Inequalities in cancer mortality trends in people with type 2 diabetes: 20-year population-based study in England

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Tweet: Persistent #inequalities in #cancer mortality across gender, deprivation and smoking status in people with type 2 #diabetes in England, study shows using Clinical Practice Research Datalink (CPRD) data @lrweunit @LDC_tweets

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Research in context

What is already known about this subject?

- People with type 2 diabetes have an increased risk of some cancers
- Mortality rates have declined in type 2 diabetes in some countries, primarily due to a reduction in cardiovascular mortality
- There is a possible transition from cardiovascular diseases to other diversified causes of death, including cancer, in type 2 diabetes

What is the key question?

- Are there inequalities by sociodemographic characteristics (age, gender, ethnicity and socioeconomic status) and risk factors (obesity and smoking) in cancer mortality trends in people with type 2 diabetes?

What are the new findings?

- We observed decreasing trends in all-cause mortality rates at all ages but increasing trends in cancer mortality at older ages
- There were persistent inequalities in cancer mortality trends across gender and socioeconomic status but widening disparities by smoking status
- We observed increasing trends of pancreatic, liver, colorectal, breast, prostate, lung, and endometrial cancer at different ages

How might this impact on clinical practice in the foreseeable future?

- In people with type 2 diabetes, cancer would deserve at least a similar level of attention as other complications such as cardiovascular diseases, and targeted cancer prevention, early detection, and screening strategies should be tailored to address persistent and widening inequalities.

Abstract

Aims: To describe the long-term trends in cancer mortality in people with type 2 diabetes in subgroups based on sociodemographic characteristics and risk factors.

Methods: We defined a cohort of individuals aged ≥35 years who had newly diagnosed type 2 diabetes in the Clinical Practice Research Datalink between Jan 1, 1998, and Nov 30, 2018. We assessed trends by age, gender, ethnicity, socioeconomic status, obesity, and smoking for all-cause, all cancer, and cancer-specific mortality rates. We used Poisson regression to calculate age- and calendar year-specific mortality rates and Joinpoint regression to assess trends for each outcome. We estimated standardised mortality ratios comparing mortality rates in people with type 2 diabetes vs. general population.

Results: Among 137,804 individuals, during a median follow-up of 8.4 years all-cause mortality rates decreased at all ages between 1998 and 2018; cancer mortality rates also decreased for 55- and 65-year-old but increased for 75- and 85-year-old individuals, with an average annual percentage change (AAPC) of -1.4% (-1.5, -1.3), -0.2% (-0.3, -0.1), 1.2% (0.8, 1.6), and 1.6% (1.5, 1.7), respectively. Although both subgroups showed upward trends in cancer mortality rates, higher AAPCs were observed in women than men (1.5% vs. 0.5%), in the least than the most deprived (1.5% vs. 1.0%), and in people with morbid obesity than in those with normal body weight (5.8% vs. 0.7%). Increasing cancer mortality rates were also observed in people of White ethnicity and former/current smokers, but downward trends in their respective counterparts of other ethnic groups and non-smokers. These results led to persistent inequalities by gender and deprivation but widening disparities by smoking status. Constant upward trends were also observed for pancreatic, liver, and lung cancer mortality at all ages, colorectal cancer at most ages, breast cancer at younger ages, and prostate and endometrial cancer at older ages. Compared to the general population, people with type 2 diabetes had more than 1.5-fold increased risk of colorectal, pancreatic, liver, and endometrial cancer mortality during the whole study period.

Conclusions: In contrast to the declines in all-cause mortality rates at all ages, the cancer burden has increased in older people with type 2 diabetes, especially for colorectal, pancreatic, liver, and endometrial cancer. Tailored cancer prevention and early detection strategies are needed to address persistent inequalities in the older population, the most deprived, and smokers.

Keywords: type 2 diabetes; cancer; mortality trends; inequalities; electronic health records

Introduction

It was estimated that 537 million adults aged 20-79 years were living with diabetes worldwide in 2021, with more than 90% of them having type 2 diabetes.[1] Type 2 diabetes is associated with a higher risk of several vascular complications, including myocardial infarction, stroke, peripheral artery disease, and kidney disease, leading to premature deaths.[2] Previous studies have reported declining rates in the last two decades of major cardiovascular complications and mortality in people with diabetes in some high-income countries,[3, 4] with a parallel greater contribution of other diseases, such as cancer, as underlying causes of death.[5] Accumulating epidemiological evidence has indeed shown a higher risk of incidence and mortality for some cancer in individuals with type 2 diabetes,[6, 7] with the prolonged exposure to the effect of hyperglycaemia, hyperinsulinemia, insulin resistance, and chronic inflammation being the potential underlying biological mechanisms.[6, 8] Robust evidence indicates that there is a causal relationships between type 2 diabetes and pancreatic, liver, and endometrial cancer;[7] both diabetes and cancer have also been linked to obesity and smoking.[6, 8]

While previous studies have extensively investigated inequalities in vascular outcomes among people with type 2 diabetes by sociodemographic factors,[9-12] less is known about whether such inequalities exist in cancer mortality. In this study, we aimed therefore to describe long-term trends of cancer mortality rates in people with type 2 diabetes based on subgroups defined by sociodemographic characteristics and risk factors.

Methods

Data sources

We conducted this study following a pre-specified research protocol – approved by the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee (No. 19_120Mn) – and the RECORD guidelines (checklist in the **Electronic Supplementary Material [ESM]**).[13]

We used the CPRD GOLD to identify a cohort of individuals with type 2 diabetes in the UK. CPRD routinely collects de-identified patient data which are generally representative of the national population in terms of age, sex, and ethnicity.[14] Data were linked to the Hospital Episodes Statistics (HES), patient-level index of multiple deprivation (IMD) 2010, and the Office for National Statistics (ONS) Death Registration to extract further information on ethnicity and hospitalisations, socioeconomic status, and date and cause of death, respectively. Linkages were available only for patients in England.

Study population

Individuals were included if they had a first ever diagnosis code of type 2 diabetes in CPRD between 1st Jan 1998 and 30th Nov 2018, were aged 35 years or over at the first diagnosis date of type 2 diabetes (i.e., the index date), and were registered with an up-to-standard practice for minimum 1 year at index date. To rule out the potential misclassification by clinical coding, individuals with a code of type 1 diabetes any time in either CPRD or HES were excluded. As the main outcome was cancer mortality, we only included individuals with linkage to ONS.

Procedures

Individuals were categorised into subgroups defined by gender, ethnicity, socioeconomic status, body mass index (BMI) groups, and smoking status. Ethnicity was grouped as White and other than White, predominantly extracted from HES and supplemented with CPRD records when data were missing in HES. We used patient-level IMD 2010, the mid-point year of the study period, to define socioeconomic status and stratified it into quintiles (1st quintile: least deprived; 5th quintile: most deprived). IMD measures the relative deprivation for small areas in England which includes seven domains: income, employment, health and disability, education, skills and training, barriers to housing and other services, crime, and living environment.[15] Information on BMI (underweight: <18.5; normal weight: 18.5-24.9; overweight: 25.0-29.9; obese: 30.0-34.9; and severely obese: $\geq$35.0 kg/m^2) and smoking status (non-smoker, current smoker, and ex-smoker) were extracted from CPRD using the closest value before the index date.

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Outcomes

The underlying cause of death was used to ascertain cancer mortality. To estimate the proportion of cancer deaths out of all-cause deaths, we also collected information on all-cause mortality. We further investigated deaths due to some specific cancer sites, including the four most common cancers in the UK (lung, colorectal, breast, prostate) and the four cancers causally linked to diabetes in a previous meta-analysis (i.e., diabetes-related cancers: pancreas, liver, endometrium, gallbladder).[7] All individuals were followed-up from the index date until death or end of study (linkage date for ONS: Jan 14, 2019).

Statistical analysis

We reported baseline characteristics (at index date) as median and interquartile range (IQR) for continuous variables and number and proportion for categorical variables; we also calculated person-years and number of events overall and in each subgroup. To estimate trends in mortality rates, we first split the risk time into 1-year's intervals by attained age and attained calendar time and then modelled the outcomes with Poisson regressions including an interaction between a natural spline transformation of age and calendar year (5 knots placed at 10th, 30th, 50th, 70th, and 90th percentile distribution in those with events) and adjusting for diabetes duration.[16, 17] Using log-person-time as offset, we predicted age-specific mortality rates at the mid-point of each calendar year and the median diabetes duration of exiting the cohort (8.4 years). To further assess the cancer burden over time, we calculated the proportion of cancer death out of all-cause death and used non-parametric bootstrap (500 samples with replacement) to derive 95% confidence intervals (CIs). We conducted stratified analyses by gender, ethnicity, deprivation, BMI groups, and smoking status to investigate potential inequalities. Individuals with missing data on ethnicity, socioeconomic status, BMI or smoking status were not included in the corresponding stratified analyses (<10% missingness). For stratified models, we predicted the mortality rates at the median age of exiting the cohort (72 years old) to make rates comparable across subgroups. We then used the predicted rates to explore mortality trends and estimated the Annual Percentage Changes (APC) for each calendar year segment and the Average Annual Percentage Changes (AAPC) for the whole study period using the Joinpoint Regression Program.[18] We also calculated the age and sex standardised mortality ratios (SMRs) (age standardised only in sex-stratified analyses) for all outcomes by the calendar periods identified in the Joinpoint regressions, with corresponding mortality rates in the general population obtained from publicly available data in England and Wales.[19] Analyses were conducted in R 4.2.1 ("Epi" package,[16]), Joinpoint Regression Program 4.9.1.0, and Stata/BE 17.0.

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Results

The details and the flowchart of the cohort definition are reported in **ESM Fig. 1**: 137,804 individuals were included in the analysis. Characteristics at type 2 diabetes diagnosis are shown in **Table 1**: the median age was 63.8 years (IQR: 54.2, 73.0); 61,444 (44.6%) were women; 114,394 (83.0%) were of White ethnicity; 64,652 (46.9%) were non-smokers; 16,126 (11.7%) had a normal body weight; and the median BMI was 30.6 (IQR: 27.1, 34.9) kg/m^2. During a median follow-up of 8.4 years (IQR: 5.0, 12.2) and a total of 1,194,444 person-years, 39,212 (28.5%) deaths occurred: **Table 2** reports the number of person-years and events stratified by each sociodemographic characteristic and risk factor.

All cancer mortality rates

Figure 1, **ESM Table 1-6**, and **Table 3** present trends in all-cause and all cancer mortality rates in different subgroups. Trends of all-cause mortality rates are described in details in the **ESM**, **Additional results** section. **Figure 2** shows the proportion of cancer death out of all-cause death.

Trends and magnitudes of all cancer mortality rates differed across age groups (**Figure 1g**). During the whole study period, reductions were observed in younger whilst increases in older individuals: for 55-year-old individuals, all cancer mortality rate was 2.1 (95% CI: 1.5, 3.1) per 1000 person-years in 1998, 2.4 (2.1, 2.7) in 2008, and 1.6 (1.2, 2.1), with an AAPC of -1.4% (-1.5, -1.3) indicating an annual reduction of 1.4%. Corresponding rates and AAPC were 5.2 (4.2, 6.4), 6.6 (6.0, 7.1), 4.9 (4.3, 5.7), and -0.2% (-0.3, -0.1) for 65-year-old; 8.8 (7.0, 11.1), 14.9 (13.7, 16.2), 11.3 (9.9, 12.9), and 1.2% (0.8, 1.6) for 75-year-old; and 14.7 (11.2, 19.4), 22.5 (20.6, 24.7), 19.8 (17.3, 22.6), and 1.6% (1.5, 1.7) for 85-year-old individuals (**Figure 1g**; **Table 3**; **ESM Table 1**). Compared to other ages, the proportion of cancer deaths was noticeably lower in 85-year-old individuals during the whole study period; proportions increased at older (**Figure 2c-d**; **ESM Table 1**) while were constant at younger (**Figure 2a-b**; **ESM Table 1**) ages.

Cancer mortality rates and proportions of cancer deaths were higher in men than women for most of the 1998-2018 period, being the gap for both rates and proportions closer around 2012-2014 and wider in more recent years (**Figure 1h**; **Figure 2e-f; ESM Table 2**). AAPCs were 0.5% (0.2, 0.8) in men and 1.5% (1.1, 1.8) in women (**Table 3**).

