Age-drift	699	1815.5
		Age-Cohort	695	843.1
		Age-Period-Cohort	691	831.1
		Age-Period	695	1780.8
		Age-drift	699	1815.5
	Women	Age	700	3781.7
		Age-drift	699	1972.0
		Age-Cohort	695	964.0
		Age-Period-Cohort	691	911.3
		Age-Period	695	1780.4
		Age-drift	699	1972.0
Western Europe	Men	Age	799	4314.0
		Age-drift	798	2410.4
		Age-Cohort	794	1248.1
		Age-Period-Cohort	790	1082.3
		Age-Period	794	1980.8
		Age-drift	798	2410.4
	Women	Age	799	2433.1
		Age-drift	798	1745.5
		Age-Cohort	794	1361.2
		Age-Period-Cohort	790	1083.1
		Age-Period	794	1369.0
		Age-drift	798	1745.5
Central Europe	Men	Age	559	4099.8

Region	Sex	Model	Residual degrees of freedom	Residual Deviance
		Age-drift	558	1537.4
		Age-Cohort	554	914.6
		Age-Period-Cohort	550	701.8
		Age-Period	554	1162.0
		Age-drift	558	1537.4
	Women	Age	559	2572.76
		Age-drift	558	1188.98
		Age-Cohort	554	941.74
		Age-Period-Cohort	550	643.74
		Age-Period	554	818.22
		Age-drift	558	1188.98
	Southern Europe	Men	Age	740
Age-drift			739	2241.2
Age-Cohort			735	1350.4
Age-Period-Cohort			731	922.8
Age-Period			735	1453.8
Age-drift			739	2241.2
Women		Age	740	6574.7
		Age-drift	739	1956.0
		Age-Cohort	735	1566.5
		Age-Period-Cohort	731	963.9
		Age-Period	735	1057.8
		Age-drift	739	1956.0

Figure S1a: Absolute numbers of melanoma deaths by age (<50; 50 to 69; ≥70) in Oceania

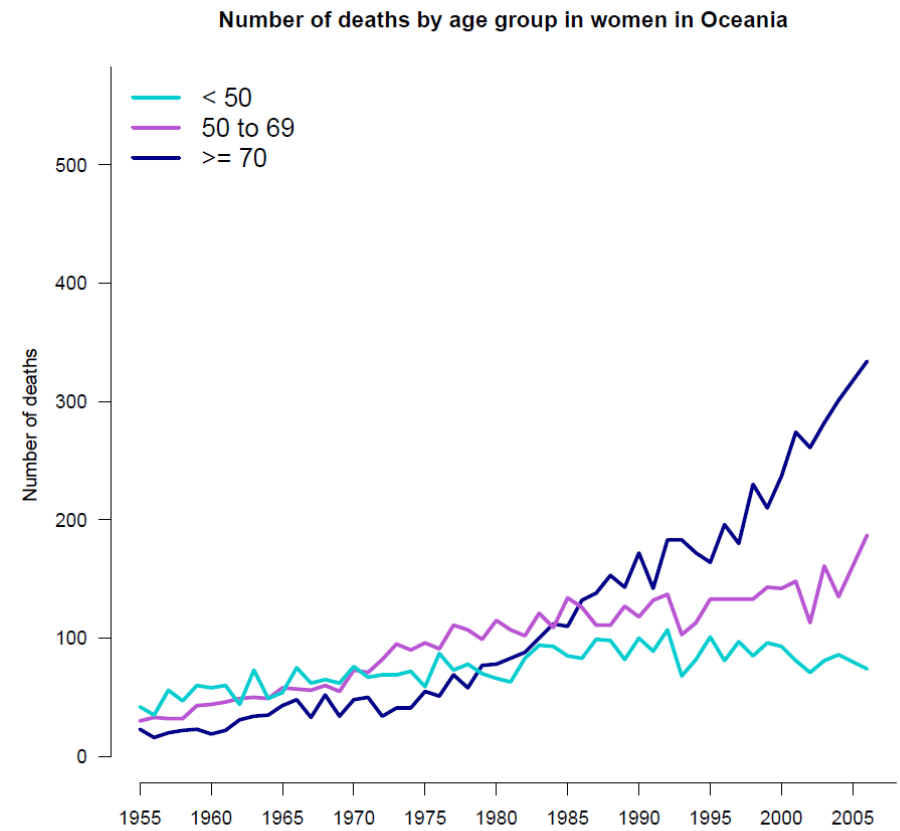
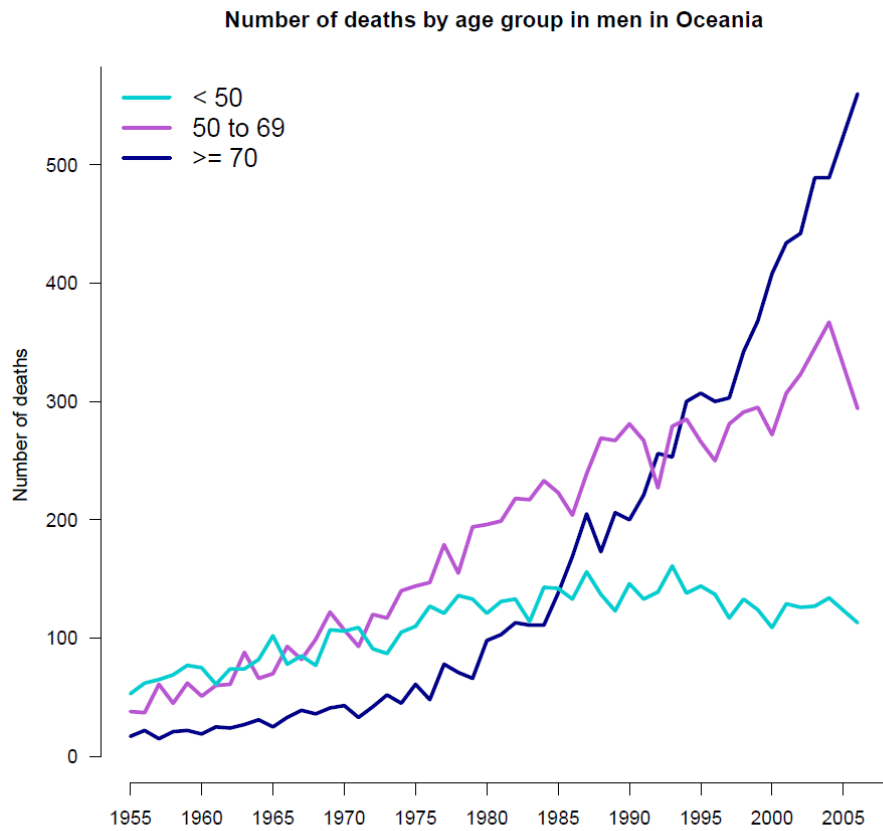


Figure S1b: Absolute numbers of melanoma deaths by age (<50; 50 to 69; ≥70) in North America

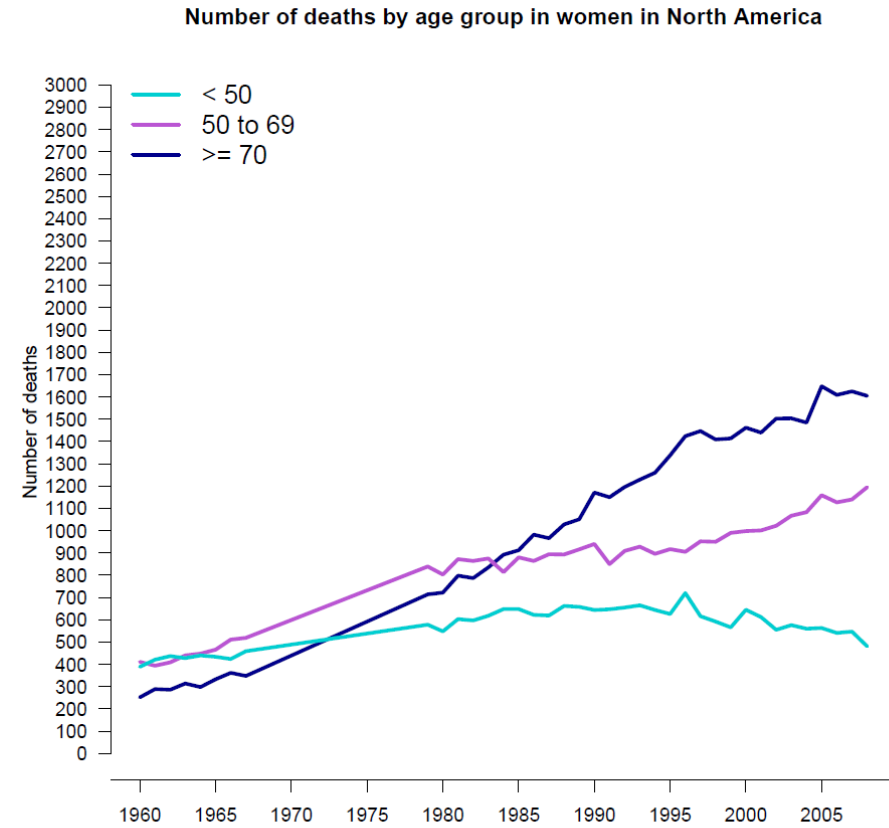
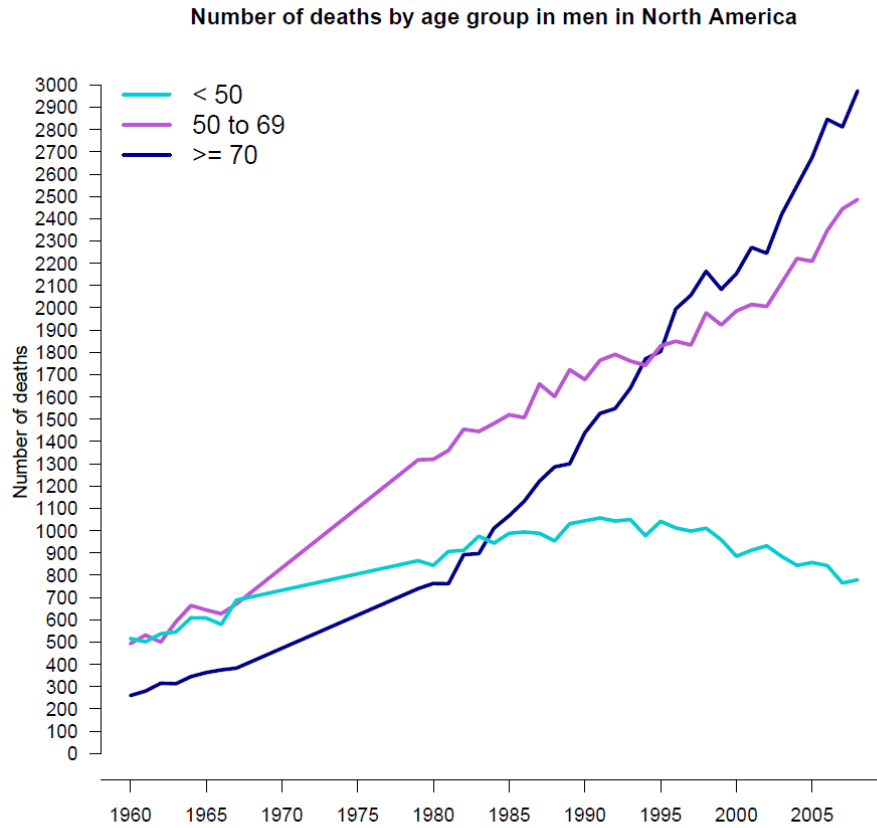


Figure S1c: Absolute numbers of melanoma deaths by age (<50; 50 to 69; ≥70) in Northern Europe

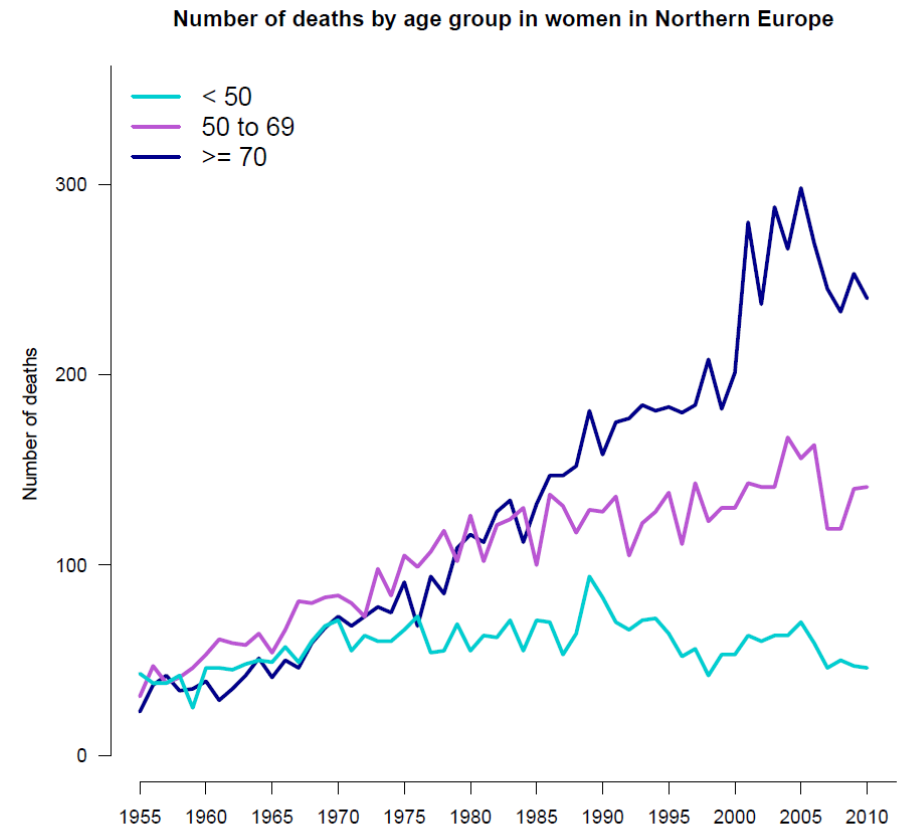
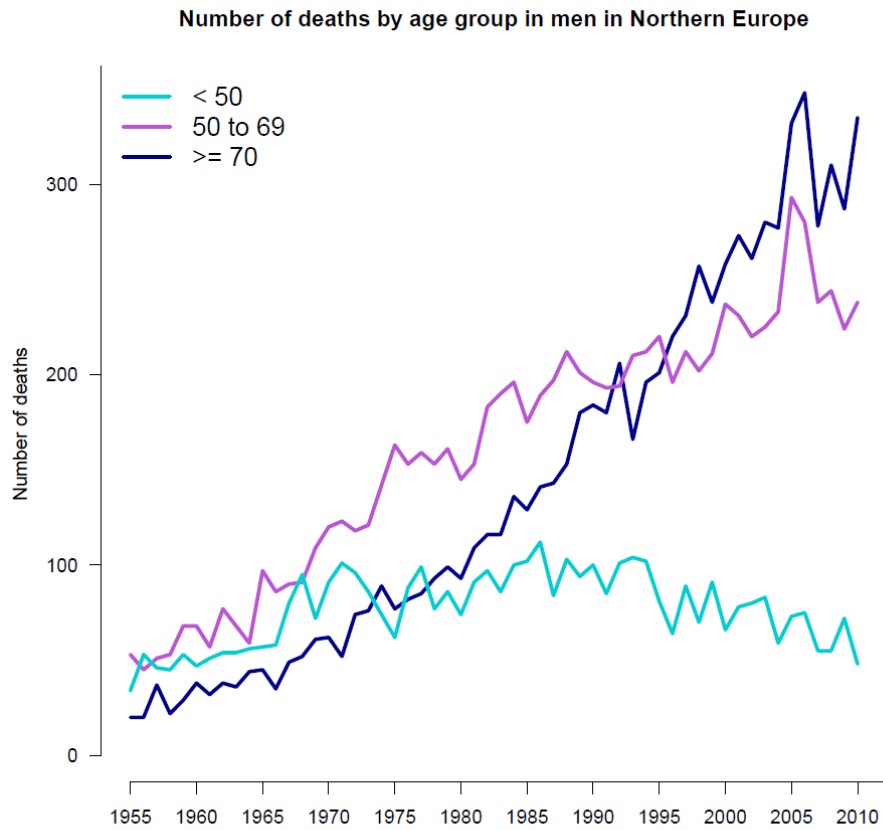


Figure S1d: Absolute numbers of melanoma deaths by age (<50; 50 to 69; ≥70) in Ireland and United Kingdom