While rates increased before flattening and decreasing in people of White ethnicity, they decreased and then increased in other ethnicities, resulting in an overall increase in White (AAPC: 2.4%; 2.1, 2.6) and reduction in other ethnicities (AAPC: -3.4%; -3.6, -3.2) (**Figure 1i**; **Table 3**; **ESM Table 3**). The proportion of cancer deaths was slowly increasing in White (**Figure 2g**) while it was not estimable in other ethnicities due to the small number of cancer deaths.

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The deprivation gap in cancer mortality rates (most vs. least deprived) was smaller around 2008 and wider thereafter (**Figure 1j**; **ESM Table 4**): while the trends indicated increases in the rates in both the least and most deprived group from 1998 to 2018, the AAPC was slightly larger in the least deprived (1.5%; 0.7, 2.2) than the most deprived (1.0%; 0.9, 1.1) (**Table 3**). The proportions of cancer deaths increased from 1998 to 2008-2013 and then decreased and flattened in both groups, but were higher in the least than most deprived group during virtually all years (**Figure 2h** and **2i**).

Cancer mortality rates were higher in people with normal weight than in people with overweight or morbid obesity. However, there were smaller increases in cancer mortality rates in individuals with normal weight (AAPC: 0.7%; 0.6, 0.9) than in those who were severely obese (5.8%; 5.6, 6.1), resulting in no differences in cancer mortality rates between the two groups after 2012 (**Figure 1k**; **Table 3**; **ESM Table 5**). During the entire study period, we observed a sharply increasing trend in the proportions of cancer deaths in people who were overweight (**Figure 2k**) or (severely) obese (**Figure 2l** and **2m**) but a small increase in people with normal weight (**Figure 2j**). Further, the proportions were similar in all BMI groups during the last years of observations.

Cancer mortality rates were appreciably higher in current than former or non-smokers, particularly in recent years, with a progressively wider gap due to an increase in the rates in current smokers (3.4%; 3.4, 3.5) and former smokers (0.6%; 0.5, 0.8) but a reduction in non-smokers (-1.4%; -1.4, -1.3) (**Figure 1l**; **Table 3**; **ESM Table 6**). The proportions of cancer deaths increased and then flattened in current (**Figure 2n**) and former smokers (**Figure 2p**) while were stable in never smokers (**Figure 2o**); proportions across smoking groups were, however, similar during the last years of observations.

Cancer-specific mortality rates

Figure 3 shows trends of mortality rates for breast, prostate, lung, and colorectal cancer, the four most common cancers; **ESM Table 7** reports the corresponding APCs and AAPCs by age, gender, ethnicity, socioeconomic status, BMI, and smoking status. Of the four cancers causally linked to type 2 diabetes (pancreas, liver, gallbladder, and endometrium), **Figure 4** shows trends of mortality rates only for pancreatic and liver cancer: due to a small number of events (**Table 2**), trends for gallbladder and endometrial cancer could not be estimated and stratified analyses were possible; **ESM Table 8** reports the corresponding APCs and AAPCs by sociodemographic characteristics and risk factor.

Breast cancer mortality rates (**Figure 3a-e**) increased slightly before decreasing in 55-, 65-, and 75-year-old individuals while remained relatively stable in 85-year-old individuals, with AAPCs of 4.1% (95% CI: 3.6, 4.7), -0.1% (-1.4, 1.2), -0.6% (-0.9, -0.3), and -0.5% (-0.5, -0.4), respectively. Prostate cancer mortality rates (**Figure 3f-j**) increased in 75-year-old (0.8%; 0.6, 1.0) and 85-year-old (5.6%; 5.5, 5.7) but decreased in 55-year-old (-3.1%; -3.3, -2.8) and 65-year-old (-1.2%; -1.4, -1.0). Lung cancer mortality rates (**Figure 3k-p**) increased slightly and then decreased at all ages, with small

increases during 1998-2018 at young [0.4% (0.2, 0.5) and 0.7% (0.6, 0.7) at 55- and 65-year-old, respectively] and larger increases at old [2.8% (2.5, 3.0) and 1.3% (1.1, 1.6) at 75- and 85-year-old, respectively] ages. Except at 75-year-old, colorectal cancer mortality rates (**Figure 3q-v**) increased at other ages: 3.1% (2.4, 3.9), 1.4% (1.2, 1.5), -0.5% (-0.7, -0.2), and 1.7% (1.6, 1.9) at 55-, 65-, 75-, and 85-year-old, respectively. Pancreatic cancer mortality rates (**Figure 4a-f**) increased at all ages [AAPCs: 2.0% (1.8, 2.2), 6.5% (6.0, 7.0), 2.6% (2.4, 2.9), and 6.1% (6.0, 6.3) at 55-, 65-, 75-, and 85-year-old, respectively (**ESM Table 8**)]. Steady increasing trends were also observed for liver cancer mortality rates (**Figure 4g-l**) at all ages (AAPC range: 1.7% to 4.8%; **ESM Table 8**) and for endometrial cancer, except in the youngest group (**ESM Table 8**).

Compared to women, men had higher lung, colorectal, and liver cancer mortality but the gender gaps were smaller during the last years of observation (**Figure 3l, 3r, 4b, 4h**; **ESM Table 7-8**). We observed strong inequalities by socioeconomic status for lung cancer mortality, with markedly higher rates in the most than least deprived groups (**Figure 3n**). Lung cancer mortality rates were also higher in current than former or non-smokers (**Figure 3p**), with increasing trends in current (AAPC: 2.6%; 1.9, 3.3) and former (5.7%; 5.5, 5.9) smokers and decreasing in non-smokers (-11.0%; -11.1, -10.9) (**ESM Table 7**).

Standardised mortality ratio

SMRs of all-cause, all cancer, and cancer-specific mortality comparing type 2 diabetes to the general population were estimated for the whole study period and three stratified periods: 1998-2007, 2008-2012, and 2013-2018 (**Table 4**). Individuals with type 2 diabetes had higher rates of all-cause, all cancer, and colorectal, pancreatic, liver, breast, and endometrial cancer mortality, with SMRs ranging from 1.08 to 2.40.

SMRs for all-cause and all cancer mortality increased and then levelled off after 2008, with a SMR of 1.01 (0.99, 1.04) during 1998-2007, 1.19 (1.17, 1.21) during 2008-2012, and 1.17 (1.15, 1.19) during 2013-2018 for all-cause mortality; corresponding values for all cancer mortality were 1.14 (1.09, 1.19), 1.26 (1.22, 1.30), and 1.21 (1.18, 1.24). SMRs for colorectal, pancreatic, liver, and endometrial cancer mortality were consistently high (>1.5) during the whole study period while there was no evidence of an association with prostate cancer mortality (0.99; 0.92, 1.05). SMRs for non-sex-specific cancers were higher in women than men.

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Discussion

To a variable extent, we confirmed reductions in all-cause mortality at all ages in people with type 2 diabetes; conversely, all cancer mortality rates declined at younger (<65 years) but increased at older ages, with an increasing proportions of cancer death out of all-cause death in older people. Upward trends in all cancer mortality were observed in both men and women, people of White ethnicity, in both the least and most deprived quintiles, and in people with normal weight and with severe obesity. With higher baseline rates but smaller increases in all cancer mortality in men than women, and in the most deprived than the least deprived group, we still observed persistent inequalities by gender and deprivation. However, higher rates and increasing trends in current/former smokers led to widening disparities in both all-cause and cancer mortality rates by smoking status. Furthermore, there was evidence of constantly increasing trends in pancreatic, liver, and lung cancer mortality at all ages; colorectal cancer mortality at most ages; breast cancer mortality at younger ages; and prostate and endometrial cancer mortality at older ages. Compared to the general population, people with type 2 diabetes had more than 1.5-fold increased risk of colorectal, pancreatic, liver, and endometrial cancer mortality.

Temporal variations in the definitions and ascertainment of populations and exposures may influence trend estimates in epidemiological studies. As the quality of diabetes recording in CPRD has changed over time, possibly in relation to the implementation of the UK Quality and Outcomes Framework in 2004,[20] there could be variations in the characteristics of people with type 2 diabetes across the years, being those with pre-existing complications and at a higher mortality risk more common during the initial years of the cohort. At the same time, a more proactive identification of cases of type 2 diabetes earlier in the trajectory of the disease, alongside changes in the diagnostic criteria, the increasing incidences of early onset type 2 diabetes,[21] and the availability of newer glucose-lowering treatments with robust cardioprotective effects may have also contributed to the pattern of a slightly increase followed by declining trends in mortality rates.[22, 23] Furthermore, the reduced risk of fatal cardiovascular events and the resulting prolonged exposure to diabetes increase the likelihood of being diagnosed with conditions other than cardiovascular diseases, including cancer: this could partly explain the overall increasing rates and proportions of cancer deaths over time in the older age groups.[24] Lastly, as evident by improved survival,[25] early detection and cancer treatment may have also improved over time, and this may disproportionally benefit different subgroups of people with type 2 diabetes.

Our investigations has some strengths and limitations. First, we derived our cohort from electronic health records of primary care patients representative of the general population in England. However, these data are not collected for research purpose and the generalisability of our findings is limited by

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the characteristics of the included individuals and the potential differences in the healthcare system between the UK and other countries. Although we excluded individuals with type 1 diabetes and our clinical codes were reviewed by clinicians practicing in England, misclassification is still possible. Second, to our knowledge this is the first study describing cancer-specific mortality trends by sociodemographic characteristics and risk factors in people with type 2 diabetes in England. Despite the large sample size, there were small numbers of deaths in some groups (e.g., across ethnicity), which precluded the possibility to obtain precise and robust assessment of some trends or investigate more granularly ethnic differences. Third, we used a modelling approach to estimate age-specific mortality rates to control for the impact of age and diabetes durations: indeed, the mean/median age of individuals with type 2 diabetes differs across countries (e.g., 58.5 years in a previous Australian study [26] vs. 63.8 year in our study), and the overall trends across risk factors might simply reflect differences in the age compositions or diabetes duration.[27, 28] Fourth, as our analyses are descriptive, they should not be interpreted as definitively indicating a causal relationship between sociodemographic characteristics or risk factors and cancer. For example, lung cancer mortality rates were higher in the most than least deprived group and in smokers than non-smokers but deprivation and smoking status were not mutually adjusted for when estimating rates in these subgroups. In this respect, it is worth noting that removing the causal exposure associated with the higher cancer mortality rates results in a reduction in the cancer-specific mortality but, at the same time, the risk of competing cause(s) of death could remain the same or even increase, potentially leading to a higher overall risk of death. Whether the magnitude of the effect for the same change of an exposure (e.g., most vs. least deprived) differs across competing causes of deaths should be specifically explored in competing risk analyses. Fifth, many contextual factors, such as changes in timings and treatments of diabetes and/or cancer, may contribute to our observed trends but were not accounted for in our analyses. Lastly, individuals with missing data on each factor were not included in the corresponding subgroup analysis but our results are unlikely to be largely biased, given the small amount of missing data (<10%).[29]

While declining trends in the rates of all-cause mortality among people with diabetes – mainly due to a reduced vascular mortality [26, 27, 30, 31] – have been consistently reported in the literature,[4, 5, 26, 27, 30-37] the evidence is less clear for cancer, making a coherent understanding of the cancer burden in people with diabetes more difficult. Downward trends of cancer mortality rates have been observed in several studies [5, 26, 27, 30, 31, 33] while upward ones reported in Sweden and Taiwan;[35, 36] proportions of cancer deaths remained stable in the US [30, 32] but increased in Australia and UK.[5, 38] Notably, these studies estimated the overall rates or proportions, while we investigated in more detail age-specific rates and proportions of cancer death. In contrast to an increasing trend of mortality in young adults with type 2 diabetes reported in other countries,[27, 28] we observed increasing trends only at older ages with a parallel reduction in both rates and proportions of cancer deaths at younger ages (<65 years). Our findings also suggest a slightly increased SMR for cancer mortality, which

stabilised over time at 1.2, in line with a previous systematic review with trend analysis.[39] While a similar analysis in Australia suggested an initial reduction in SMRs followed by a stable trend, SMR also stabilised at approximately 1.2 around 2010.[28, 38] Taken together, our results confirmed that the burden of cancer has increased in individuals with type 2 diabetes in England; at the same time, we evidenced relevant differences across age groups as such increase occurred mainly in older individuals.

Inequalities in cancer mortality by sociodemographic factors were persistent in our cohort. Consonant with some previous findings from meta-analyses, [12, 40, 41] in our study SMRs of some cancer-specific mortality were higher in women; however, these results should be interpreted alongside the lower baseline cancer mortality rates in women than men. Moreover, in line with cancer mortality data in people with diabetes in US,[42] we also observed a higher risk of cancer in White than other ethnicities, and in the most than least deprived group. However, in contrast to the stable gaps across ethnicity and deprivation observed in the same US study,[42] we observed a narrowing but persistent gap across ethnicity and socioeconomic status. These divergent findings may be related to differences in the social and healthcare systems and their reforms in the last two decades,[43, 44] and in the measurements of socioeconomic status and classifications of ethnicities between the two countries. Of note, clinical coding of ethnicities has improved over time in CPRD,[45] which may have also influenced our results.

Few studies have reported cancer mortality rates by risk factors (i.e., smoking and obesity) in people with type 2 diabetes. Our results showed that the cancer mortality rates in people with obesity were not higher than those in people with normal weight, similar to a previous study in US.[42] However, we also evidenced a smaller increase in people with normal weight than those with severely obesity, leading to similar rates between these two groups during in the last years of observation. To our knowledge, this is the first study in people with type 2 diabetes showing constantly higher cancer mortality rates in current and former smokers than non-smokers, in parallel with a steady increase among smokers, leading to widening gaps in cancer mortality rates between smokers and non-smokers.

Our study has important clinical and public health implications. The prevention of cardiovascular disease has been, and it is still considered as, a priority in people with diabetes. Our results challenge this view by showing that cancer may have overtaken cardiovascular diseases as a leading cause of death in people with type 2 diabetes; cancer prevention strategies would therefore deserve at least a similar attention as cardiovascular disease prevention,[46] particularly in older people and for some cancer sites such as liver, colorectal, and pancreas. Tailored interventions should be also considered for smokers, who had higher and steadily increased cancer mortality rates. Early cancer detection through changes to existing screening programmes – or more in-depth investigations for suspected/non-specific symptoms [47] – may reduce the number of avoidable cancer deaths in people with type 2 diabetes. From this perspective, our results suggest the opportunity to extend breast cancer screening in young women with type 2 diabetes. However, given the high cost and the potentially longer exposure to

screening procedures, cost-effectiveness analyses are required to define the appropriate time window and identify subgroups who could benefit more. Lastly, the number of people with concurrent cancer and type 2 diabetes will likely increase in the future, highlighting the importance of enhancing a multi-disciplinary clinical management in these patients.

In conclusion, our findings underline the growing cancer burden in people with type 2 diabetes, particularly in older individuals, and highlight the necessity to prioritise cancer prevention, research, early detection, and management in this population, especially for colorectal, pancreatic, liver, and endometrial cancer, whose mortality rates were substantially higher in individuals with type 2 diabetes than in the general population. Persistent inequalities in cancer mortality by sociodemographic factors and widening disparities by smoking suggest that tailored cancer prevention and detection strategies are needed, as some subgroups such as smokers not only experienced higher mortality rates but also increasing mortality trends during the study period.

Contributions

SL, FZ and KB designed the study; KB, EI and KK acquired research funding; FZ and EI defined clinical codes; SL extracted, cleaned and analysed data, and drafted the article; FZ supported data analysis; all authors contributed to the interpretation of the data, critically revised the article, and approved the final version.

SL and FZ had full access to all the data. SL is responsible for the integrity of the work as a whole.

Conflicts of interest

KK has acted as a consultant, speaker or received grants for investigator-initiated studies for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer. All other authors declare no conflict of interest related this work.

Data sharing

Data access is through permission from CPRD only: please send any enquiries to enquiries@cprd.com. All clinical code lists and statistical codes are available online (https://github.com/supingling/cancerindiabetes).

Reference

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Figure legend

Figure 1. Trends in all-cause mortality rates and all cancer mortality rates

Legend: Age-specific mortality rates (per 1,000 person-years) for all-cause mortality (a) and all cancer mortality (g). All rates were estimated for the median of diabetes duration (8.4 years). Rates stratified by gender (b and h), ethnicity (c and i), socioeconomic status (d and j), body mass index groups (e and k), and smoking (f and l) were also age-adjusted and presented for median age at end of follow-up (72 years old).
Bars indicate 95% confidence interval.
The number of all cancer deaths in people of other ethnicities (other than White) was small in some years, leading to predicted rates with large uncertainties.
All estimates are also reported in Electronic Supplemental Material Table 1-6.

Figure 2. Proportion of cancer deaths out of all-cause deaths

Legend: The proportion was calculated as all cancer mortality rate divided by all-cause mortality rate in each stratum and calendar year; 95% confidence intervals were estimated using non-parametric bootstrap method with 500 replicates. Proportion of cancer deaths out of all-cause deaths at different ages (a, b, c, and d), gender (e and f), deprivation (h and i), body mass index groups (j, k, l, and m), and smoking status (n, o, and p).
Bars indicate 95% confidence interval.
The number of all cancer deaths in people of ethnicity other than White was small in some years, leading to predicted rates with large uncertainties and unstable proportion estimates; only proportions for White ethnicity are shown (g).
All estimates are also reported in Electronic Supplemental Material Table 1-6.

Figure 3. Trends in cancer-specific mortality rates for four common cancers

Legend: Age-specific mortality rates (per 100,000 person-years) for breast (a), prostate (f), lung (k) and colorectal cancer (q). All rates were estimated for the median of diabetes duration (8.4 years). Rates stratified by gender (l and r), ethnicity (b, g, m, and s), socioeconomic status (c, h, n, and t), body mass index groups (d, i, o and u), and smoking (e, j, p, and v) were also age-adjusted and presented for median age at end of follow-up (72 years old).
Bars indicate 95% confidence intervals.
Stratified analysis by gender not applicable for breast and prostate cancer. The number of breast and prostate cancer deaths in people of ethnicity other than White was small in some years, leading to predicted rates with large uncertainties.

Figure 4. Trends in cancer-specific mortality rates for type 2 diabetes-related cancers

Legend: Age-specific mortality rates (per 100,000 person-years) for cancer of pancreas (a), and liver (g). All rates were estimated for the median of diabetes duration (8.4 years). Rates stratified by gender (b and h), ethnicity (c and i), socioeconomic status (d and j), body mass index groups (e and k), and smoking (f and l) were also age-adjusted and presented for median age at end of follow-up (72 years old).

Bars indicate 95% confidence intervals.

The number of liver cancer deaths in people of ethnicity other than White and in the most deprived group was small in some years, leading to predicted rates with large uncertainties. Due to a small number of events, trends for gallbladder and endometrial cancer mortality rates are not shown but estimates are reported in Electronic Supplemental Material Table 8.

Table 1. Baseline characteristics of individuals at type 2 diabetes diagnosis

	Total N=137,804
Year at type 2 diabetes diagnosis	
1998	1,804 (1.3%)
1999	2,277 (1.7%)
2000	3,592 (2.6%)
2001	5,278 (3.8%)
2002	6,710 (4.9%)
2003	8,225 (6.0%)
2004	8,705 (6.3%)
2005	8,822 (6.4%)
2006	10,228 (7.4%)
2007	8,886 (6.4%)
2008	9,102 (6.6%)
2009	9,321 (6.8%)
2010	9,045 (6.6%)
2011	8,492 (6.2%)
2012	8,745 (6.3%)
2013	8,512 (6.2%)
2014	6,300 (4.6%)
2015	5,235 (3.8%)
2016	3,859 (2.8%)
2017	2,514 (1.8%)
2018	2,152 (1.6%)
Age at diagnosis, years	
Median (interquartile range)	63.8 (54.2-73.0)
<55	37,055 (26.9%)
55-64.9	36,478 (26.5%)
65-74.9	36,479 (26.5%)
75-84.9	22,230 (16.1%)
≥85	5,562 (4.0%)
Gender	
Men	76,360 (55.4%)
Women	61,444 (44.6%)
Ethnicity	
White	114,394 (83.0%)
Others*	11,777 (8.5%)
South Asian	4,820 (3.5%)
Black	2,771 (2.0%)
Other	4,186 (3.0%)
Missing	11,633 (8.4%)
Index of multiple deprivation 2010, quintiles	
1st quintile – Least deprived	26,484 (19.2%)
2	30,691 (22.3%)
3	28,075 (20.4%)
4	28,198 (20.5%)
5th quintile – Most deprived	24,242 (17.6%)
Missing	114 (0.1%)
Body mass index, kg/m^2	
Median (interquartile range)	30.6 (27.1-34.9)
<18.5	579 (0.4%)
18.5-24.9	16,126 (11.7%)
25.0-29.9	43,026 (31.2%)
30.0-34.9	37,203 (27.0%)
≥35.0	31,262 (22.7%)
Missing	9,608 (7.0%)
Smoking status	
Current smoker	23,044 (16.7%)
Ex-smoker	45,616 (33.1%)
Non-smoker	64,652 (46.9%)
Missing	4,492 (3.3%)

*Others include South Asian, Black and other ethnic groups.

Table 2. Follow-up person-years and number of events by gender, ethnicity, socioeconomic status, body mass index, and smoking status

| | No. of individuals | Person-years | No. of deaths, n (%) | | | | | | | | | | |
| | | | All-cause | All cancer | Type 2 diabetes-related cancer | | | | Common cancer | | | |
					Pancreas	Liver	Gallbladder	Endometrium	Breast	Prostate	Colorectal	Lung
Total sample	137,804	1,194,444	39,212 (28.5)	11,309 (8.2)	1,033 (0.7)	471 (0.3)	43 (0.0)	-	-	-	1,093 (0.8)	2,164 (1.6)
Gender												
Men	76,360	665,406	20,788 (27.2)	6,613 (8.7)	536 (0.7)	328 (0.4)	11 (0.0)	-	-	848 (1.1)	647 (0.8)	1,305 (1.7)
Women	61,444	529,038	18,424 (30.0)	4,696 (7.6)	497 (0.8)	143 (0.2)	32 (0.1)	148 (0.2)	616 (1.0)	-	446 (0.7)	859 (1.4)
Ethnicity												
White	114,394	999,933	35,835 (31.3)	10,514 (9.2)	945 (0.8)	434 (0.4)	<10	<10	563 (0.5)	795 (0.7)	1,015 (0.9)	2,037 (1.8)
Others*	11,777	97,177	1,128 (9.6)	338 (2.9)	30 (0.3)	26 (0.2)	<10	<10	29 (0.2)	31 (0.3)	30 (0.3)	43 (0.4)
South Asian	4,820	41,827	392 (8.1)	107 (2.2)	<10	10 (0.2)	<10	<10	<10	<10	<10	<10
Black	2,771	21,682	303 (10.9)	114 (4.1)	11 (0.4)	<10	<10	<10	<10	21 (0.8)	11 (0.4)	<10
Other	4,186	33,668	433 (10.3)	117 (2.8)	<10	<10	<10	<10	<10	<10	<10	<10
IMD 2010												
1st quintile (Least deprived)	26,484	232,646	6,833 (25.8)	2,104 (7.9)	236 (0.9)	88 (0.3)	<10	33 (0.1)	118 (0.4)	184 (0.7)	198 (0.7)	321 (1.2)
2	30,691	269,942	8,922 (29.1)	2,691 (8.8)	261 (0.9)	115 (0.4)	<10	28 (0.1)	158 (0.5)	216 (0.7)	269 (0.9)	431 (1.4)
3	28,075	245,218	8,169 (29.1)	2,297 (8.2)	210 (0.7)	98 (0.3)	<10	28 (0.1)	124 (0.4)	183 (0.7)	227 (0.8)	430 (1.5)
4	28,198	241,539	8,064 (28.6)	2,241 (7.9)	190 (0.7)	96 (0.3)	<10	36 (0.1)	126 (0.4)	156 (0.6)	213 (0.8)	471 (1.7)
5th quintile (Most deprived)	24,242	204,130	7,172 (29.6)	1,961 (8.1)	136 (0.6)	73 (0.3)	<10	22 (0.1)	96 (0.4)	108 (0.4)	185 (0.8)	509 (2.1)
BMI, kg/m^2												
18.5-24.9	16,126	128,701	6,821 (42.3)	1,698 (10.5)	185 (1.1)	47 (0.3)	<10	11 (0.1)	89 (0.6)	130 (0.8)	137 (0.8)	360 (2.2)
25.0-29.9	43,026	376,630	12,982 (30.2)	3,955 (9.2)	381 (0.9)	162 (0.4)	<10	31 (0.1)	185 (0.4)	334 (0.8)	381 (0.9)	759 (1.8)
30.0-34.9	37,203	327,139	8,833 (23.7)	2,846 (7.6)	239 (0.6)	135 (0.4)	<10	37 (0.1)	149 (0.4)	237 (0.6)	278 (0.7)	528 (1.4)
≥35.0	31,262	268,578	5,674 (18.1)	1,686 (5.4)	131 (0.4)	79 (0.3)	<10	53 (0.2)	126 (0.4)	77 (0.2)	156 (0.5)	301 (1.0)
Smoking status												
Current smoker	23,044	199,498	6,789 (29.5)	2,302 (10.0)	214 (0.9)	78 (0.3)	<10	<10	66 (0.3)	104 (0.5)	140 (0.6)	859 (3.7)
Ex-smoker	45,616	378,798	13,859 (30.4)	4,262 (9.3)	358 (0.8)	170 (0.4)	<10	<10	175 (0.4)	374 (0.8)	414 (0.9)	955 (2.1)
Non-smoker	64,652	566,117	16,291 (25.2)	4,261 (6.6)	427 (0.7)	204 (0.3)	<10	<10	352 (0.5)	339 (0.5)	480 (0.7)	280 (0.4)

*Others include South Asian, Black and other ethnic groups.