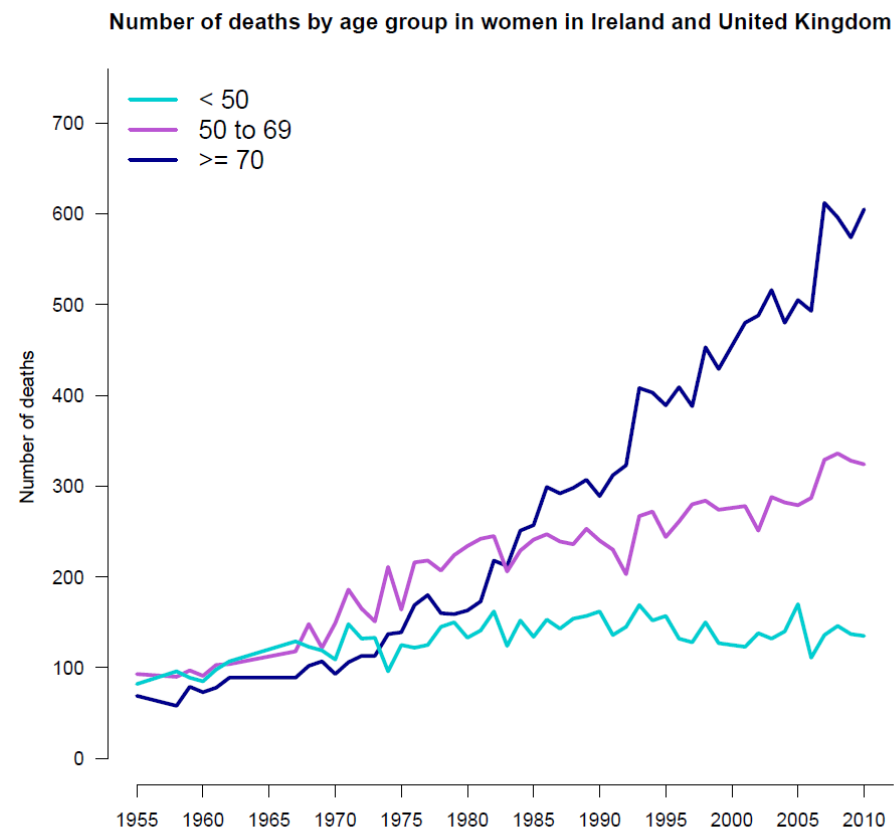
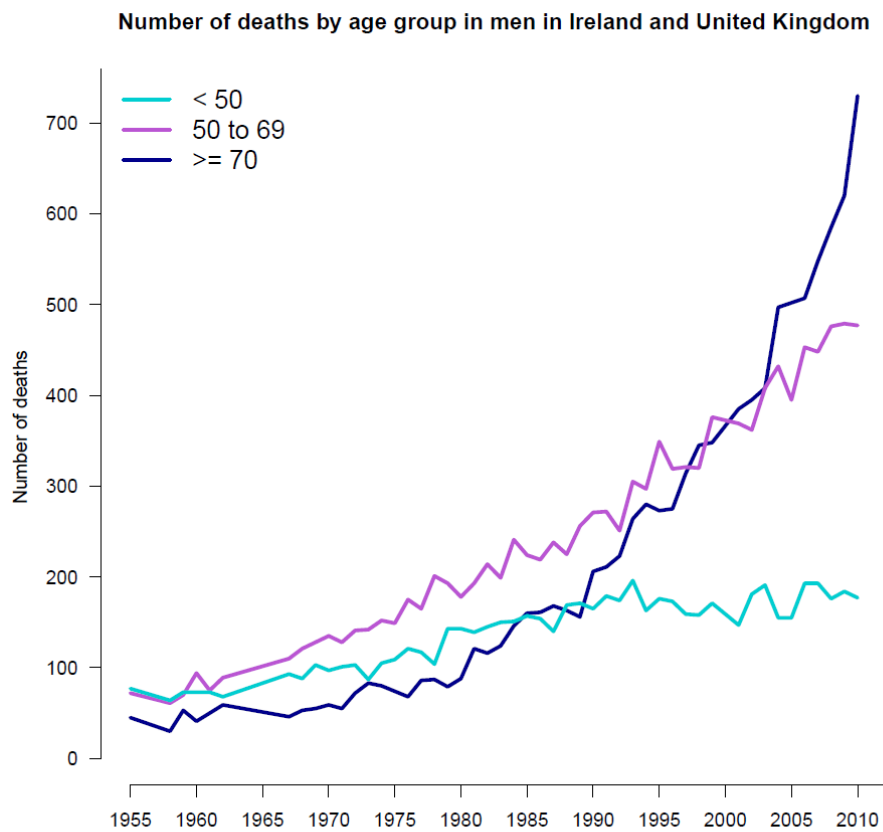
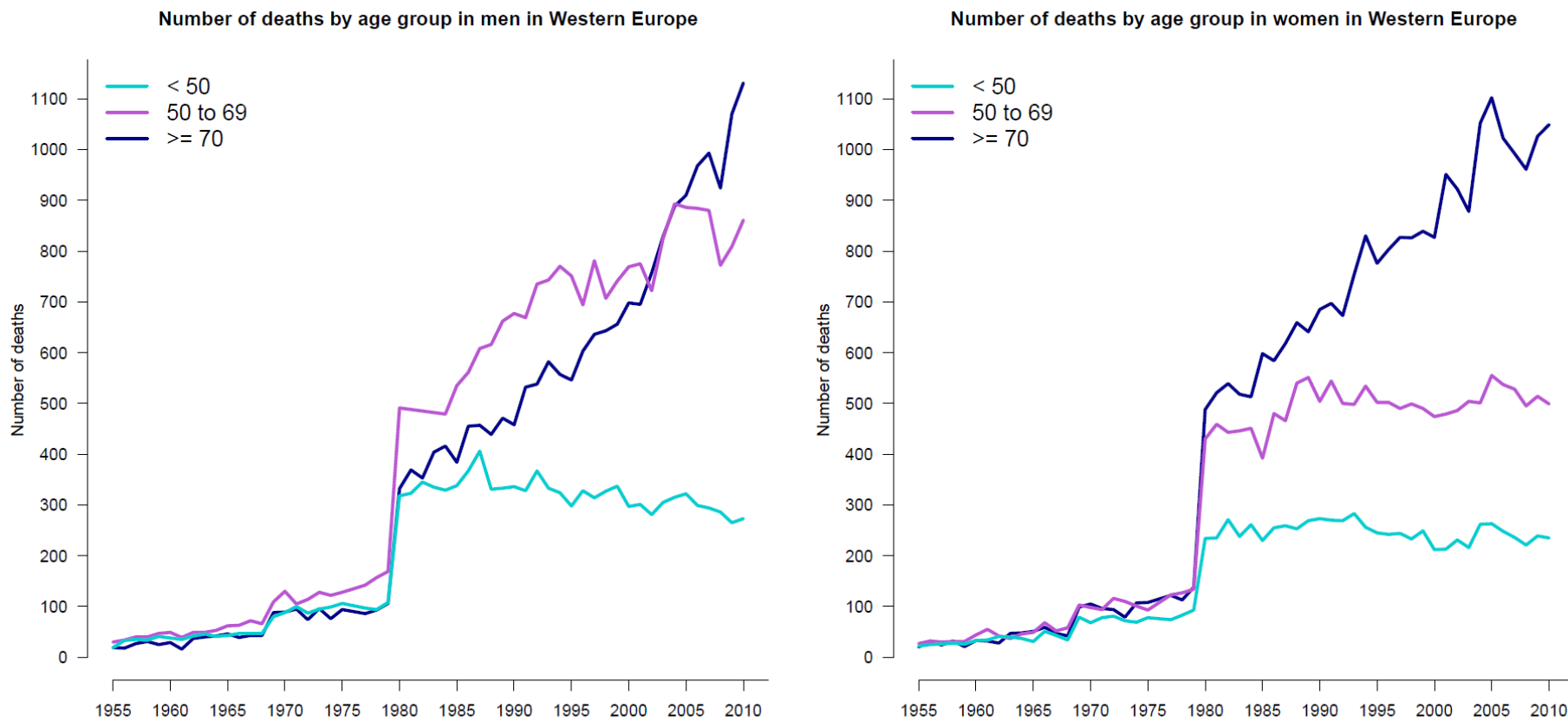


Figure S1e: Absolute numbers of melanoma deaths by age (<50; 50 to 69; ≥70) in Western Europe



Note: the sudden increase of 1980 in Western Europe was due to the introduction of mortality data of the former German Federal Republic (GFR) and the German Democratic Republic (GDR). Mortality data in the Germany (GDR and GFR) did not exist before 1980.

Figure S1f: Absolute numbers of melanoma deaths by age (<50; 50 to 69; ≥70) in Central Europe

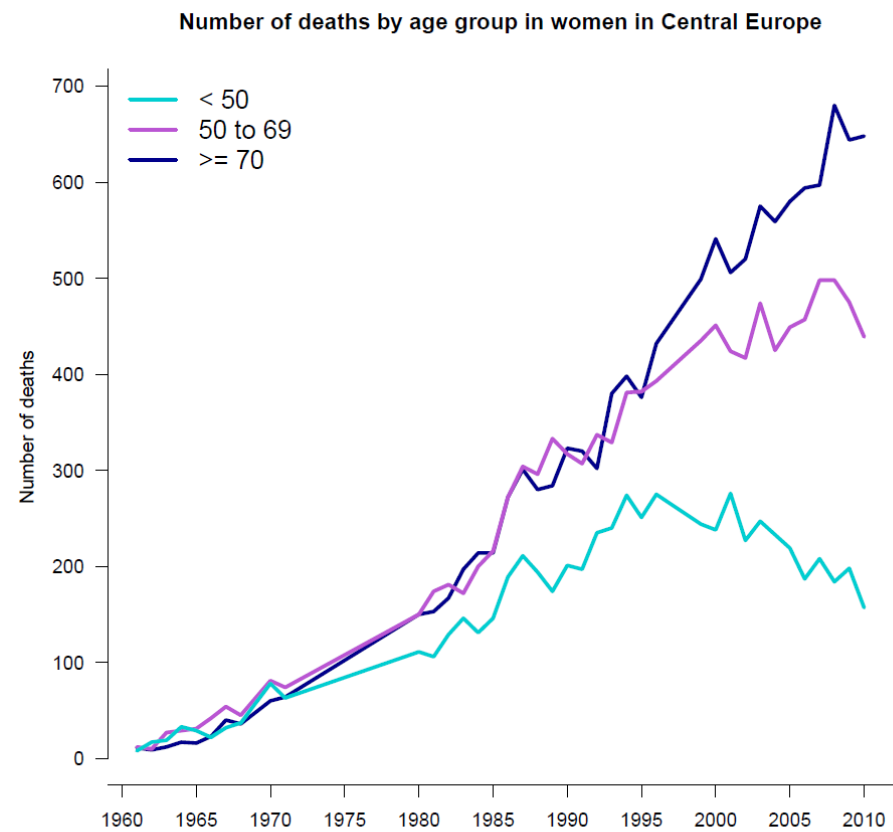
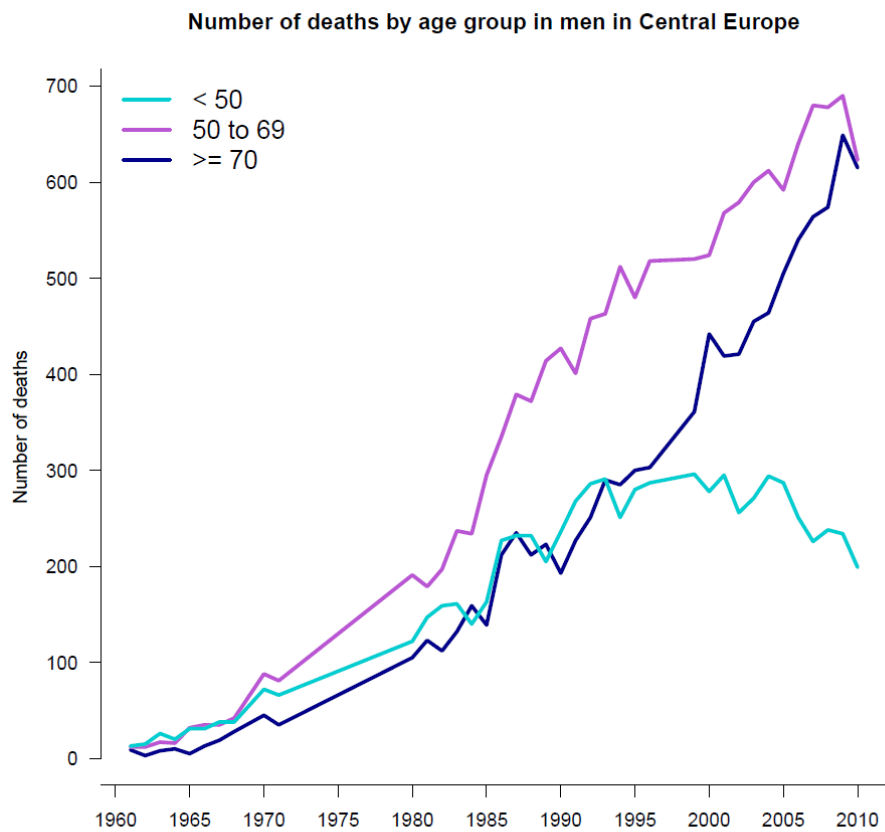


Figure S1g: Absolute numbers of melanoma deaths by age (<50; 50 to 69; ≥70) in Southern Europe

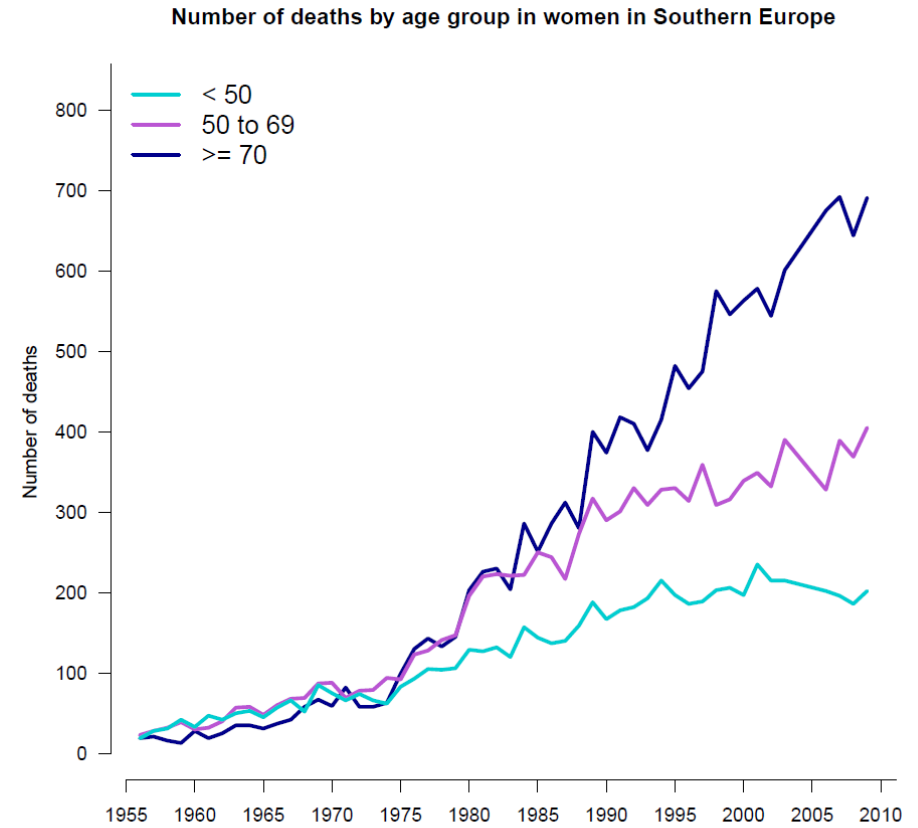
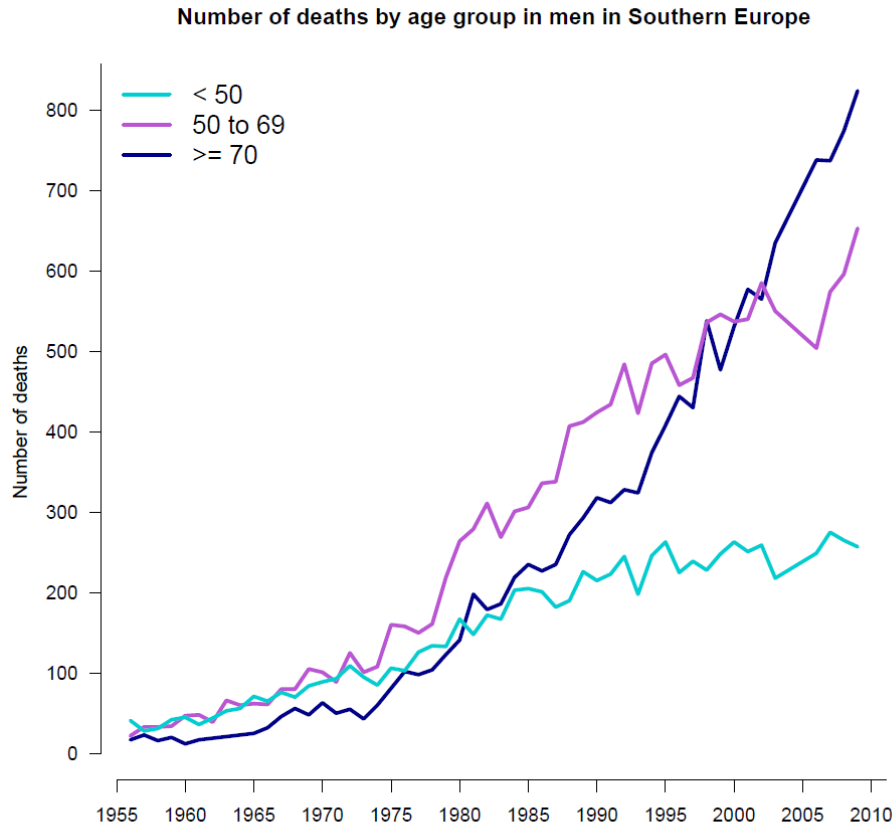