IMD: index of multiple deprivation; BMI: body mass index; -: not applicable.

Individuals with missing data on ethnicity, socioeconomic status, BMI or smoking status, or individuals with underweight (<18.5 kg/m^2 of BMI) were not included in the corresponding stratified analyses.

No. of deaths (%) are shown; cells with values of frequency lower than 10 (or could be used to identify other cells as lower than 10) are not shown due to the data privacy protection.

Table 3. Annual percentage change and average annual percentage change in all-cause and all cancer mortality rates

	Period 1	APC, %	Period 2	APC, %	Period 3	APC, %	Period 4	APC, %	AAPC for whole period, %
All-cause death									
Age, years									
55	1998-2008	2.8 (2.5, 3.1)	2008-2015	-2.7 (-3.0, -2.4)	2015-2018	-9.9 (-11.6, -8.1)	–	–	-1.1 (-1.4, -0.8)
65	1998-2008	1.5 (1.4, 1.6)	2008-2012	-4.4 (-4.8, -3.9)	2012-2015	0.4 (-0.6, 1.4)	2015-2018	-7.3 (-8.0, -6.5)	-1.2 (-1.4, -1.0)
75	1998-2008	0.4 (0.2, 0.5)	2008-2012	-5.7 (-6.2, -5.3)	2012-2016	1.1 (0.5, 1.7)	2016-2018	-10.1 (-11.8, -8.3)	-1.8 (-2.1, -1.6)
85	1998-2008	0.0 (-0.1, 0.1)	2008-2012	-3.4 (-3.6, -3.1)	2012-2015	2.5 (1.9, 3.1)	2015-2018	-7.4 (-7.8, -7.0)	-1.5 (-1.6, -1.4)
Gender									
Men	1998-2008	0.0 (-0.1, 0.2)	2008-2012	-6.0 (-6.4, -5.5)	2012-2016	1.0 (0.4, 1.5)	2016-2018	-8.7 (-10.3, -7.0)	-1.9 (-2.1, -1.7)
Women	1998-2008	1.2 (1.1, 1.3)	2008-2012	-5.6 (-6.0, -5.1)	2012-2015	3.1 (2.1, 4.2)	2015-2018	-6.4 (-7.1, -5.7)	-1.1 (-1.3, -0.9)
Ethnicity									
White	1998-2009	3.4 (3.4, 3.5)	2009-2012	-4.5 (-5.1, -3.9)	2012-2016	1.5 (1.2, 1.9)	2016-2018	-8.1 (-9.1, -7.1)	0.6 (0.5, 0.8)
Others	1998-2009	-0.8 (-0.8, -0.7)	2009-2013	-8.4 (-8.8, -8.0)	2013-2016	6.4 (5.3, 7.5)	2016-2018	-19.0 (-20.7, -17.3)	-3.3 (-3.5, -3.1)
Deprivation									
Least deprived	1998-2008	2.9 (2.6, 3.2)	2008-2013	-7.1 (-7.8, -6.5)	2013-2016	2.9 (0.3, 5.4)	2016-2018	-11.9 (-15.6, -8.0)	-1.3 (-1.8, -0.7)
Most deprived	1998-2008	2.9 (2.6, 3.1)	2008-2012	-7.2 (-7.8, -6.5)	2012-2016	2.7 (1.9, 3.6)	2016-2018	-9.9 (-12.3, -7.5)	-0.6 (-0.9, -0.3)
BMI group, kg/m²									
18.5-24.9	1998-2008	0.6 (0.5, 0.7)	2008-2012	-4.9 (-5.3, -4.6)	2012-2015	2.0 (1.2, 2.8)	2015-2018	-5.3 (-5.8, -4.7)	-1.2 (-1.4, -1.1)
25.0-29.9	1998-2008	-1.1 (-1.2, -1.0)	2008-2012	-3.1 (-3.4, -2.8)	2012-2015	2.7 (2.0, 3.3)	2015-2018	-11.8 (-12.3, -11.3)	-2.6 (-2.8, -2.5)
30.0-34.9	1998-2009	-1.5 (-1.5, -1.4)	2009-2013	-5.9 (-6.1, -5.7)	2013-2016	1.1 (0.6, 1.6)	2016-2018	-3.8 (-4.5, -3.0)	-2.2 (-2.3, -2.1)
≥35.0	1998-2010	0.9 (0.9, 1.0)	2010-2013	-4.5 (-4.9, -4.0)	2013-2016	0.8 (0.3, 1.4)	2016-2018	-5.3 (-6.0, -4.5)	-0.6 (-0.7, -0.4)
Smoking status									
Current smoker	1998-2008	2.4 (2.3, 2.5)	2008-2013	-2.3 (-2.5, -2.0)	2013-2016	0.4 (-0.4, 1.1)	2016-2018	-3.3 (-4.3, -2.3)	0.3 (0.2, 0.5)
Ex-smoker	1998-2009	-0.9 (-0.9, -0.8)	2009-2012	-4.8 (-5.1, -4.5)	2012-2016	0.7 (0.5, 0.9)	2016-2018	-8.1 (-8.7, -7.6)	-1.9 (-2.0, -1.8)
Non-smoker	1998-2008	-0.6 (-0.7, -0.5)	2008-2012	-6.0 (-6.4, -5.6)	2012-2015	0.5 (-0.4, 1.5)	2015-2018	-7.8 (-8.5, -7.1)	-2.6 (-2.8, -2.4)
All cancer death									
Age, years									
55	1998-2012	1.3 (1.2, 1.3)	2012-2015	-2.6 (-3.1, -2.2)	2015-2018	-11.8 (-12.2, -11.3)	–	–	-1.4 (-1.5, -1.3)
65	1998-2006	2.6 (2.5, 2.7)	2006-2009	1.7 (1.0, 2.3)	2009-2015	-2.6 (-2.7, -2.5)	2015-2018	-4.4 (-4.8, -3.9)	-0.2 (-0.3, -0.1)
75	1998-2008	5.6 (5.3, 5.9)	2008-2013	-4.6 (-5.1, -4.1)	2013-2016	2.3 (0.6, 4.1)	2016-2018	-6.8 (-9.3, -4.2)	1.2 (0.8, 1.6)
85	1998-2008	4.5 (4.4, 4.6)	2008-2012	-0.7 (-1.0, -0.3)	2012-2015	3.3 (2.6, 4.0)	2015-2018	-6.1 (-6.6, -5.7)	1.6 (1.5, 1.7)
Gender									
Men	1998-2008	3.3 (3.0, 3.6)	2008-2013	-5.5 (-6.2, -4.8)	2013-2018	1.2 (0.5, 1.9)	–	–	0.5 (0.2, 0.8)
Women	1998-2008	6.7 (6.3, 7.2)	2008-2015	-2.0 (-2.3, -1.6)	2015-2018	-7.0 (-8.8, -5.1)	–	–	1.5 (1.1, 1.8)
Ethnicity									
White	1998-2009	6.3 (6.1, 6.4)	2009-2013	-4.3 (-4.8, -3.8)	2013-2016	1.4 (0.3, 2.5)	2016-2018	-3.1 (-4.6, -1.5)	2.4 (2.1, 2.6)
Others	1998-2009	-7.1 (-7.2, -7.0)	2009-2016	-3.2 (-3.5, -2.9)	2016-2018	19.0 (16.4, 21.6)	–	–	-3.4 (-3.6, -3.2)
Deprivation									
Least deprived	1998-2008	8.9 (7.9, 9.9)	2008-2012	-8.7 (-10.9, -6.3)	2012-2018	-3.3 (-4.6, -1.9)	–	–	1.5 (0.7, 2.2)
Most deprived	1998-2009	3.0 (3.0, 3.0)	2009-2012	-0.5 (-0.8, -0.2)	2012-2015	-3.9 (-4.2, -3.6)	2015-2018	0.3 (0.0, 0.5)	1.0 (0.9, 1.1)
BMI group, kg/m²									
18.5-24.9	1998-2007	1.9 (1.8, 2.0)	2007-2012	-2.3 (-2.5, -2.1)	2012-2015	5.1 (4.5, 5.8)	2015-2018	-1.9 (-2.3, -1.5)	0.7 (0.6, 0.9)
25.0-29.9	1998-2008	5.6 (4.8, 6.3)	2008-2016	-2.6 (-3.2, -2.0)	2016-2018	-8.4 (-16.0, -0.1)	–	–	0.8 (-0.1, 1.7)
30.0-34.9	1998-2009	2.7 (2.6, 2.8)	2009-2013	-7.3 (-7.7, -6.9)	2013-2016	2.8 (1.8, 3.9)	2016-2018	-3.2 (-4.6, -1.8)	0.0 (-0.2, 0.3)
≥35.0	1998-2010	11.3 (10.9, 11.6)	2010-2014	-7.3 (-8.1, -6.6)	2014-2018	4.1 (3.4, 4.7)	–	–	5.8 (5.6, 6.1)
Smoking status									
Current smoker	1998-2008	6.5 (6.4, 6.6)	2008-2011	2.8 (2.6, 3.1)	2011-2015	-1.5 (-1.6, -1.4)	2015-2018	0.8 (0.6, 0.9)	3.4 (3.4, 3.5)
Ex-smoker	1998-2009	3.6 (3.5, 3.7)	2009-2013	-5.2 (-5.5, -4.9)	2013-2016	2.3 (1.5, 3.1)	2016-2018	-5.5 (-6.6, -4.5)	0.6 (0.5, 0.8)
Non-smoker	1998-2006	1.8 (1.8, 1.8)	2006-2009	0.1 (-0.1, 0.3)	2009-2013	-5.7 (-5.8, -5.6)	2013-2018	-3.8 (-3.8, -3.7)	-1.4 (-1.4, -1.3)

APC: Annual Percentage Change; **AAPC**: Average Annual Percentage Change; –: Not applicable. Different number of segments for each stratum (period 1 to 4) are identified by Joinpoint regressions.

Table 4. Standardised mortality ratios compared to corresponding sex-specific general population

|	Standardised mortality ratio (95% confidence interval)			
	1998-2007	2008-2012	2013-2018	Whole period
Overall				
All-cause	1.01 (0.99, 1.04)	1.19 (1.17, 1.21)	1.17 (1.15, 1.19)	1.08 (1.07, 1.09)
All cancer	1.14 (1.09, 1.19)	1.26 (1.22, 1.30)	1.21 (1.18, 1.24)	1.18 (1.16, 1.20)
Common cancers				
Lung	0.87 (0.79, 0.97)	1.16 (1.08, 1.25)	1.08 (1.02, 1.15)	1.04 (1.00, 1.08)
Colorectal	2.10 (1.83, 2.39)	3.26 (2.93, 3.62)	2.81 (2.57, 3.06)	2.40 (2.26, 2.54)
Diabetes-related cancers				
Pancreatic	2.75 (2.41, 3.13)	2.36 (2.12, 2.62)	1.69 (1.54, 1.85)	2.12 (1.99, 2.25)
Liver	2.08 (1.60, 2.67)	1.85 (1.55, 2.20)	1.86 (1.65, 2.09)	2.13 (1.94, 2.33)
Gallbladder	1.26 (0.51, 2.60)	0.64 (0.24, 1.40)	1.77 (1.19, 2.52)	1.36 (0.99, 1.83)
Men				
All-cause	0.95 (0.92, 0.98)	1.14 (1.11, 1.17)	1.13 (1.11, 1.15)	1.02 (1.01, 1.04)
All cancer	1.08 (1.02, 1.15)	1.15 (1.10, 1.21)	1.14 (1.10, 1.18)	1.09 (1.06, 1.12)
Common cancers				
Prostate	0.85 (0.71, 1.01)	0.98 (0.86, 1.11)	1.11 (1.02, 1.22)	0.99 (0.92, 1.05)
Lung	0.78 (0.68, 0.89)	1.03 (0.93, 1.13)	1.03 (0.95, 1.11)	0.91 (0.86, 0.96)
Colorectal	2.03 (1.71, 2.40)	2.73 (2.37, 3.13)	2.36 (2.11, 2.64)	2.10 (1.94, 2.27)
Diabetes-related cancers				
Pancreatic	2.77 (2.31, 3.28)	2.11 (1.82, 2.44)	1.47 (1.28, 1.67)	1.90 (1.75, 2.07)
Liver	2.35 (1.73, 3.12)	1.85 (1.49, 2.28)	1.83 (1.58, 2.11)	2.12 (1.90, 2.36)
Gallbladder	1.49 (0.31, 4.36)	0.65 (0.08, 2.34)	1.07 (0.39, 2.34)	1.00 (0.50, 1.79)
Women				
All-cause	1.03 (0.99, 1.06)	1.20 (1.17, 1.23)	1.16 (1.14, 1.19)	1.09 (1.08, 1.11)
All cancer	1.14 (1.07, 1.22)	1.34 (1.27, 1.41)	1.22 (1.18, 1.28)	1.22 (1.19, 1.26)
Common cancers				
Breast	1.07 (0.89, 1.27)	1.11 (0.96, 1.29)	1.20 (1.07, 1.34)	1.09 (1.01, 1.18)
Lung	0.95 (0.79, 1.13)	1.29 (1.15, 1.44)	1.08 (0.98, 1.19)	1.15 (1.07, 1.23)
Colorectal	1.98 (1.57, 2.46)	3.86 (3.25, 4.54)	3.29 (2.87, 3.76)	2.61 (2.38, 2.87)
Diabetes-related cancers				
Pancreatic	2.62 (2.14, 3.19)	2.59 (2.23, 3.00)	1.92 (1.67, 2.19)	2.30 (2.11, 2.51)
Liver	1.29 (0.70, 2.16)	1.63 (1.18, 2.21)	1.65 (1.32, 2.04)	1.82 (1.54, 2.15)
Gallbladder	1.19 (0.32, 3.05)	0.68 (0.19, 1.74)	2.28 (1.46, 3.39)	1.68 (1.15, 2.36)
Endometrial	1.97 (1.24, 2.99)	2.18 (1.62, 2.88)	1.75 (1.38, 2.19)	2.08 (1.76, 2.44)

Age- and sex-standardised mortality ratios for the overall population (men and women); age-standardised mortality ratios in sex-specific estimates.