Figure S2a: melanoma mortality by age (<50; 50 to 69; ≥70) and joinpoint modelling in Oceania

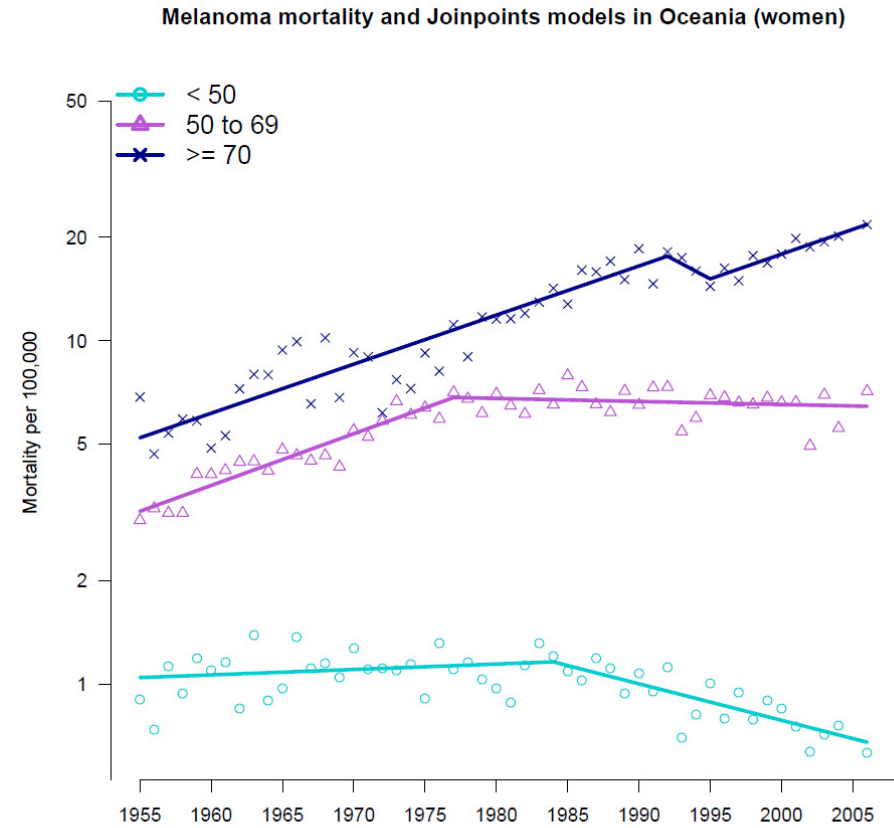
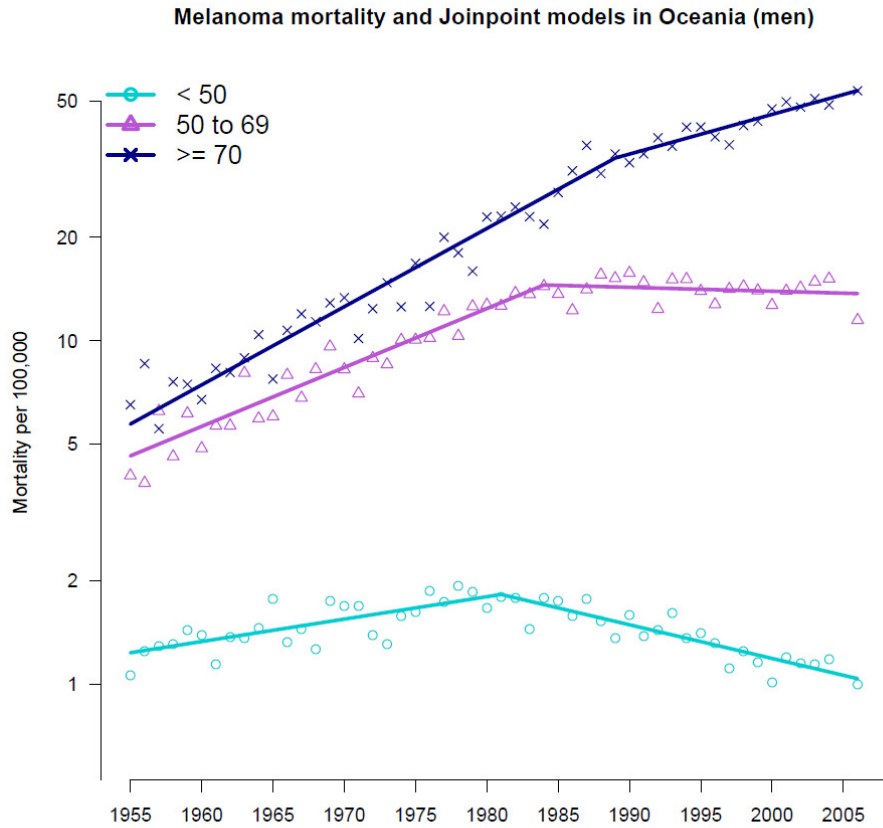


Figure S2b: melanoma mortality by age (<50; 50 to 69; ≥70) and joinpoint modelling in North America

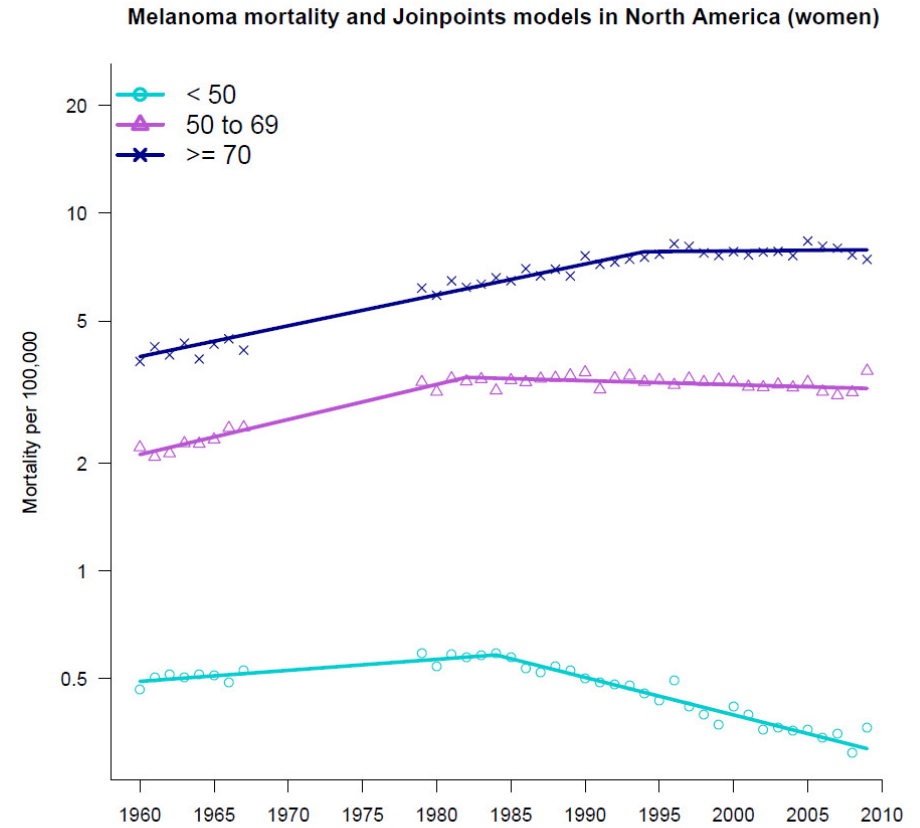
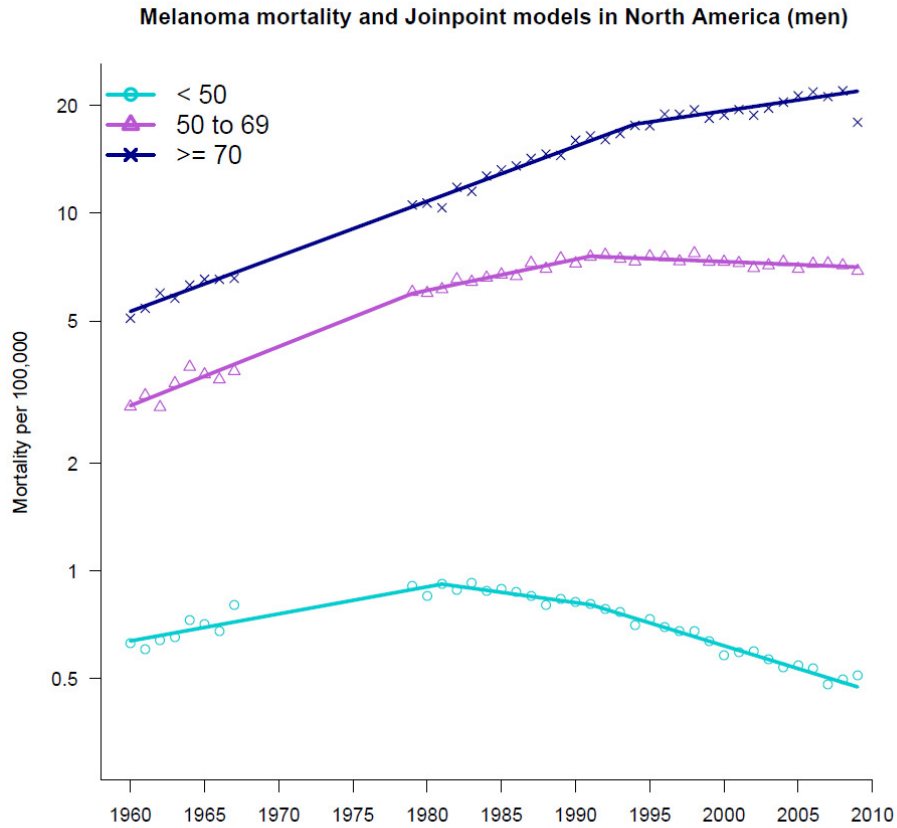


Figure S2c: melanoma mortality by age (<50; 50 to 69; ≥70) and joinpoint modelling in Northern Europe

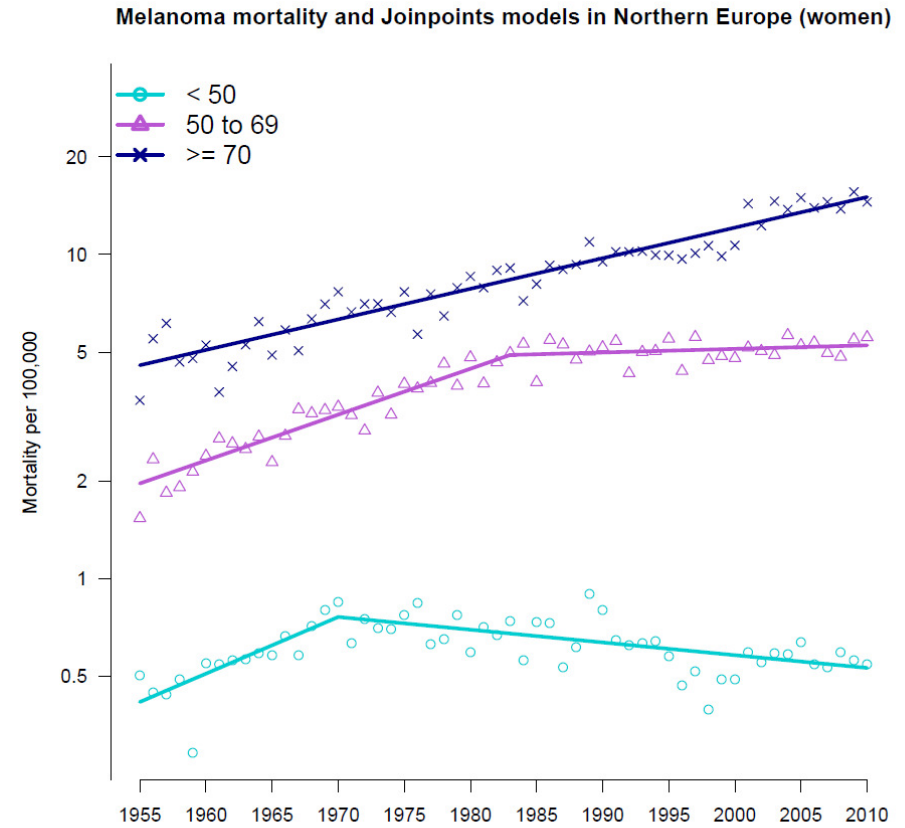
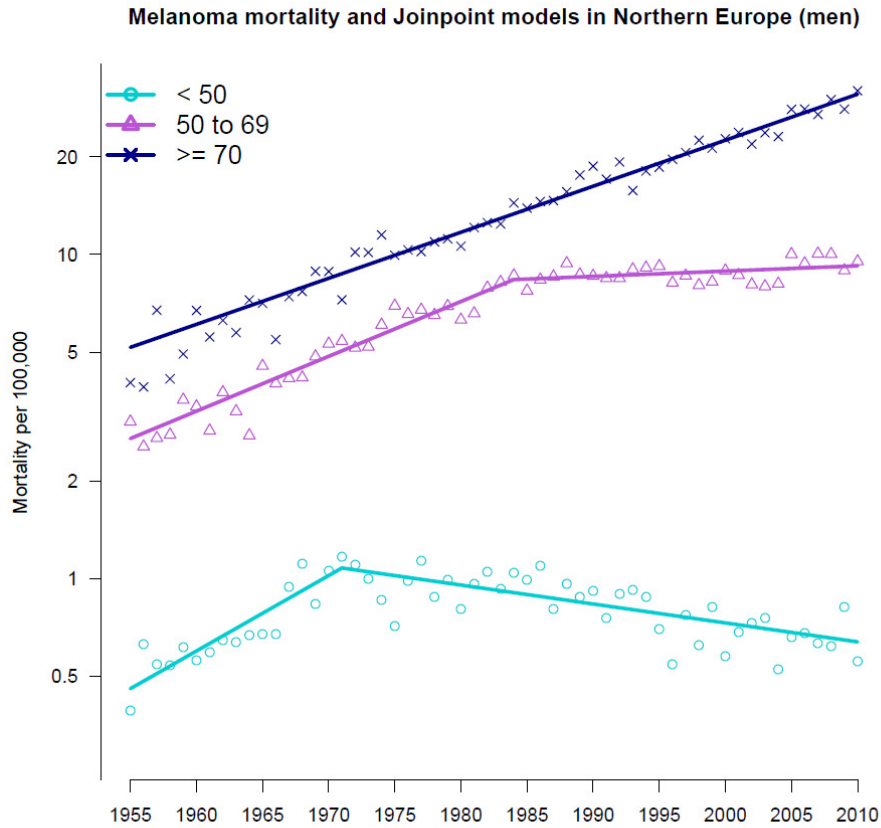


Figure S2d: melanoma mortality by age (<50; 50 to 69; ≥70) and joinpoint modelling in Ireland and United Kingdom

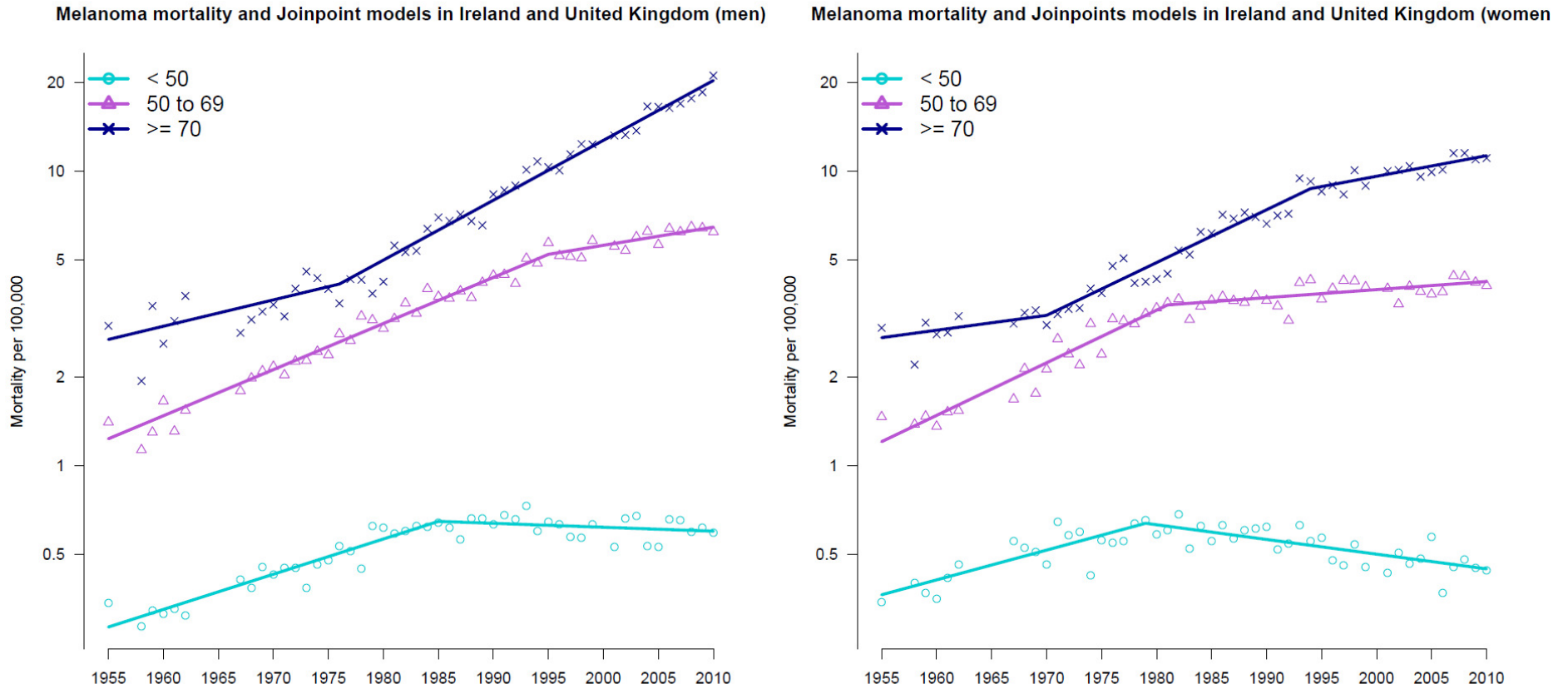


Figure S2e: melanoma mortality by age (<50; 50 to 69; ≥70) and joinpoint modelling in Western Europe

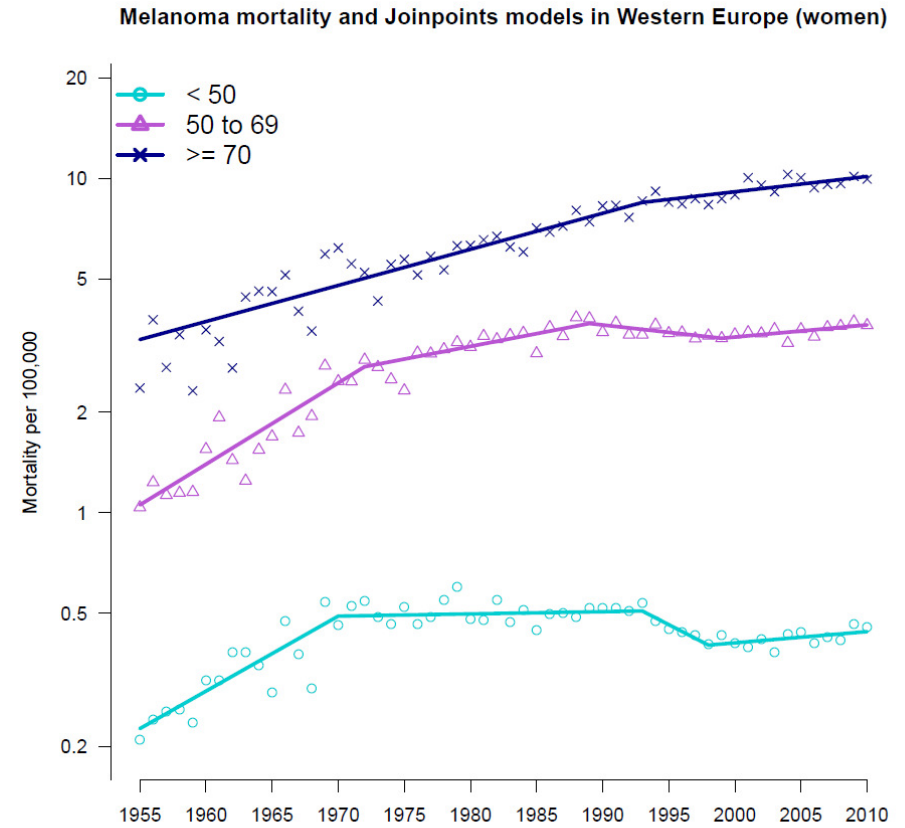
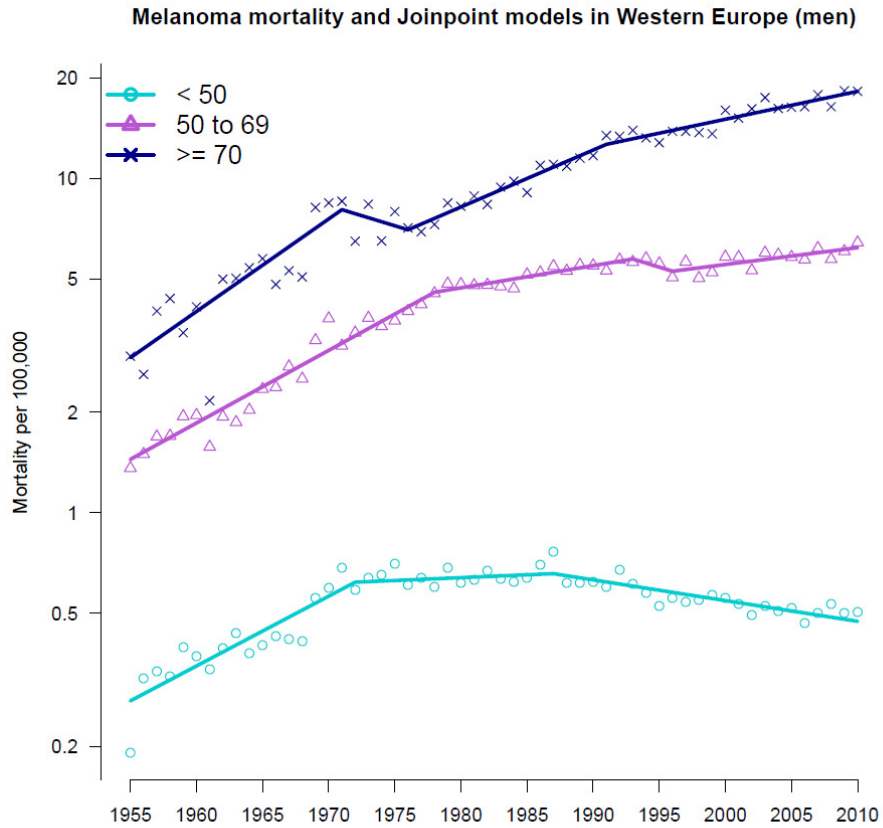


Figure S2f: melanoma mortality by age (<50; 50 to 69; ≥70) and joinpoint modelling in Central Europe

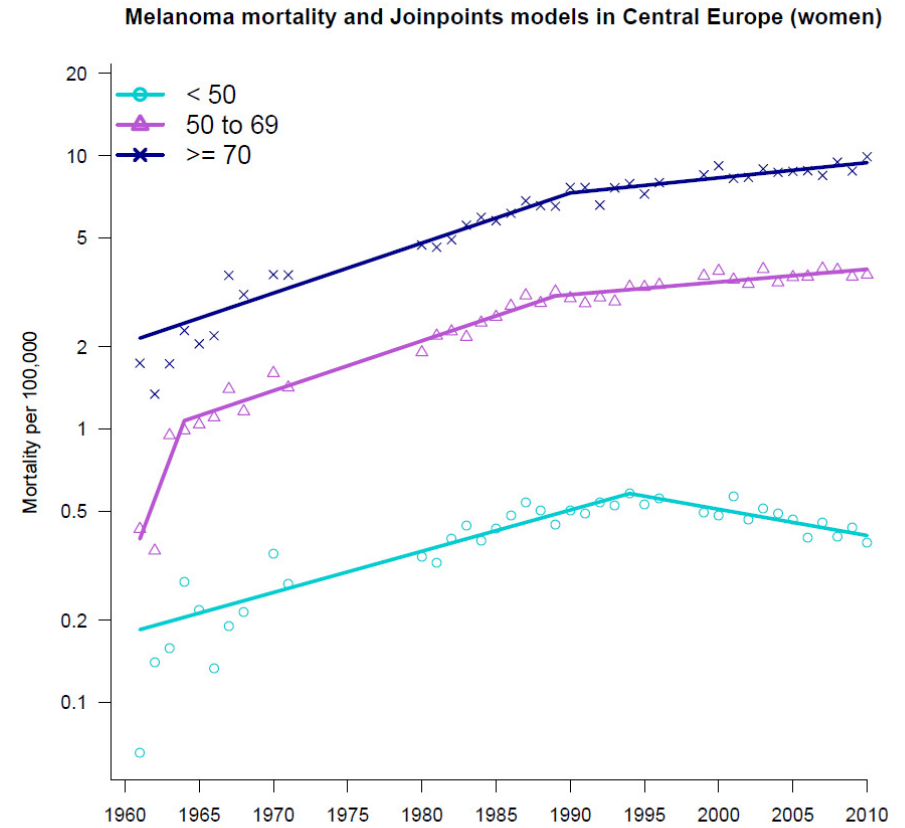
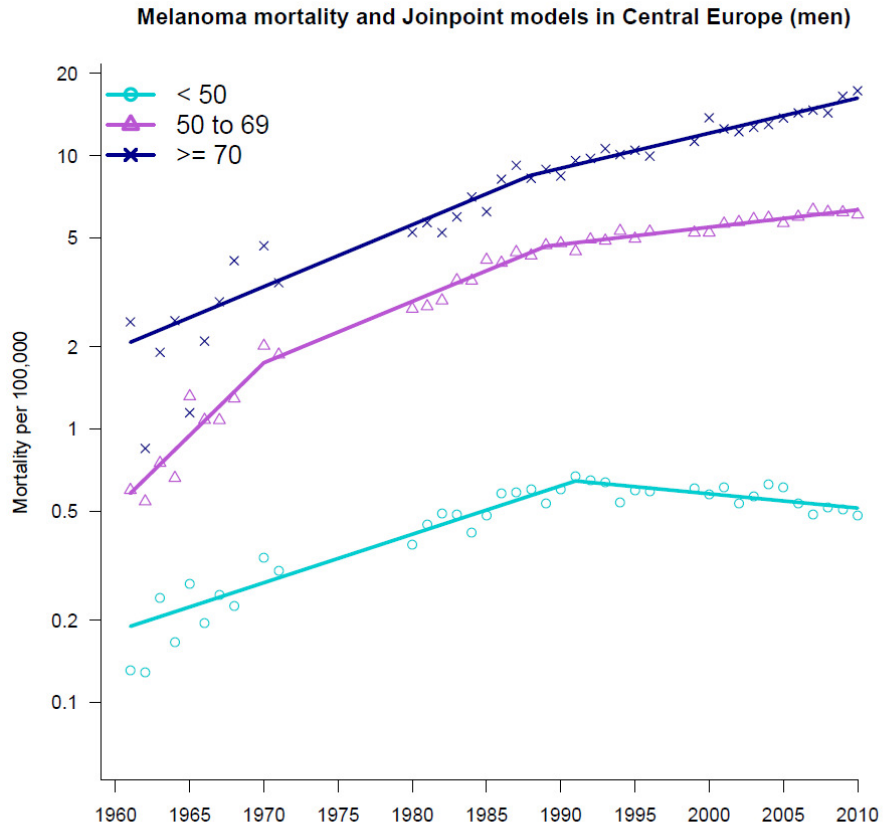


Figure S2g: melanoma mortality by age (<50; 50 to 69; ≥70) and joinpoint modelling in Southern Europe

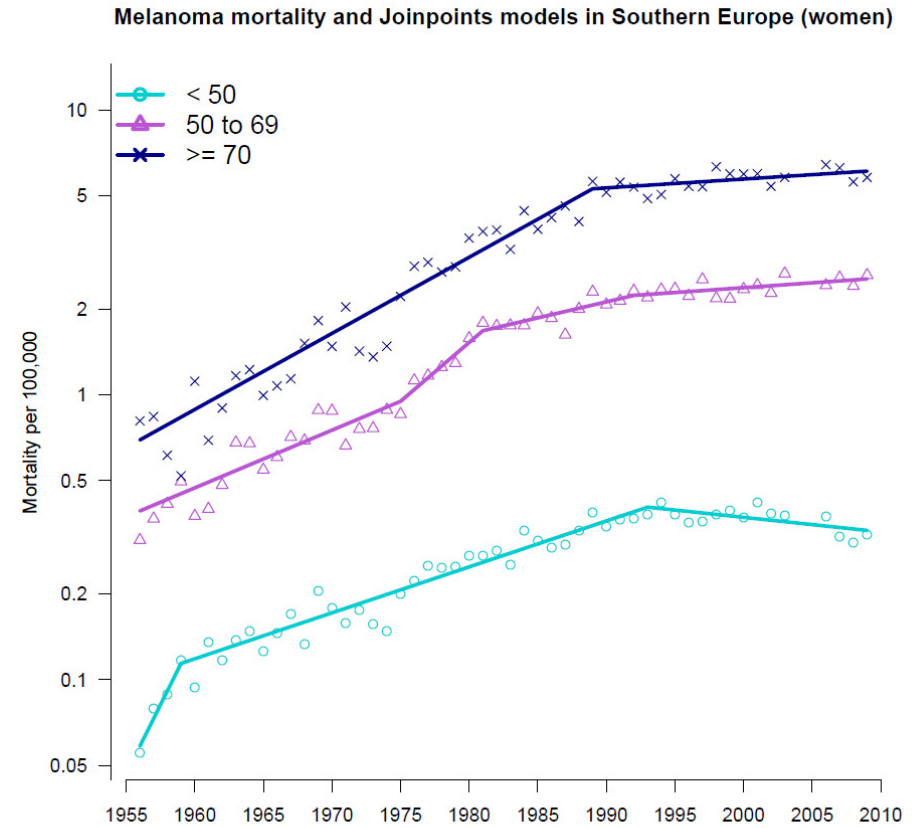
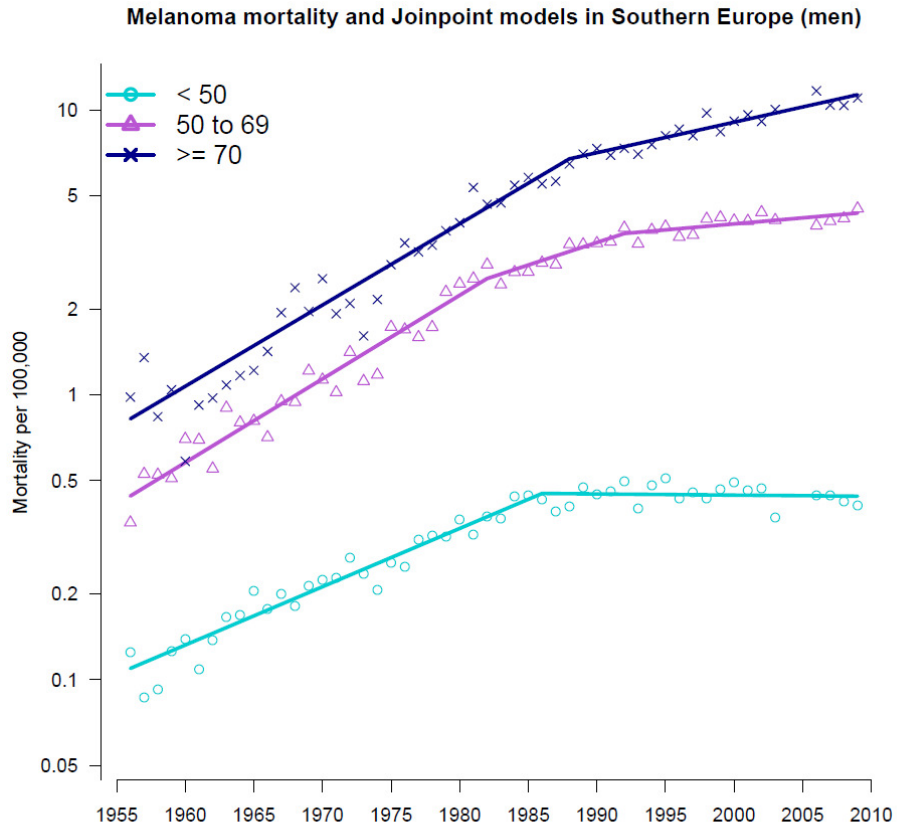