Standardised mortality ratios estimated for all-cause mortality, all cancer mortality, and cancer-specific mortality of four most common cancers and four type 2 diabetes-related cancers.
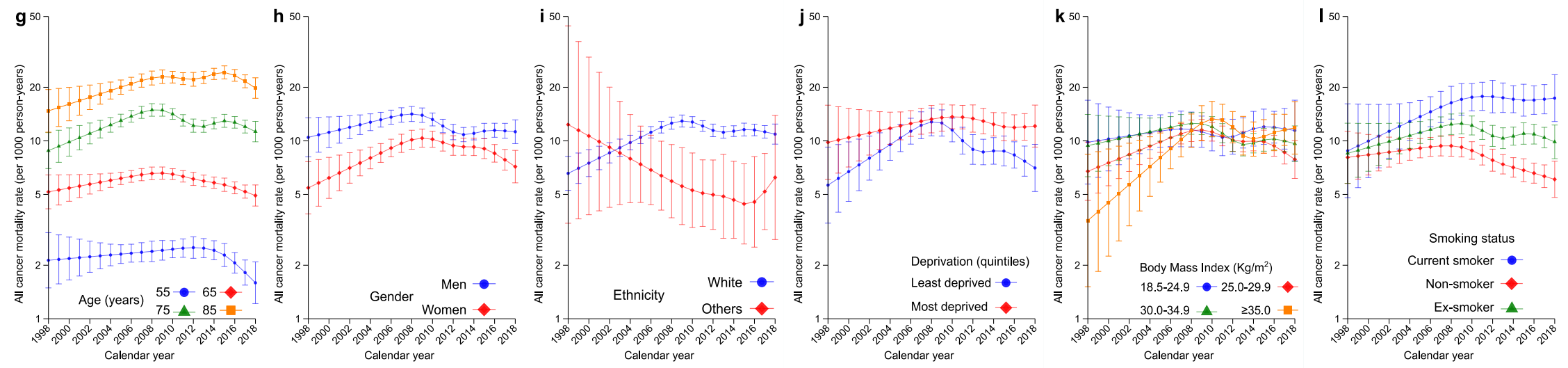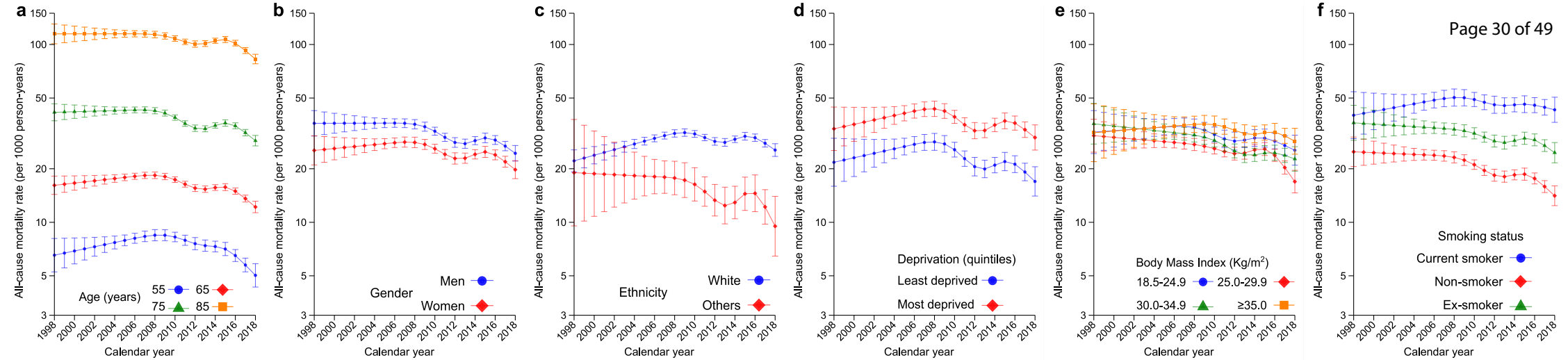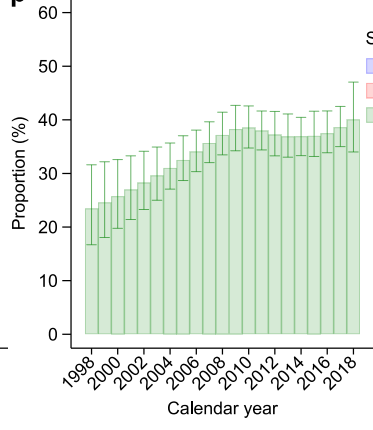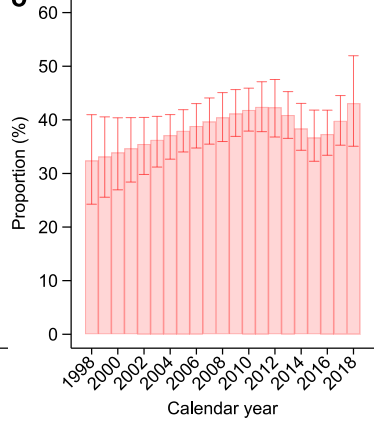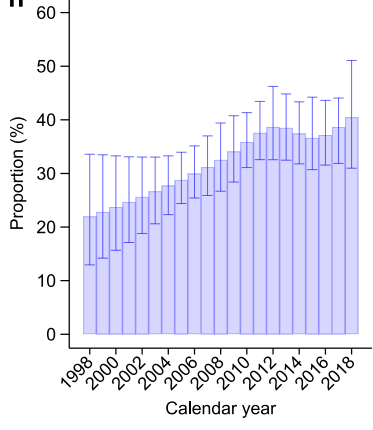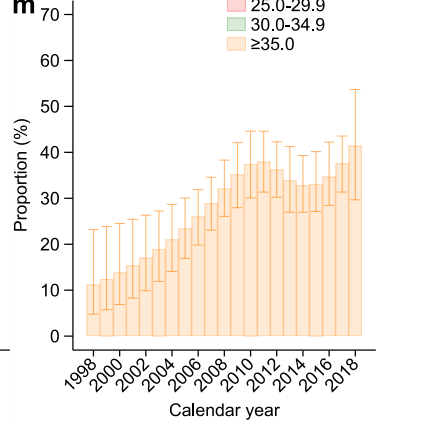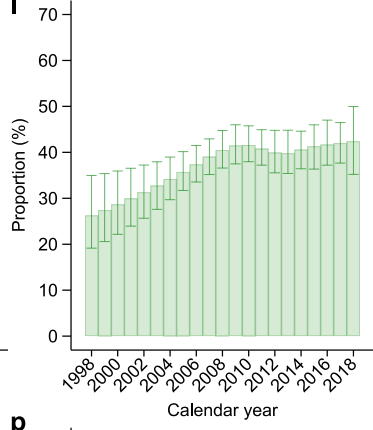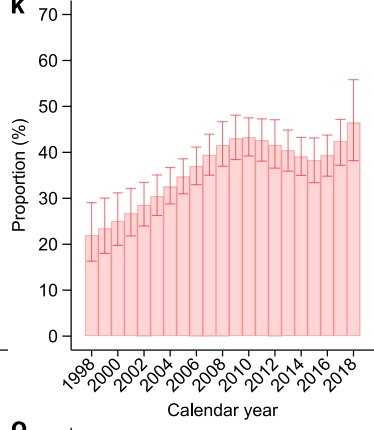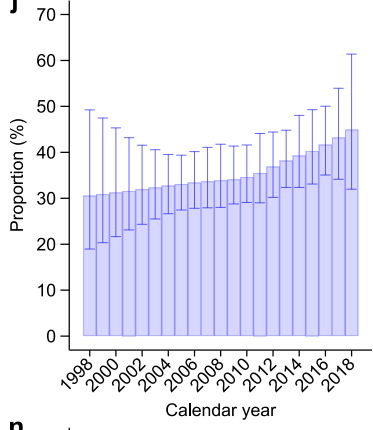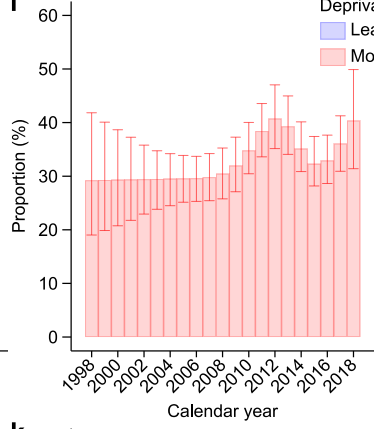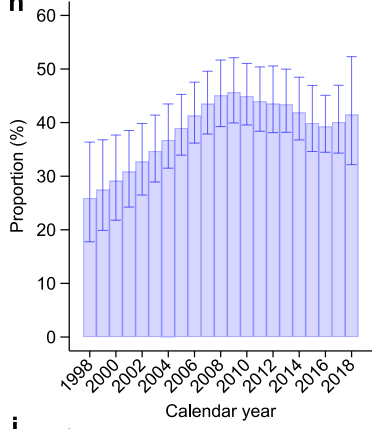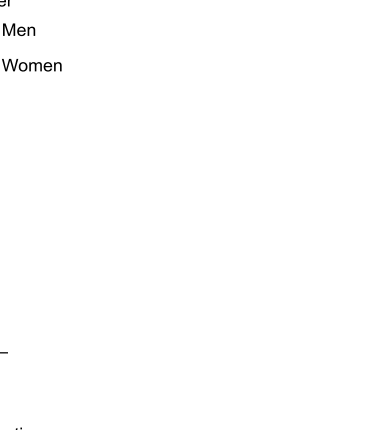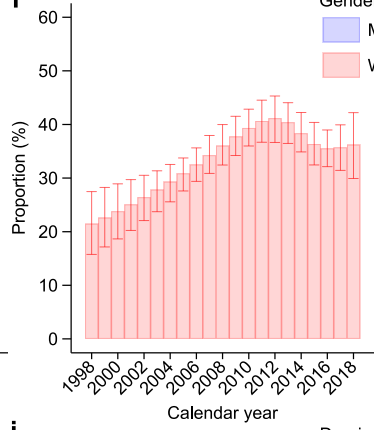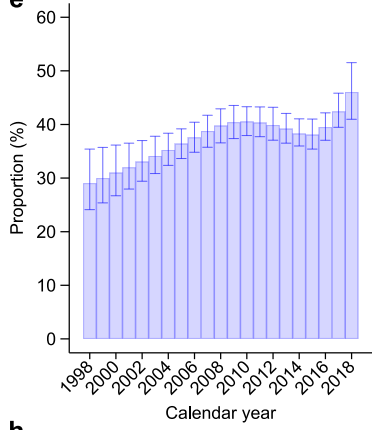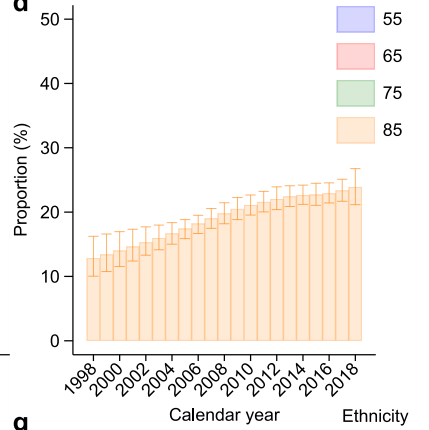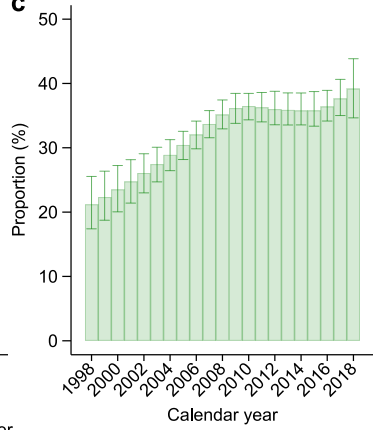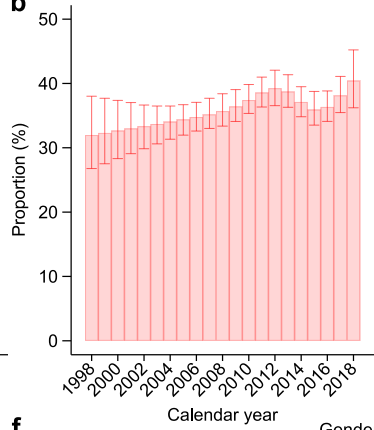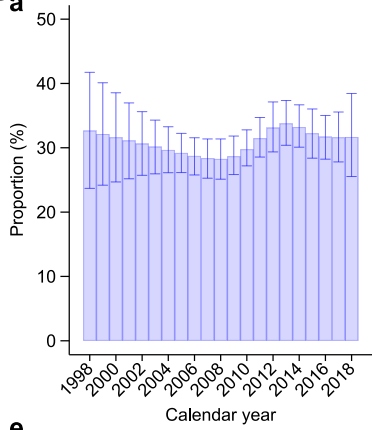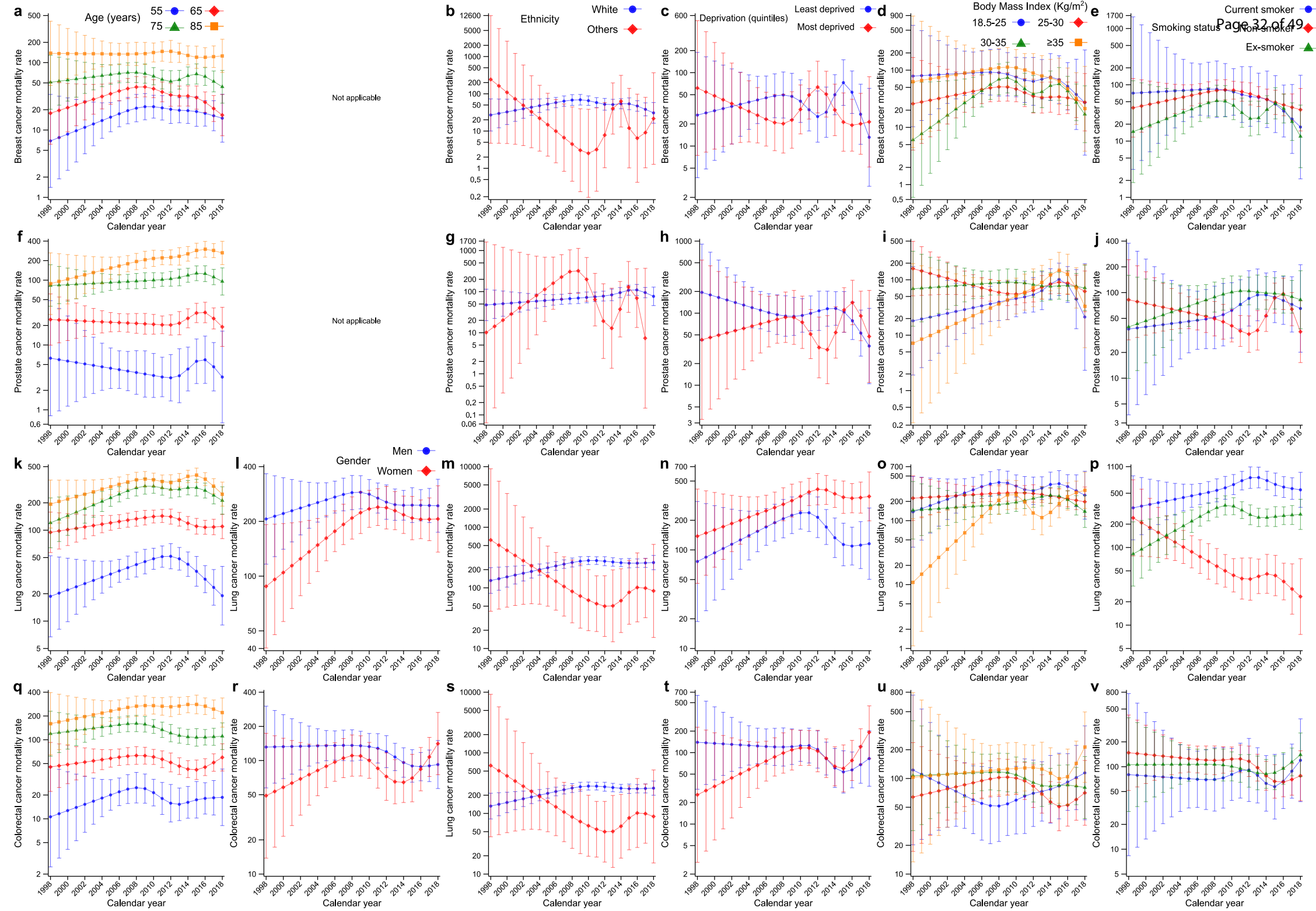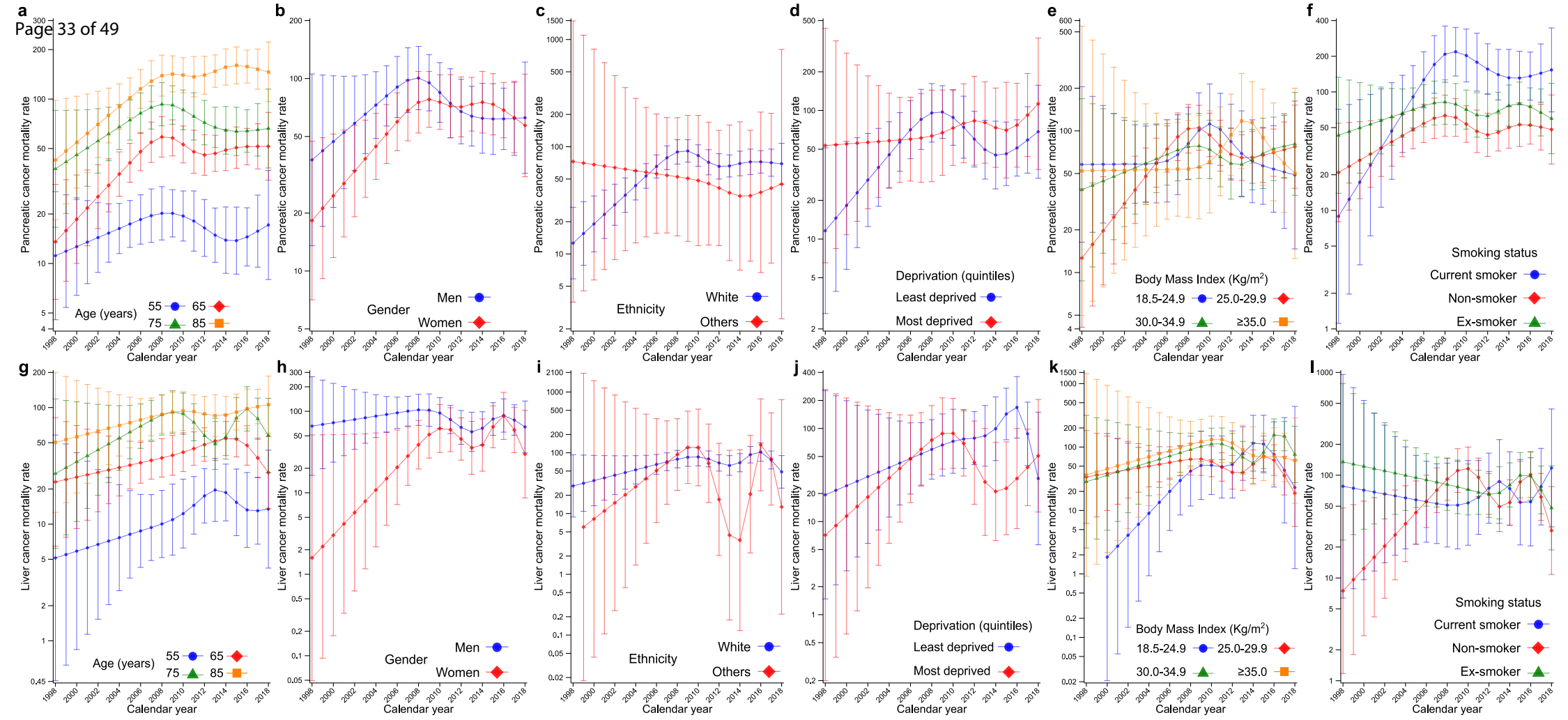
Electronic Supplementary Material

Inequalities in cancer mortality trends in people with type 2 diabetes:

20-year population-based study in England

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Contents

Additional results: All-cause mortality rates

Figure 1 shows all-cause mortality rates and corresponding 95% confidence intervals (CIs) from 1998 to 2018 by age (**Figure 1a**), gender (**Figure 1b**), ethnicity (**Figure 1c**), socioeconomic status (**Figure 1d**), BMI groups (**Figure 1e**), and smoking status (**Figure 1f**) with corresponding values in **ESM Tables 1-6**; APCs and AAPCs are presented in **Table 3**.

Overall, mortality rates in individuals with type 2 diabetes declined, with a small increase from 1998 to 2008 but a reduction thereafter, at all ages (**Figure 1**; **ESM Table 1**). For 55-year-old individuals, the mortality rate was 6.5 (95% CI: 5.3, 8.1) per 1000 person-years in 1998, 8.5 (7.9, 9.1) in 2008, and 5.0 (4.3, 5.9) in 2018; the resulting AAPC for the whole study period was -1.1% (-1.4, -0.8), indicating an annual 1.1% reduction from 1998 to 2018 (i.e., 22% reduction in the whole period of 20 years). Corresponding AAPCs for 65-, 75-, and 85-year-old were -1.2% (-1.4, -1.0), -1.8% (-2.1, -1.6), and -1.5% (-1.6, -1.4), respectively (**Table 3**).