Figure S3a: Age-specific mortality rates by birth cohorts in Oceania

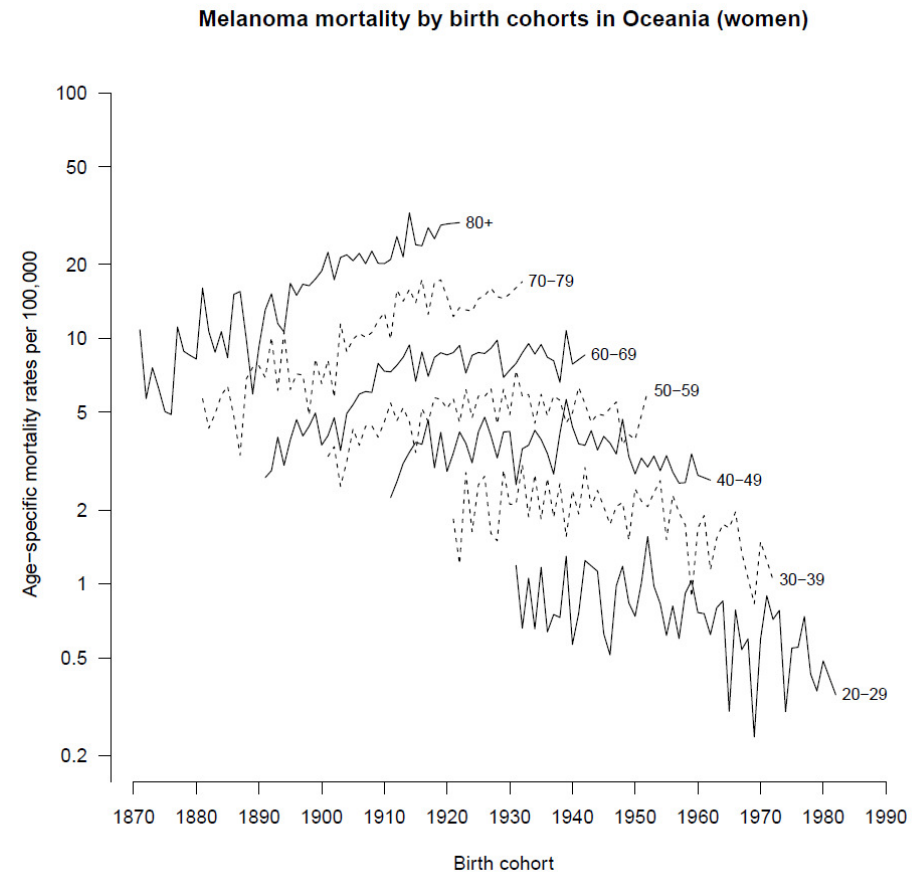
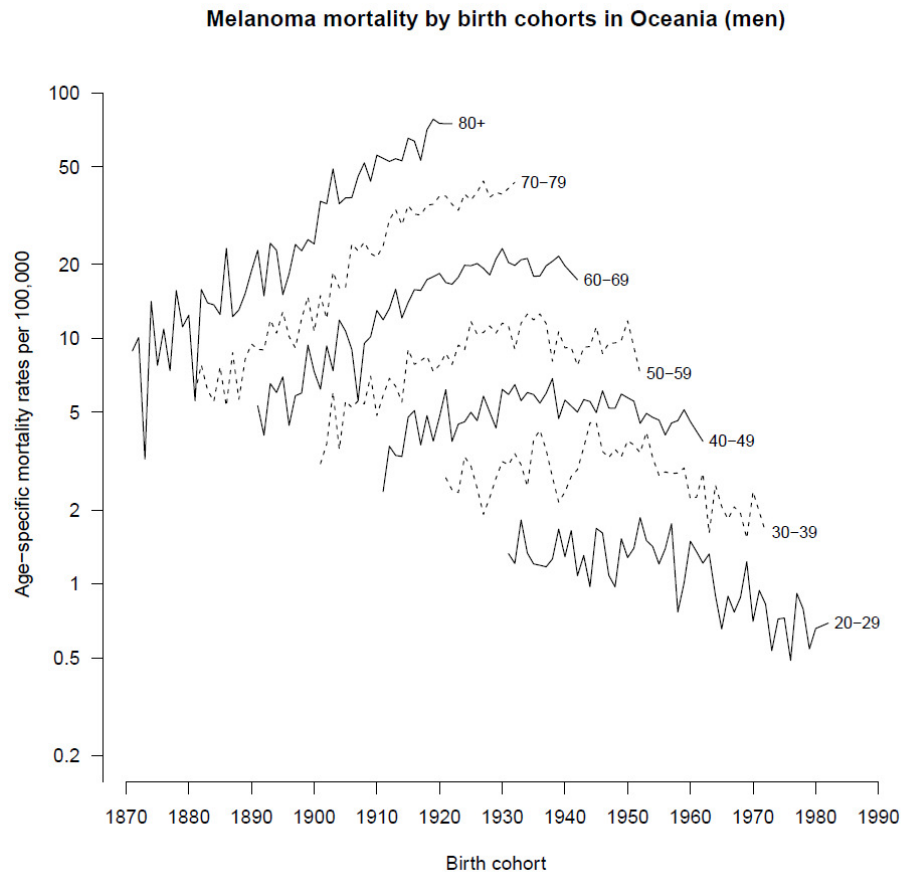


Figure S3b: Age-specific mortality rates by birth cohorts in North America

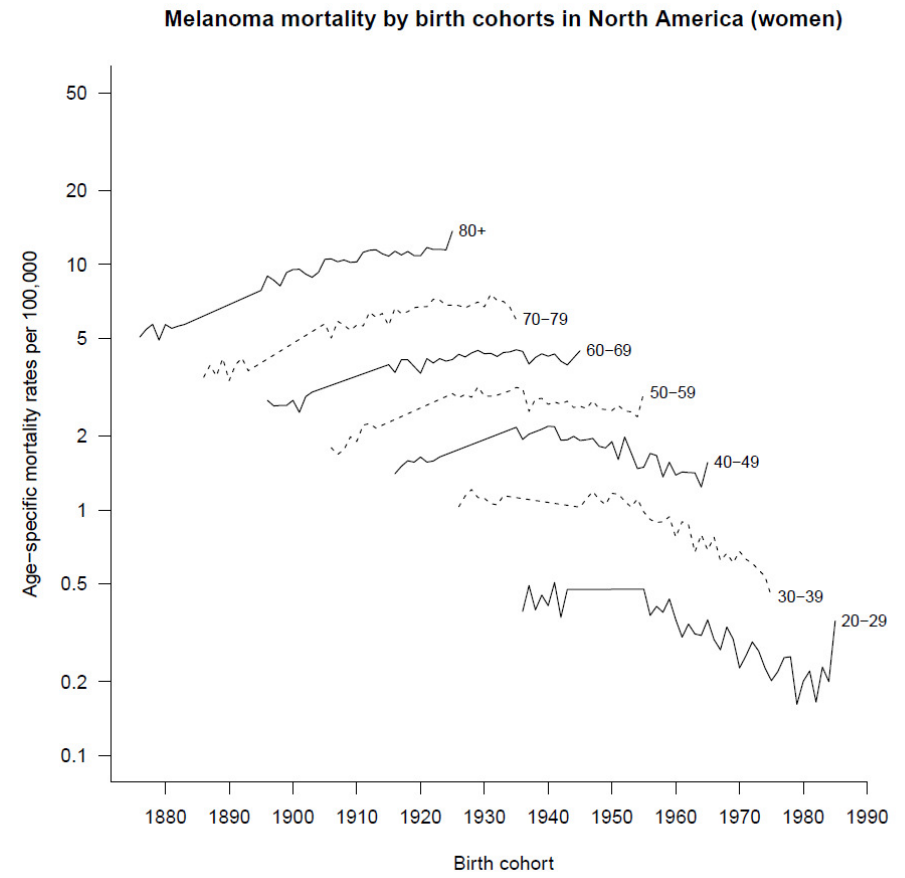
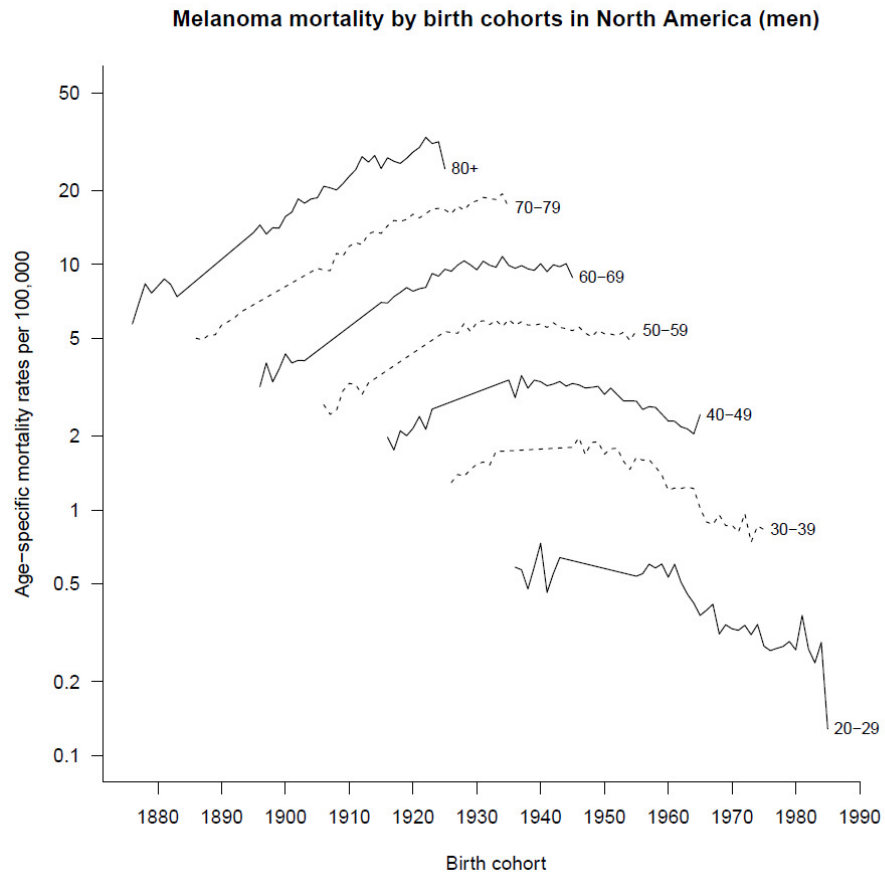


Figure S3c: Age-specific mortality rates by birth cohorts in Northern Europe

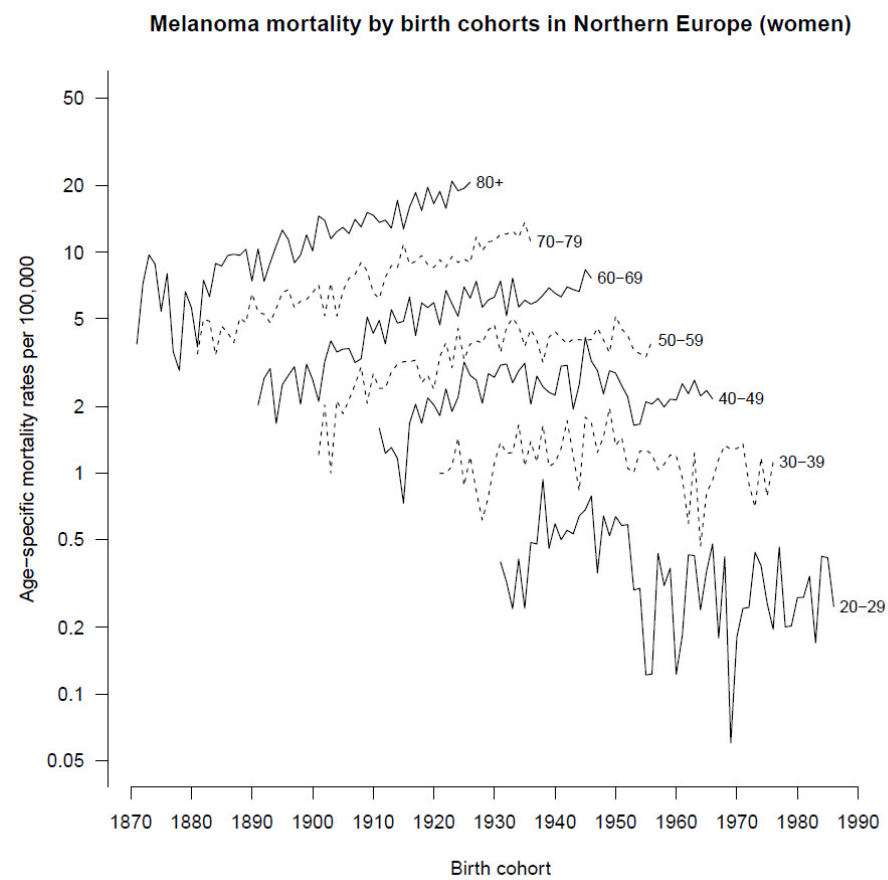
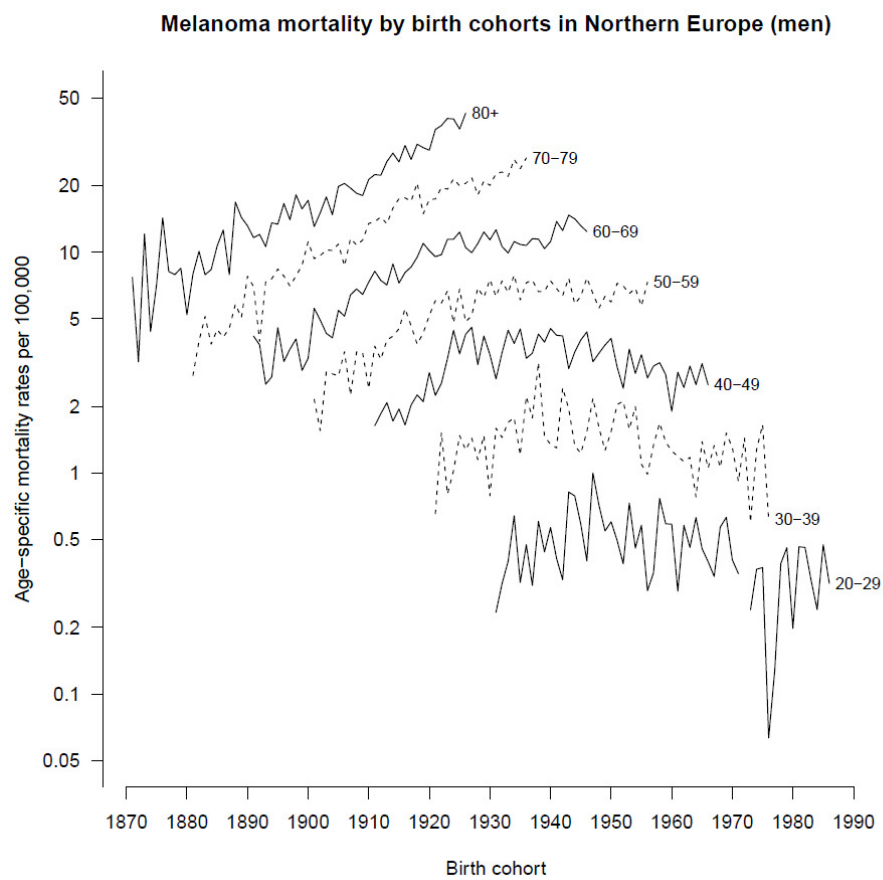


Figure S3d: Age-specific mortality rates by birth cohorts in Ireland and United Kingdom

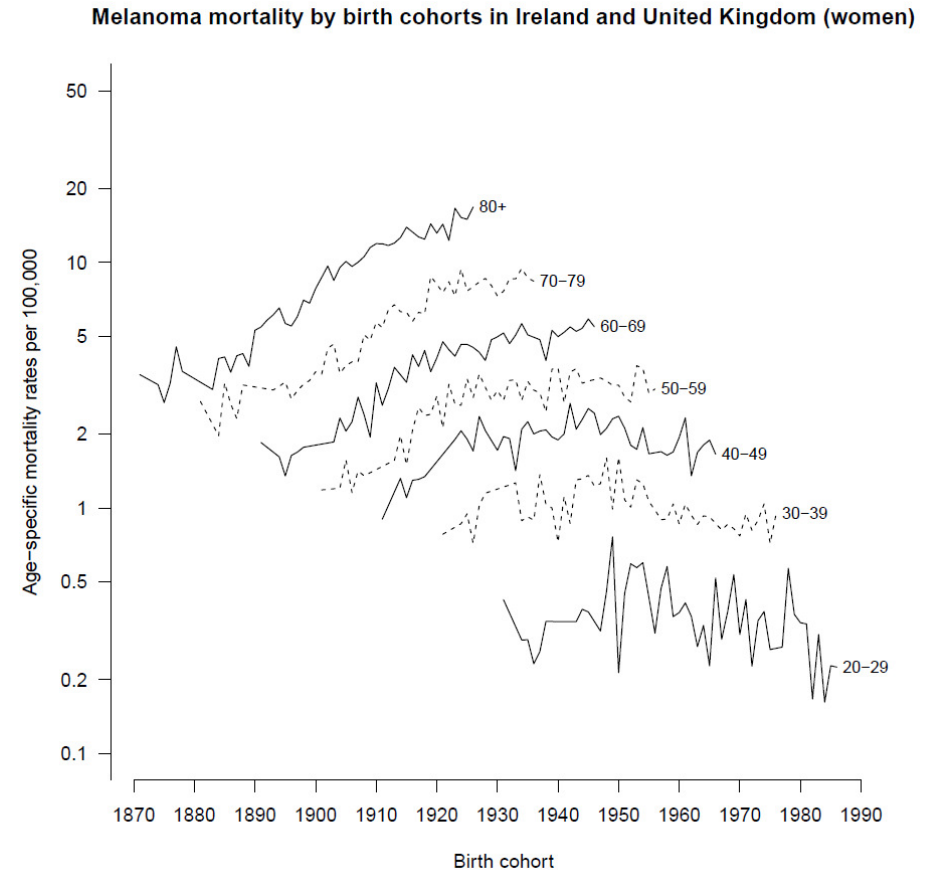
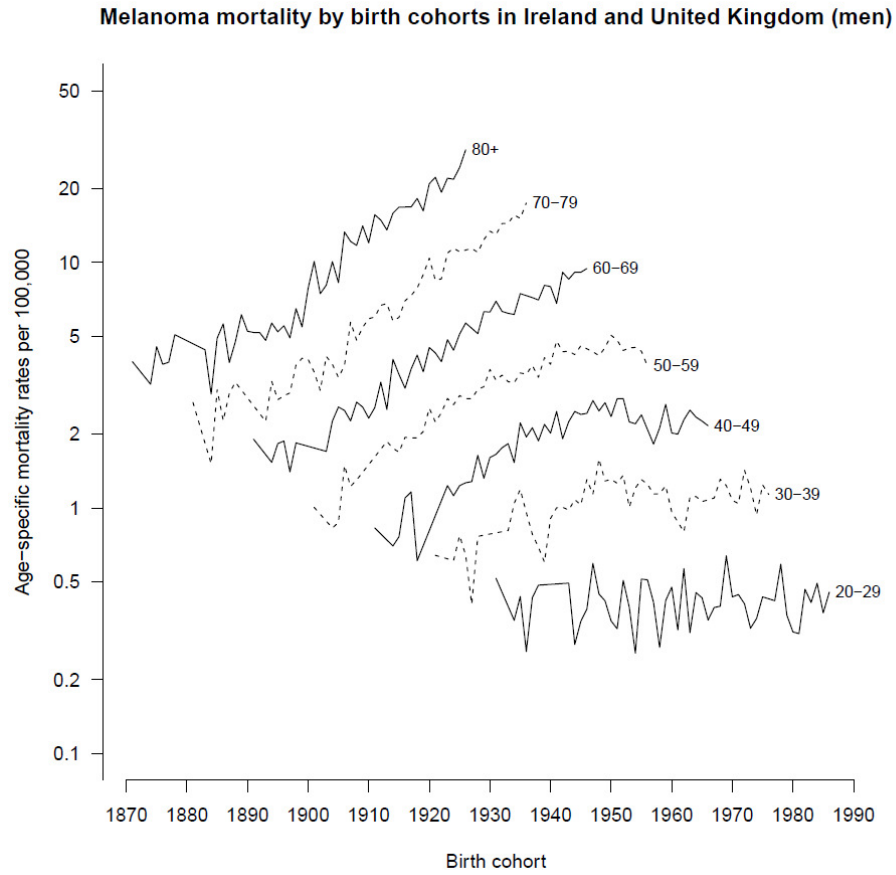


Figure S3e: Age-specific mortality rates by birth cohorts in Western Europe

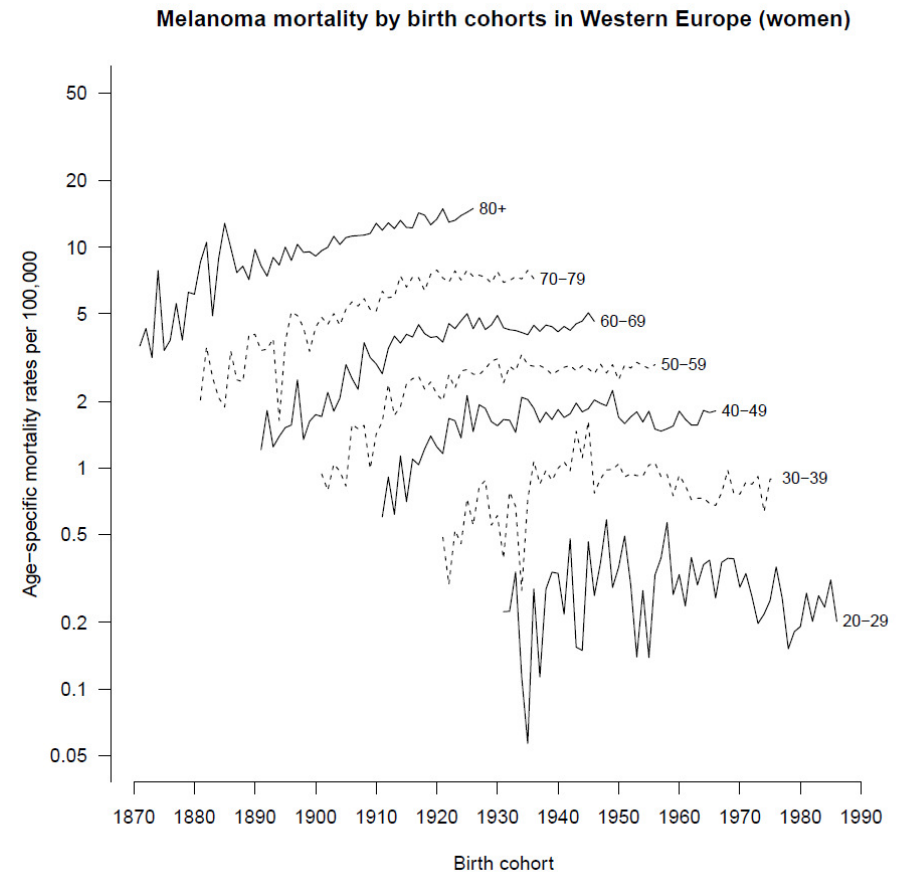
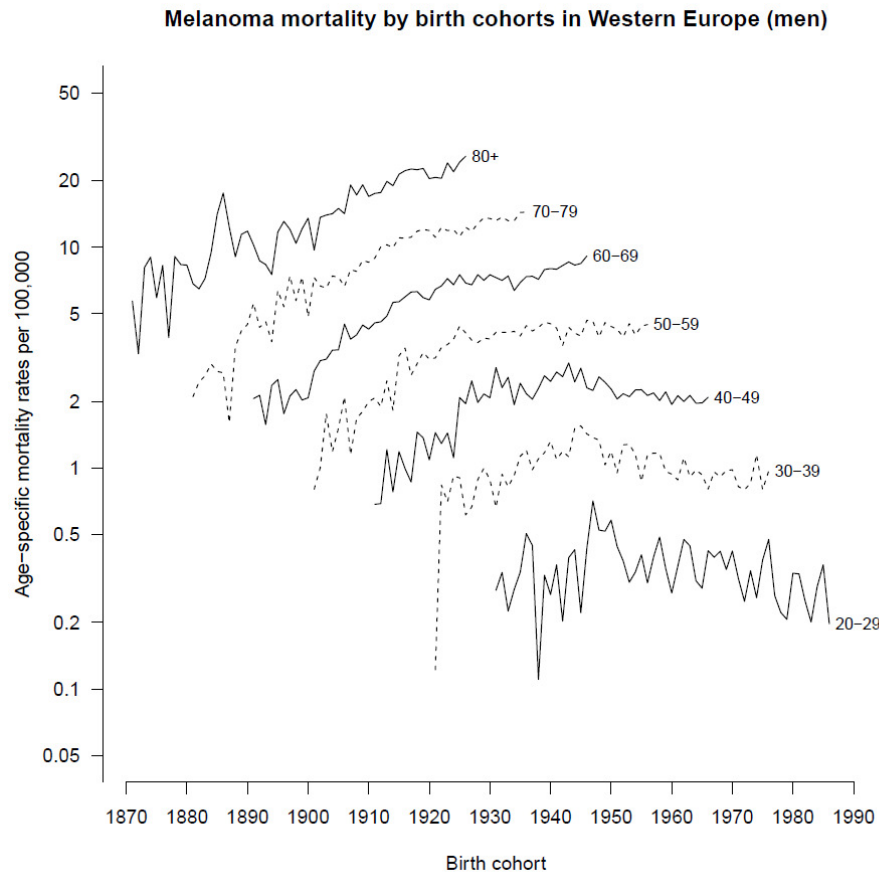


Figure S3f: Age-specific mortality rates by birth cohorts in Central Europe

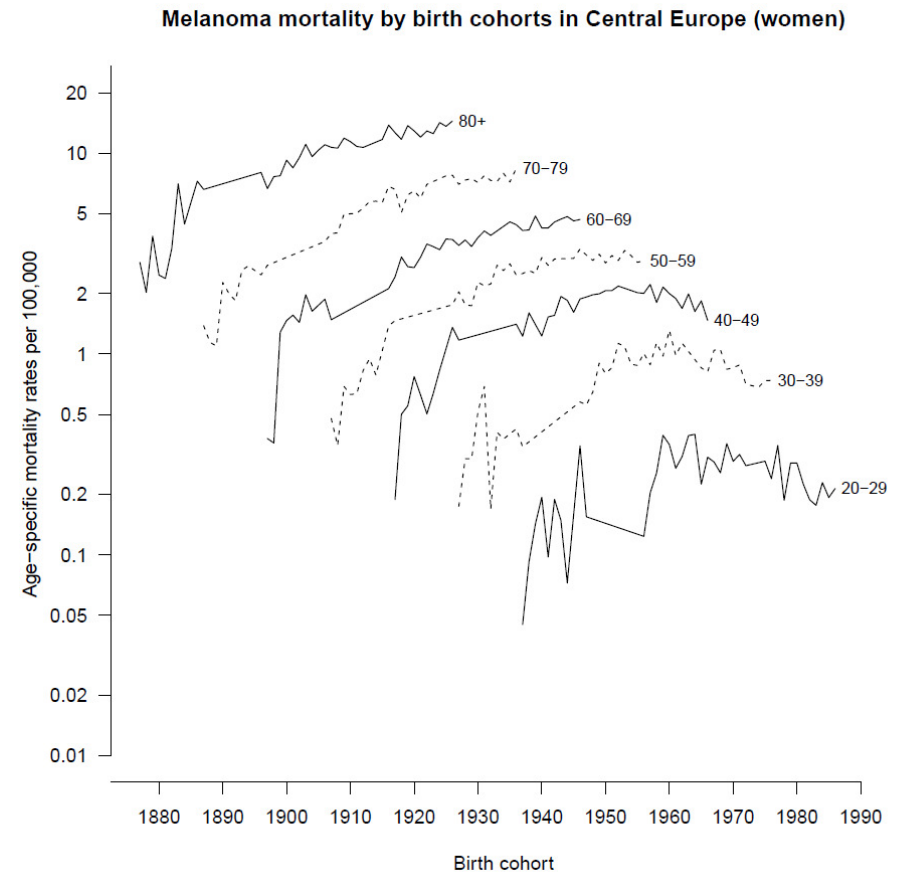
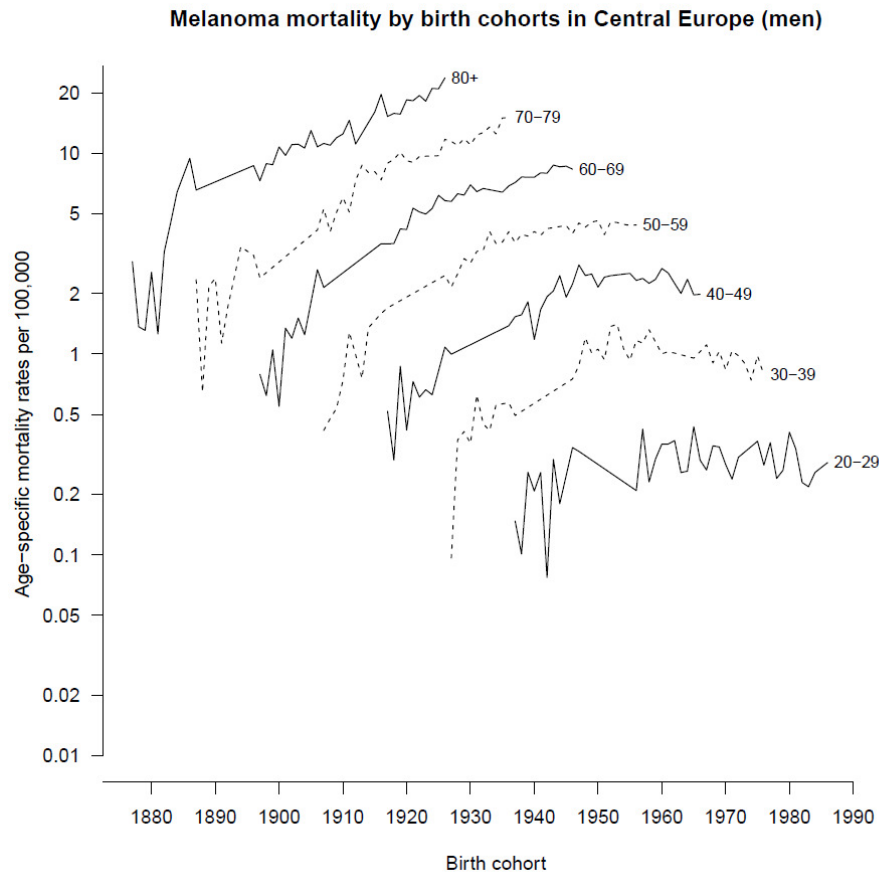