Similar trends were observed in men and women. Although all-cause mortality rates were higher in men throughout the study period, there was a greater annual reduction in men [AAPC: -1.9% (95% CI: -2.1, -1.7)] than women [-1.1% (-1.3, -0.9)], leading to a narrowed gap by gender in more recent years (**Figure 1b**; **Table 3**; **ESM Table 2**).

Trends among people of White ethnicity were slightly different to other ethnicities, with an overall increase in White (0.6%; 0.5, 0.8) but a reduction in other ethnicities (-3.3%; -3.5, -3.1) over the entire study period (**Figure 1c**; **Table 3**; **ESM Table 3**).

When stratified by IMD quintiles, rates in the most deprived group were always higher than in least deprived. Reductions in all-cause mortality rates were higher in the least deprived (-1.3%; -1.8, -0.7) than in the most deprived (-0.6%; -0.9, -0.3), resulting in wider socioeconomic inequalities (**Figure 1d**; **Table 3**; **ESM Table 4**).

All-cause mortality rates or its trends were not differentiated across BMI groups, with reductions observed in all groups, yet such reduction was smallest in people who were severely obese (-0.6%; -0.7, -0.4) compared to other groups (**Figure 1e**; **Table 3**; **ESM Table 5**).

Rates were markedly higher in current than former or non-smokers, and gaps were wider in recent years, with an increase in the rates in current smoker (0.3%; 0.2, 0.5) and a reduction in former (-1.9%; -2.0, -1.8) or non-smoker (-2.6%; -2.8, -2.4) (**Figure 1f**; **Table 3**; **ESM Table 6**).

ESM Table 1. Trends in all-cause and all cancer mortality rates and proportions of cancer death by age

Period	55-year-old			65-year-old		
	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion
1998	6.5 (5.3, 8.1)	2.1 (1.5, 3.1)	32.7 (23.7, 41.7)	16.2 (14.3, 18.2)	5.2 (4.2, 6.4)	32.0 (26.8, 38.0)
1999	6.7 (5.5, 8.1)	2.2 (1.6, 3.0)	32.1 (24.2, 40.1)	16.4 (14.7, 18.2)	5.3 (4.4, 6.4)	32.3 (27.5, 37.7)
2000	6.9 (5.8, 8.2)	2.2 (1.7, 2.9)	31.6 (24.7, 38.6)	16.6 (15.2, 18.3)	5.4 (4.6, 6.4)	32.7 (28.3, 37.4)
2001	7.1 (6.1, 8.2)	2.2 (1.7, 2.8)	31.1 (25.2, 37.0)	16.9 (15.6, 18.3)	5.6 (4.8, 6.5)	33.0 (29.1, 37.0)
2002	7.3 (6.4, 8.2)	2.2 (1.8, 2.7)	30.6 (25.7, 35.6)	17.1 (16.0, 18.3)	5.7 (5.0, 6.5)	33.3 (29.8, 36.6)
2003	7.5 (6.8, 8.3)	2.3 (1.9, 2.7)	30.2 (25.9, 34.3)	17.4 (16.4, 18.4)	5.9 (5.3, 6.5)	33.7 (30.6, 36.5)
2004	7.7 (7.1, 8.4)	2.3 (2.0, 2.6)	29.7 (26.1, 33.3)	17.6 (16.8, 18.5)	6.0 (5.5, 6.6)	34.0 (31.3, 36.5)
2005	7.9 (7.4, 8.5)	2.3 (2.0, 2.6)	29.2 (26.2, 32.2)	17.9 (17.1, 18.7)	6.2 (5.7, 6.7)	34.4 (32.0, 36.7)
2006	8.1 (7.6, 8.7)	2.3 (2.1, 2.6)	28.8 (25.8, 31.6)	18.1 (17.4, 18.9)	6.3 (5.8, 6.8)	34.8 (32.6, 37.1)
2007	8.3 (7.8, 8.9)	2.4 (2.1, 2.7)	28.4 (25.3, 31.4)	18.4 (17.6, 19.1)	6.5 (6.0, 7.0)	35.2 (33.0, 37.7)
2008	8.5 (7.9, 9.1)	2.4 (2.1, 2.7)	28.3 (25.1, 31.4)	18.4 (17.6, 19.2)	6.6 (6.0, 7.1)	35.7 (33.4, 38.4)
2009	8.5 (7.9, 9.1)	2.4 (2.1, 2.8)	28.7 (25.8, 31.8)	18.1 (17.4, 18.9)	6.6 (6.1, 7.1)	36.4 (34.1, 39.1)
2010	8.3 (7.8, 8.8)	2.5 (2.2, 2.8)	29.8 (27.2, 32.8)	17.4 (16.7, 18.0)	6.5 (6.1, 7.0)	37.4 (35.3, 39.8)
2011	7.9 (7.4, 8.5)	2.5 (2.2, 2.8)	31.5 (28.6, 34.7)	16.4 (15.8, 17.0)	6.3 (5.9, 6.8)	38.6 (36.3, 41.0)
2012	7.6 (7.0, 8.2)	2.5 (2.2, 2.9)	33.1 (29.4, 37.1)	15.6 (14.9, 16.3)	6.1 (5.6, 6.7)	39.3 (36.5, 42.1)
2013	7.4 (6.9, 8.0)	2.5 (2.2, 2.8)	33.8 (30.4, 37.3)	15.4 (14.7, 16.0)	5.9 (5.5, 6.4)	38.7 (36.3, 41.4)
2014	7.3 (6.8, 7.8)	2.4 (2.1, 2.7)	33.2 (30.1, 36.7)	15.7 (15.1, 16.3)	5.8 (5.4, 6.3)	37.1 (34.8, 39.5)
2015	7.1 (6.5, 7.7)	2.3 (2.0, 2.6)	32.3 (28.4, 36.0)	15.8 (15.1, 16.5)	5.7 (5.2, 6.2)	35.9 (33.5, 38.8)
2016	6.5 (6.0, 7.0)	2.1 (1.8, 2.4)	31.7 (28.2, 35.0)	15.0 (14.4, 15.6)	5.4 (5.0, 5.9)	36.4 (34.1, 38.8)
2017	5.8 (5.3, 6.3)	1.8 (1.5, 2.1)	31.6 (27.8, 35.6)	13.6 (13.0, 14.2)	5.2 (4.8, 5.6)	38.1 (35.5, 41.1)
2018	5.0 (4.3, 5.9)	1.6 (1.2, 2.1)	31.7 (25.5, 38.4)	12.2 (11.3, 13.1)	4.9 (4.3, 5.7)	40.4 (36.2, 45.2)

Period	75-year-old			85-year-old		
	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion
1998	41.6 (37.2, 46.4)	8.8 (7.0, 11.1)	21.2 (17.4, 25.5)	114.8 (101.0, 130.5)	14.7 (11.2, 19.4)	12.8 (10.0, 16.2)
1999	41.7 (37.8, 46.0)	9.3 (7.6, 11.5)	22.3 (18.7, 26.4)	114.8 (102.4, 128.7)	15.4 (12.0, 19.7)	13.4 (10.8, 16.6)
2000	41.9 (38.4, 45.7)	9.9 (8.2, 11.8)	23.5 (20.0, 27.2)	114.8 (103.9, 126.9)	16.1 (13.0, 20.0)	14.0 (11.5, 17.0)
2001	42.1 (39.0, 45.3)	10.4 (8.9, 12.2)	24.8 (21.4, 28.2)	114.8 (105.3, 125.3)	16.8 (13.9, 20.3)	14.6 (12.4, 17.3)
2002	42.2 (39.6, 45.0)	11.0 (9.6, 12.6)	26.1 (23.0, 29.1)	114.8 (106.6, 123.7)	17.6 (15.0, 20.6)	15.3 (13.3, 17.7)
2003	42.4 (40.1, 44.7)	11.6 (10.4, 13.0)	27.5 (24.7, 30.1)	114.9 (107.9, 122.3)	18.4 (16.1, 21.0)	16.0 (14.1, 18.0)
2004	42.5 (40.6, 44.5)	12.3 (11.2, 13.5)	28.9 (26.4, 31.3)	114.9 (109.0, 121.0)	19.2 (17.2, 21.4)	16.7 (15.0, 18.4)
2005	42.7 (41.0, 44.4)	13.0 (12.0, 14.1)	30.4 (28.2, 32.6)	114.9 (109.9, 120.1)	20.0 (18.3, 22.0)	17.4 (15.9, 18.8)
2006	42.9 (41.3, 44.5)	13.7 (12.7, 14.8)	32.1 (29.8, 34.2)	114.9 (110.4, 119.6)	20.9 (19.2, 22.8)	18.2 (16.7, 19.5)
2007	42.9 (41.3, 44.6)	14.5 (13.4, 15.6)	33.7 (31.6, 35.8)	114.7 (110.1, 119.5)	21.8 (20.0, 23.8)	19.0 (17.5, 20.6)
2008	42.4 (40.7, 44.2)	14.9 (13.7, 16.2)	35.2 (32.9, 37.4)	113.8 (109.1, 118.7)	22.5 (20.6, 24.7)	19.8 (18.2, 21.5)
2009	41.1 (39.6, 42.8)	14.9 (13.8, 16.1)	36.2 (33.8, 38.5)	111.7 (107.2, 116.4)	22.9 (21.0, 25.0)	20.5 (18.8, 22.3)
2010	38.8 (37.5, 40.2)	14.2 (13.2, 15.2)	36.5 (34.3, 38.5)	108.0 (104.3, 112.0)	22.8 (21.1, 24.6)	21.1 (19.5, 22.7)
2011	35.9 (34.7, 37.2)	13.0 (12.1, 14.0)	36.3 (34.0, 38.6)	103.6 (100.0, 107.3)	22.4 (20.7, 24.2)	21.6 (20.0, 23.2)
2012	33.8 (32.4, 35.3)	12.2 (11.2, 13.3)	36.0 (33.6, 38.8)	100.6 (96.5, 104.8)	22.2 (20.3, 24.2)	22.0 (20.4, 23.9)
2013	33.6 (32.3, 34.9)	12.1 (11.2, 13.0)	35.9 (33.6, 38.5)	101.2 (97.5, 105.2)	22.7 (21.0, 24.6)	22.4 (20.9, 24.1)
2014	35.1 (33.8, 36.3)	12.5 (11.7, 13.5)	35.8 (33.6, 38.5)	105.0 (101.6, 108.6)	23.8 (22.1, 25.6)	22.6 (21.2, 24.2)
2015	36.2 (34.7, 37.7)	13.0 (11.9, 14.1)	35.8 (33.4, 38.7)	106.8 (102.7, 111.0)	24.2 (22.3, 26.4)	22.7 (21.1, 24.5)
2016	34.9 (33.6, 36.3)	12.7 (11.8, 13.7)	36.4 (34.2, 38.9)	101.8 (98.2, 105.6)	23.3 (21.6, 25.2)	22.9 (21.4, 24.5)
2017	31.9 (30.6, 33.3)	12.0 (11.1, 13.1)	37.7 (35.0, 40.6)	92.5 (89.0, 96.1)	21.6 (19.9, 23.5)	23.4 (21.7, 25.1)
2018	28.8 (26.9, 30.8)	11.3 (9.9, 12.9)	39.2 (34.6, 43.8)	82.8 (77.9, 88.1)	19.8 (17.3, 22.6)	23.9 (21.2, 26.8)

Proportion (%) and 95% confidence interval of cancer death out of all-cause death.

Rates and 95% confidence interval are presented per 1000 person-years.