Figure S3g: Age-specific mortality rates by birth cohorts in Southern Europe

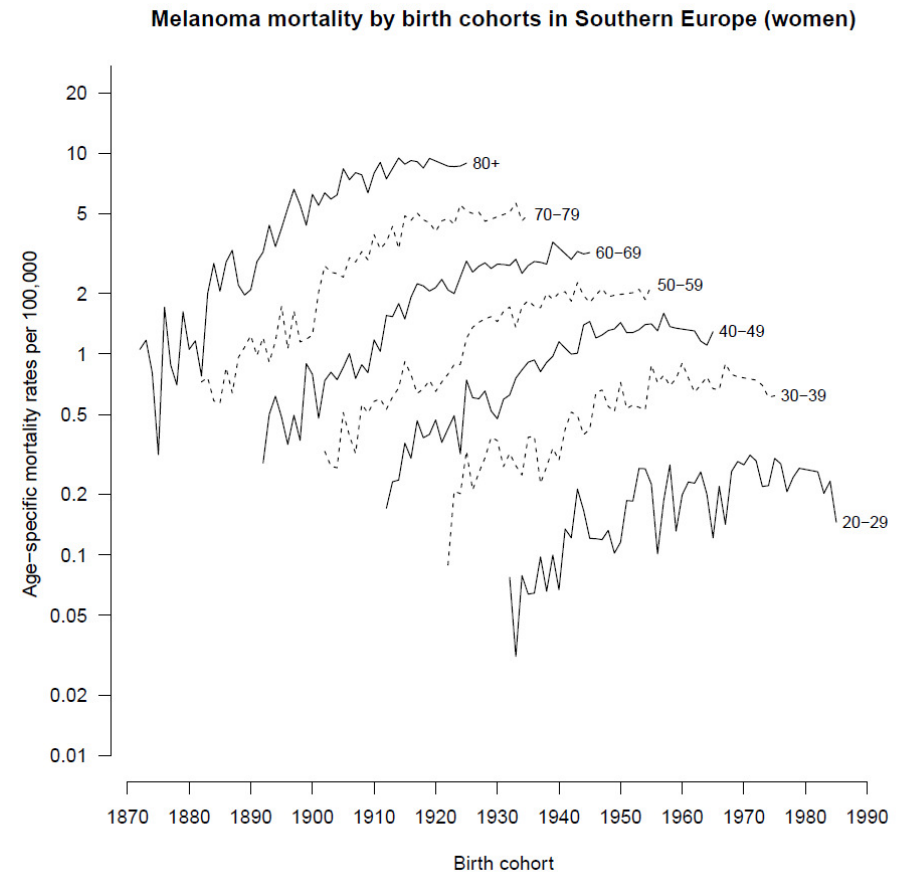
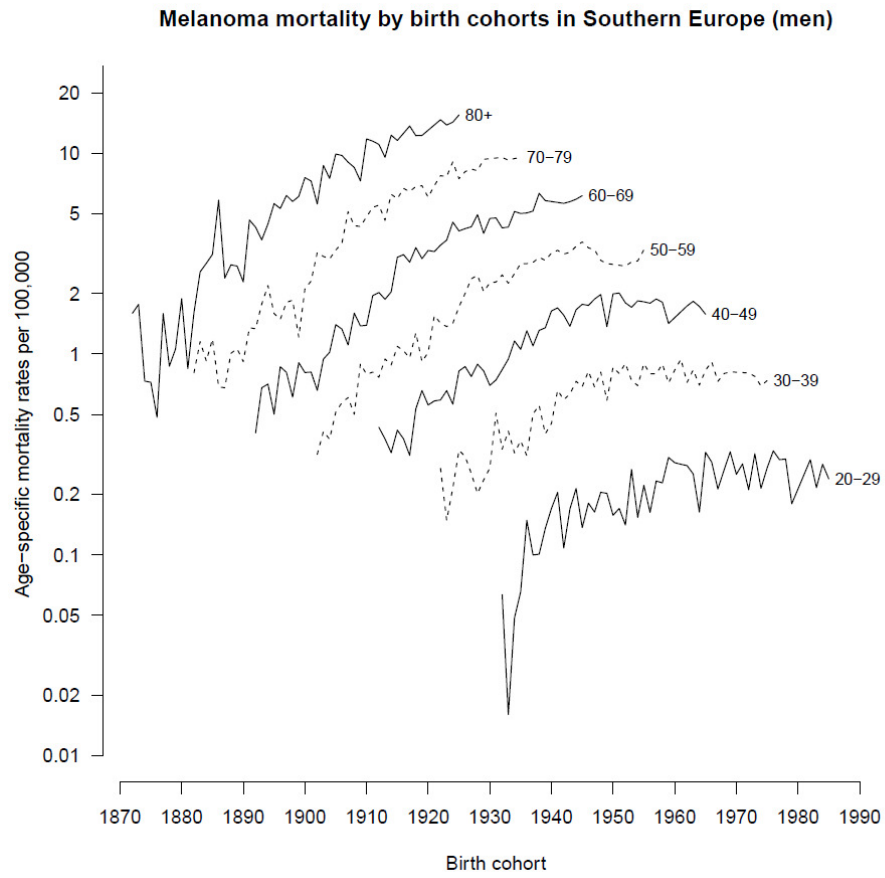


Figure S4a: Age-adjusted proportions of melanoma deaths by age (<50; 50 to 69; ≥70) in Oceania

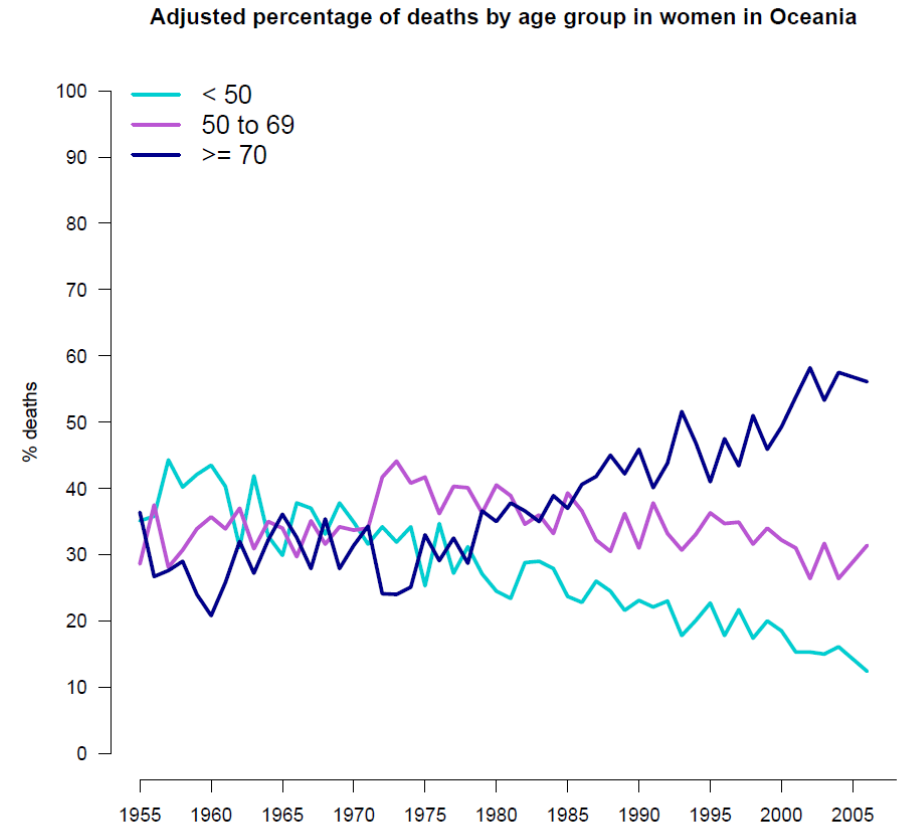
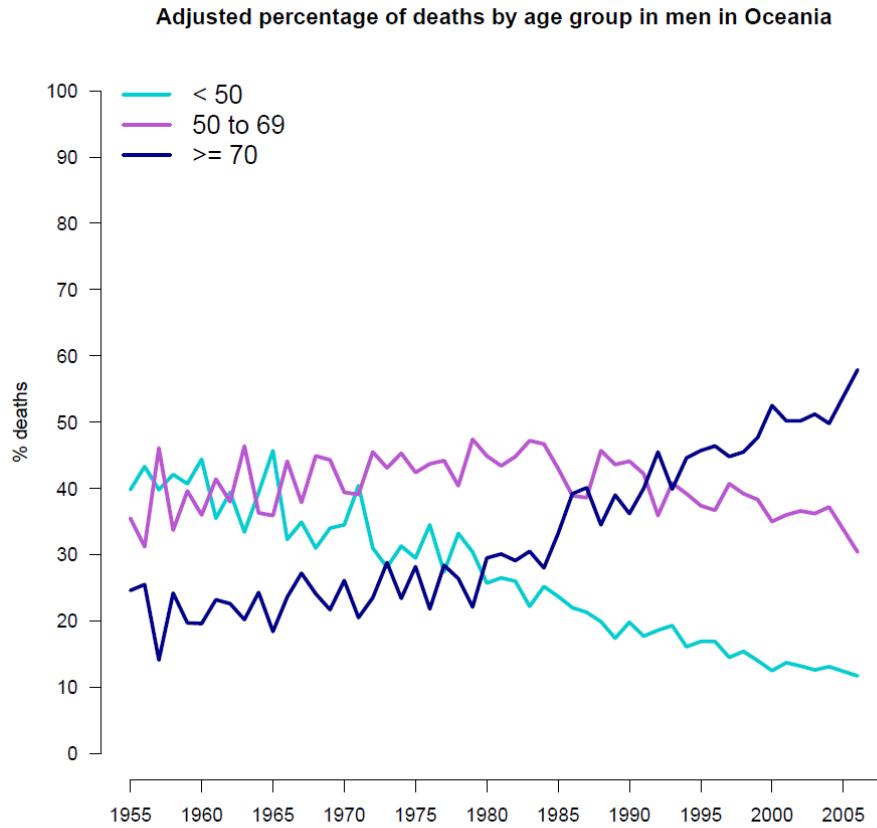


Figure S4b: Age-adjusted proportions of melanoma deaths by age (<50; 50 to 69; ≥70) in North America

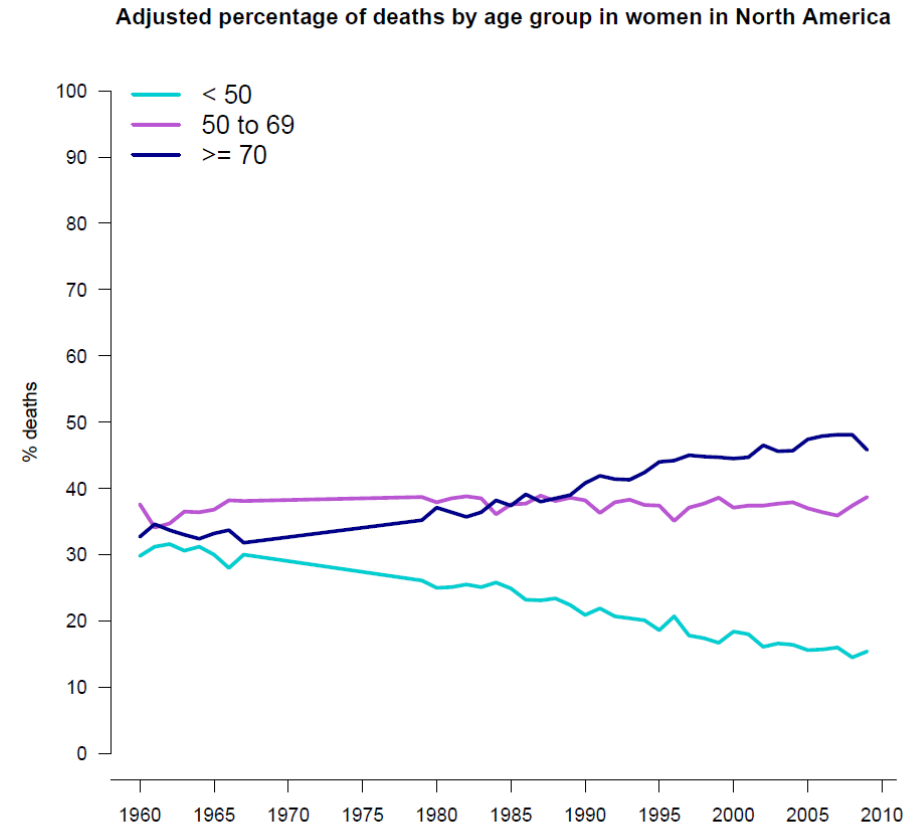
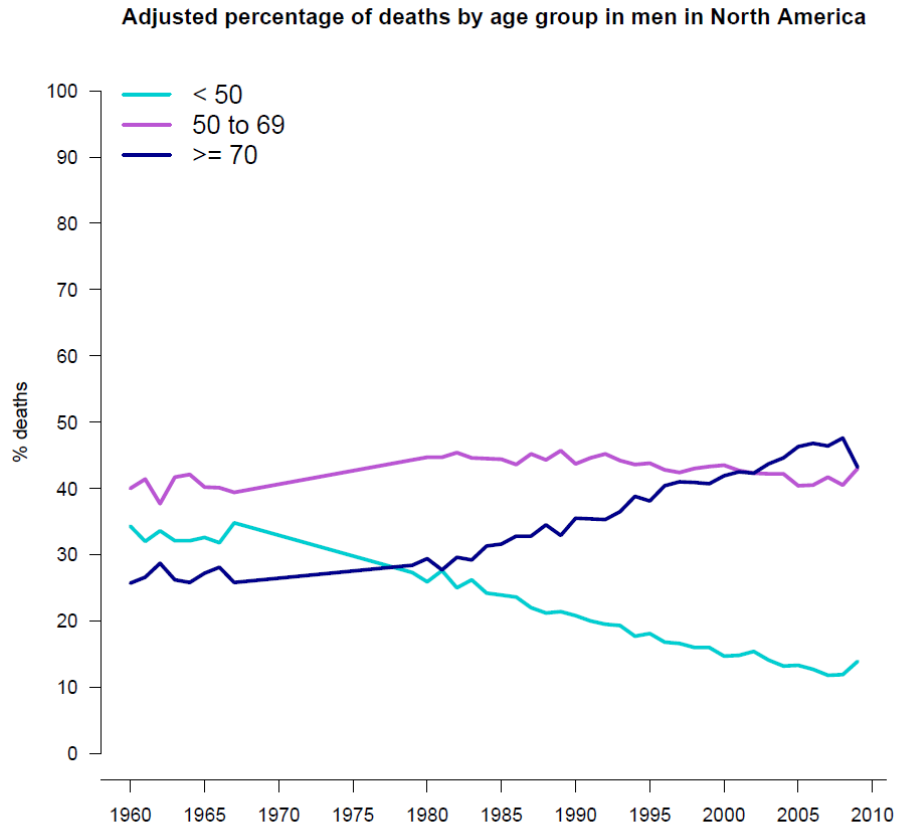


Figure S4c: Age-adjusted proportions of melanoma deaths by age (<50; 50 to 69; ≥70) in Northern Europe

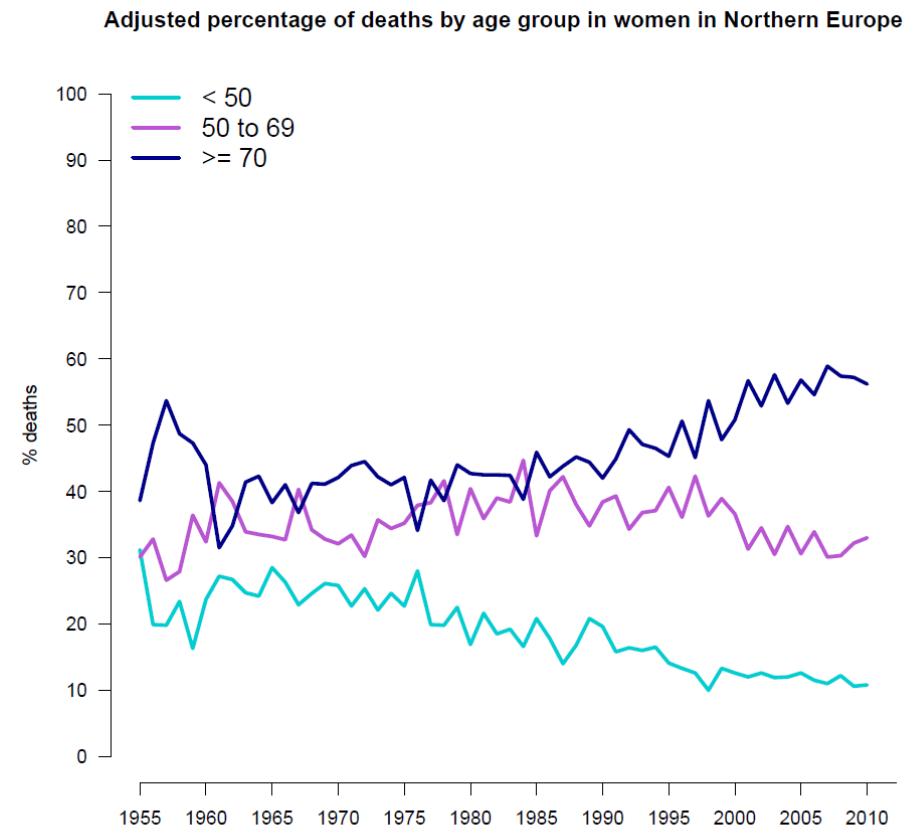
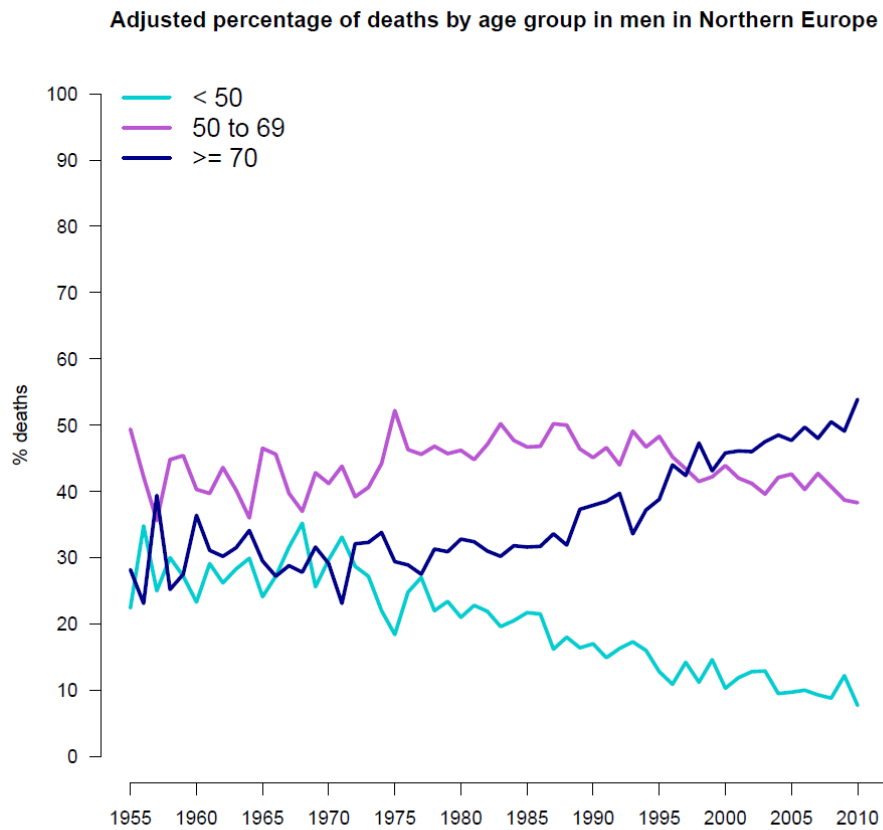


Figure S4d: Age-adjusted proportions of melanoma deaths by age (<50; 50 to 69; ≥70) in Ireland and United Kingdom

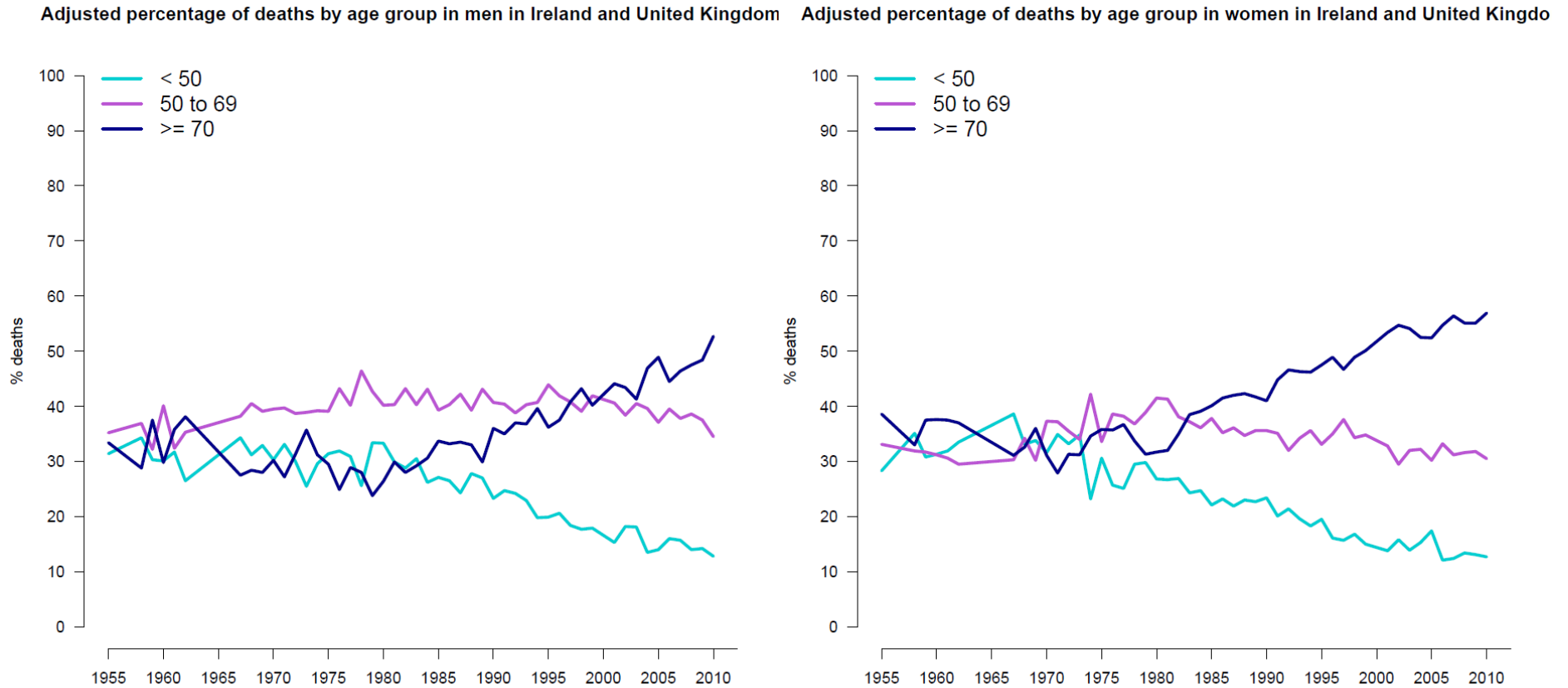


Figure S4e: Age-adjusted proportions of melanoma deaths by age (<50; 50 to 69; ≥70) in Western Europe

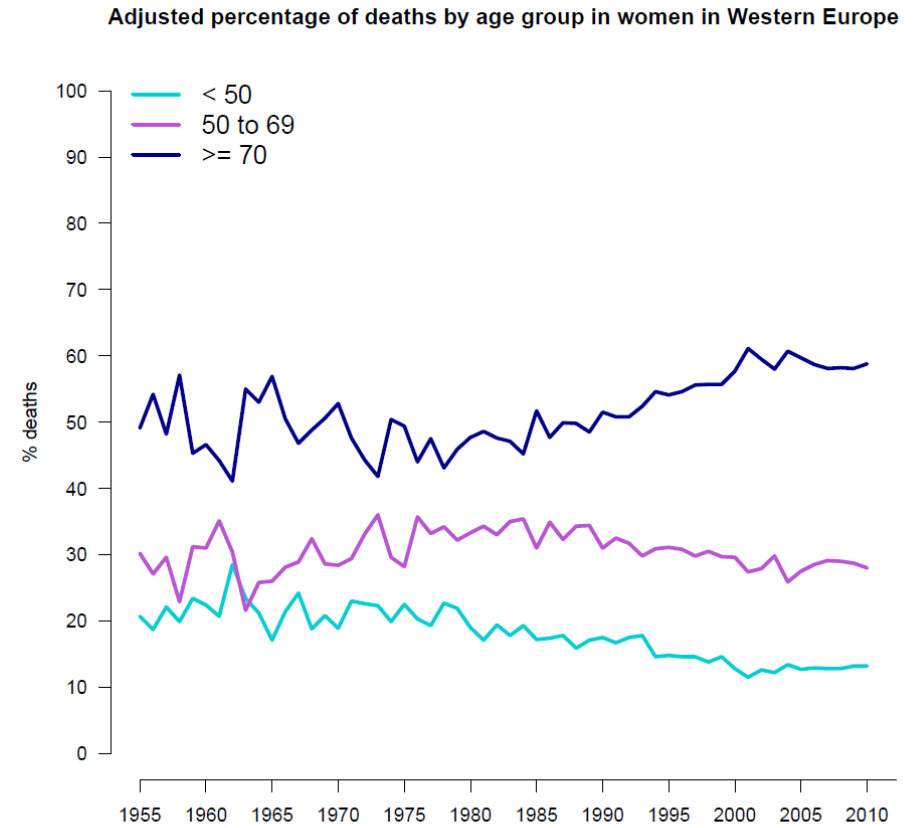
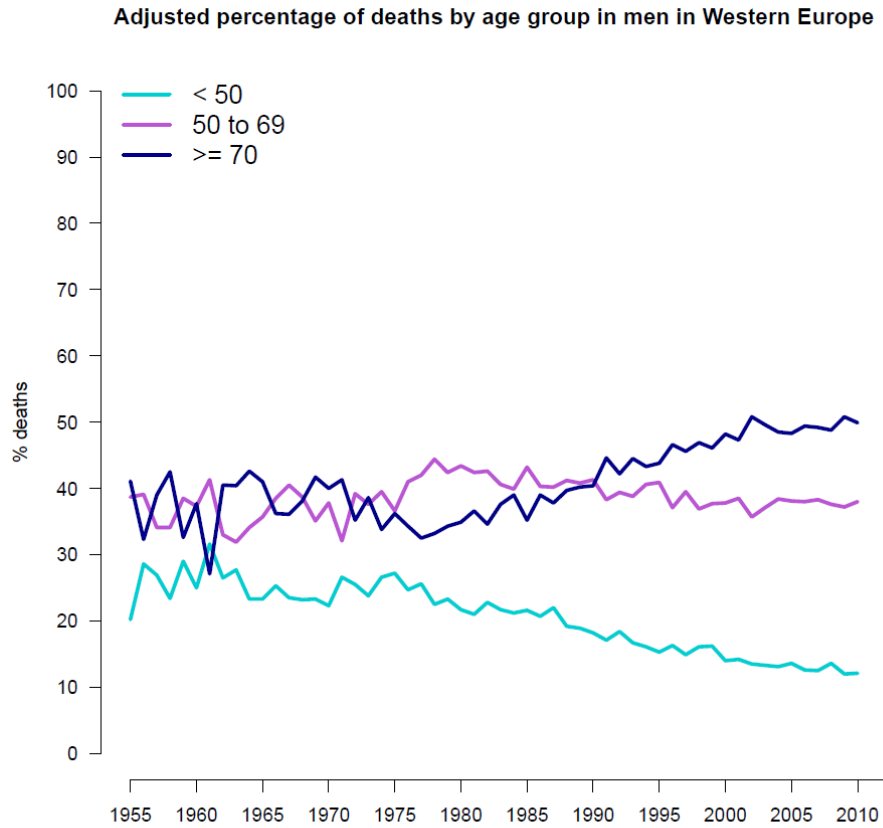


Figure S4f: Age-adjusted proportions of melanoma deaths by age (<50; 50 to 69; ≥70) in Central Europe

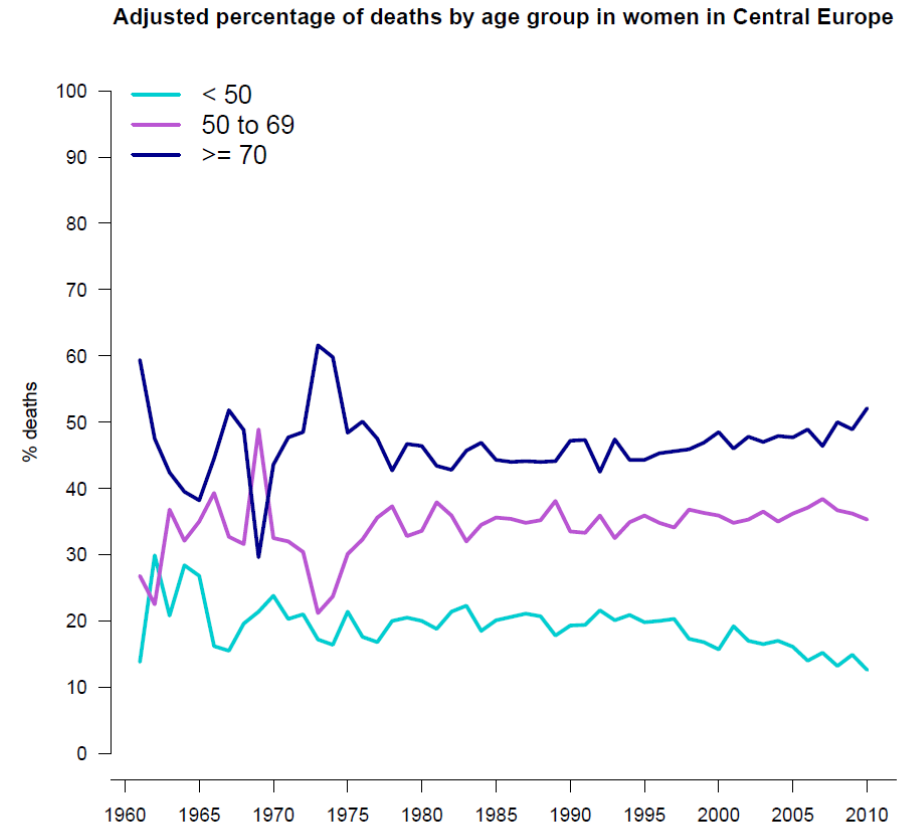
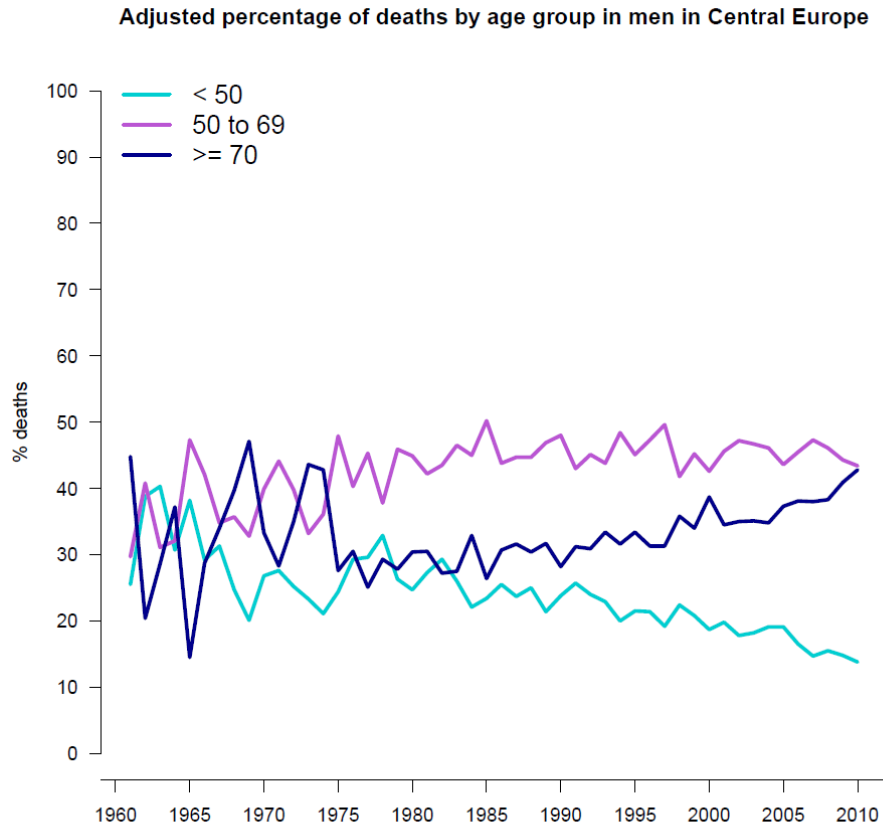


Figure S4g: Age-adjusted proportions of melanoma deaths by age (<50; 50 to 69; ≥70) in Southern Europe