ESM Table 2. Trends in all-cause and all cancer mortality rate and proportions of cancer death by gender

Period	Men			Women		
	All-cause	**All cancer**	**Proportion**	**All-cause**	**All cancer**	**Proportion**
1998	36.0 (30.6, 42.5)	10.5 (8.1, 13.5)	29.0 (24.1, 35.4)	25.4 (21.0, 30.6)	5.4 (3.9, 7.6)	21.5 (15.8, 27.5)
1999	36.1 (31.1, 41.7)	10.8 (8.6, 13.6)	30.0 (25.4, 35.7)	25.7 (21.7, 30.4)	5.8 (4.3, 7.9)	22.6 (17.2, 28.3)
2000	36.1 (31.7, 41.0)	11.2 (9.2, 13.6)	31.0 (26.7, 36.2)	26.0 (22.5, 30.1)	6.2 (4.7, 8.1)	23.8 (18.7, 28.9)
2001	36.1 (32.3, 40.4)	11.5 (9.7, 13.7)	32.0 (28.0, 36.5)	26.3 (23.2, 29.9)	6.6 (5.2, 8.3)	25.1 (20.2, 29.7)
2002	36.1 (32.8, 39.7)	11.9 (10.3, 13.8)	33.0 (29.4, 37.0)	26.7 (23.9, 29.7)	7.0 (5.8, 8.6)	26.4 (22.1, 30.5)
2003	36.1 (33.3, 39.1)	12.3 (10.8, 14.0)	34.1 (30.8, 37.8)	27.0 (24.7, 29.6)	7.5 (6.4, 8.9)	27.8 (23.7, 31.4)
2004	36.1 (33.7, 38.7)	12.7 (11.4, 14.2)	35.2 (32.4, 38.4)	27.3 (25.3, 29.5)	8.0 (7.0, 9.2)	29.3 (25.6, 32.5)
2005	36.1 (34.1, 38.3)	13.1 (12.0, 14.5)	36.4 (33.6, 39.2)	27.7 (25.9, 29.6)	8.5 (7.6, 9.7)	30.9 (27.6, 33.8)
2006	36.1 (34.2, 38.2)	13.6 (12.4, 14.9)	37.6 (34.8, 40.4)	28.0 (26.3, 29.8)	9.1 (8.1, 10.2)	32.5 (29.4, 35.6)
2007	36.1 (34.1, 38.2)	14.0 (12.7, 15.3)	38.8 (35.7, 41.7)	28.3 (26.5, 30.2)	9.7 (8.6, 10.9)	34.3 (30.9, 37.9)
2008	35.6 (33.5, 37.8)	14.2 (12.8, 15.6)	39.8 (36.6, 42.9)	28.1 (26.3, 30.1)	10.1 (9.0, 11.5)	36.0 (32.4, 40.0)
2009	34.5 (32.5, 36.6)	13.9 (12.7, 15.3)	40.4 (37.4, 43.5)	27.4 (25.7, 29.3)	10.4 (9.2, 11.6)	37.8 (34.2, 41.5)
2010	32.5 (30.9, 34.3)	13.2 (12.1, 14.3)	40.5 (37.9, 43.3)	25.9 (24.5, 27.5)	10.2 (9.2, 11.3)	39.4 (36.0, 42.8)
2011	30.0 (28.5, 31.7)	12.1 (11.1, 13.2)	40.3 (37.7, 43.3)	24.1 (22.7, 25.7)	9.8 (8.8, 11.0)	40.6 (36.7, 44.5)
2012	28.1 (26.4, 29.9)	11.2 (10.1, 12.4)	39.9 (37.1, 43.2)	22.9 (21.2, 24.6)	9.4 (8.3, 10.7)	41.2 (36.6, 45.3)
2013	27.7 (26.1, 29.4)	10.8 (9.9, 11.9)	39.2 (36.5, 42.1)	22.9 (21.5, 24.5)	9.3 (8.3, 10.4)	40.4 (36.5, 44.1)
2014	28.8 (27.3, 30.3)	11.0 (10.1, 12.0)	38.3 (36.0, 41.1)	24.1 (22.7, 25.6)	9.2 (8.3, 10.3)	38.4 (34.9, 42.2)
2015	29.8 (28.0, 31.7)	11.4 (10.3, 12.5)	38.1 (35.4, 41.0)	24.9 (23.2, 26.7)	9.0 (7.9, 10.3)	36.3 (32.4, 40.4)
2016	29.0 (27.4, 30.7)	11.5 (10.5, 12.6)	39.5 (37.1, 42.2)	24.0 (22.5, 25.5)	8.5 (7.6, 9.5)	35.5 (32.1, 39.0)
2017	26.8 (25.3, 28.5)	11.4 (10.3, 12.5)	42.4 (39.5, 45.8)	21.9 (20.4, 23.5)	7.8 (6.8, 8.9)	35.7 (31.4, 39.9)
2018	24.4 (22.1, 27.0)	11.3 (9.6, 13.1)	46.0 (41.0, 51.5)	19.8 (17.6, 22.2)	7.2 (5.8, 8.8)	36.2 (29.9, 42.2)

Proportion (%) and 95% confidence interval of cancer death out of all-cause death.

Rates and 95% confidence interval are presented per 1000 person-years.

ESM Table 3. Trends in all-cause and all cancer mortality rate and proportions of cancer death by ethnicity

Period	White			Others		
	All-cause	**All cancer**	**Proportion**	**All-cause**	**All cancer**	**Proportion**
1998	22.2 (19.2, 25.5)	6.6 (5.3, 8.2)	29.6 (25.1, 34.1)	19.0 (9.5, 37.9)	12.3 (3.4, 44.3)	-
1999	23.0 (20.2, 26.1)	7.0 (5.8, 8.5)	30.5 (26.4, 34.5)	18.9 (10.2, 35.1)	11.5 (3.6, 36.1)	-
2000	23.8 (21.3, 26.7)	7.5 (6.3, 8.9)	31.5 (27.6, 35.1)	18.8 (10.8, 32.6)	10.7 (3.8, 29.6)	-
2001	24.7 (22.4, 27.3)	8.0 (6.9, 9.3)	32.4 (28.9, 35.8)	18.7 (11.5, 30.3)	9.9 (4.0, 24.3)	-
2002	25.6 (23.6, 27.9)	8.6 (7.5, 9.8)	33.4 (30.3, 36.4)	18.5 (12.2, 28.3)	9.2 (4.2, 20.0)	-
2003	26.6 (24.8, 28.5)	9.2 (8.2, 10.2)	34.4 (31.6, 37.1)	18.4 (12.8, 26.4)	8.6 (4.4, 16.7)	-
2004	27.6 (26.0, 29.3)	9.8 (8.9, 10.7)	35.5 (32.9, 37.9)	18.3 (13.5, 24.8)	7.9 (4.5, 14.1)	-
2005	28.6 (27.2, 30.1)	10.5 (9.6, 11.3)	36.6 (34.1, 38.8)	18.2 (14.1, 23.5)	7.4 (4.5, 12.1)	-
2006	29.7 (28.4, 31.0)	11.2 (10.4, 12.0)	37.7 (35.2, 39.9)	18.1 (14.5, 22.6)	6.9 (4.4, 10.8)	-
2007	30.7 (29.4, 32.1)	11.9 (11.1, 12.9)	38.8 (36.3, 41.2)	18.0 (14.6, 22.1)	6.4 (4.1, 10.0)	-
2008	31.6 (30.1, 33.2)	12.6 (11.6, 13.6)	39.8 (37.1, 42.4)	17.7 (14.3, 22.0)	5.9 (3.7, 9.5)	-
2009	32.0 (30.5, 33.5)	12.9 (12.0, 14.0)	40.4 (38.0, 43.2)	17.3 (13.8, 21.6)	5.6 (3.4, 9.2)	-
2010	31.4 (30.1, 32.8)	12.8 (11.9, 13.7)	40.6 (38.5, 42.9)	16.3 (13.2, 20.3)	5.3 (3.3, 8.5)	-
2011	30.0 (28.8, 31.2)	12.1 (11.3, 13.0)	40.4 (38.2, 42.9)	14.9 (12.3, 18.0)	5.1 (3.3, 7.8)	-
2012	28.5 (27.1, 30.0)	11.4 (10.6, 12.4)	40.2 (37.6, 43.1)	13.3 (10.8, 16.3)	5.0 (3.2, 7.8)	-
2013	28.1 (26.8, 29.6)	11.2 (10.4, 12.1)	39.7 (37.3, 42.3)	12.4 (9.8, 15.8)	4.9 (2.8, 8.4)	-
2014	29.3 (28.1, 30.6)	11.3 (10.6, 12.2)	38.7 (36.5, 40.9)	12.9 (10.5, 16.0)	4.7 (2.8, 7.7)	-
2015	30.5 (29.0, 32.1)	11.6 (10.7, 12.6)	38.0 (35.5, 40.6)	14.5 (11.7, 17.9)	4.4 (2.6, 7.4)	-
2016	29.9 (28.5, 31.4)	11.5 (10.7, 12.4)	38.5 (36.2, 41.1)	14.6 (11.5, 18.5)	4.5 (2.5, 8.2)	-
2017	27.8 (26.5, 29.2)	11.2 (10.4, 12.2)	40.4 (37.9, 43.0)	12.2 (9.8, 15.3)	5.2 (3.2, 8.5)	-
2018	25.5 (23.5, 27.7)	10.9 (9.6, 12.4)	42.8 (38.7, 47.2)	9.5 (6.5, 14.0)	6.2 (2.8, 13.9)	-

Proportion (%) and 95% confidence interval of cancer death out of all-cause death.

Rates and 95% confidence interval are presented per 1000 person-years.

As the number of deaths among other ethnicities (South Asian, Black and other ethnic groups) that occurred in some years was very small, the proportions of cancer deaths out of all-cause deaths for other ethnicities were not estimated.

ESM Table 4. Trends in all-cause and all cancer mortality rate and proportions of cancer death by socio-economic status

Period	IMD – 1st quintile (Least deprived)			IMD – 2nd quintile			IMD – 3rd quintile		
	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion
1998	21.8 (16.0, 29.7)	5.6 (3.4, 9.2)	25.9 (17.8, 36.4)	29.2 (22.5, 38.0)	7.2 (4.7, 11.1)	24.8 (17.5, 32.7)	31.4 (23.6, 41.7)	9.4 (6.0, 14.8)	29.9 (21.3, 41.4)
1999	22.4 (17.0, 29.5)	6.2 (4.0, 9.5)	27.5 (19.9, 36.8)	29.0 (23.0, 36.7)	7.6 (5.2, 11.1)	26.2 (19.2, 33.3)	31.4 (24.4, 40.4)	9.6 (6.4, 14.3)	30.5 (22.4, 40.8)
2000	23.1 (18.1, 29.4)	6.7 (4.6, 9.9)	29.1 (21.8, 37.7)	28.9 (23.5, 35.5)	8.0 (5.7, 11.1)	27.6 (21.0, 34.3)	31.4 (25.1, 39.2)	9.8 (6.8, 13.9)	31.1 (24.0, 40.2)
2001	23.7 (19.2, 29.3)	7.3 (5.2, 10.2)	30.9 (24.2, 38.5)	28.7 (24.0, 34.3)	8.3 (6.2, 11.1)	29.1 (23.0, 35.4)	31.4 (25.9, 38.0)	10.0 (7.3, 13.6)	31.8 (25.1, 39.9)
2002	24.4 (20.4, 29.3)	8.0 (6.0, 10.6)	32.7 (26.5, 39.8)	28.5 (24.5, 33.2)	8.7 (6.8, 11.2)	30.6 (25.2, 36.6)	31.4 (26.7, 36.9)	10.2 (7.8, 13.3)	32.4 (26.5, 39.3)
2003	25.2 (21.6, 29.3)	8.7 (6.9, 11.1)	34.7 (28.9, 41.4)	28.4 (25.0, 32.3)	9.2 (7.4, 11.3)	32.3 (27.2, 37.7)	31.4 (27.4, 36.0)	10.4 (8.3, 13.0)	33.1 (27.8, 39.1)
2004	25.9 (22.8, 29.4)	9.5 (7.8, 11.7)	36.8 (31.5, 43.5)	28.2 (25.3, 31.4)	9.6 (8.0, 11.5)	34.0 (29.3, 39.0)	31.4 (28.0, 35.2)	10.6 (8.8, 12.8)	33.8 (28.8, 39.5)
2005	26.7 (23.9, 29.7)	10.4 (8.7, 12.4)	39.0 (33.9, 45.3)	28.1 (25.5, 30.8)	10.1 (8.6, 11.8)	35.9 (31.2, 40.7)	31.4 (28.4, 34.6)	10.8 (9.1, 12.8)	34.5 (30.1, 39.4)
2006	27.4 (24.8, 30.3)	11.3 (9.6, 13.4)	41.3 (36.2, 47.5)	27.9 (25.5, 30.5)	10.6 (9.1, 12.3)	37.8 (32.7, 42.9)	31.4 (28.5, 34.5)	11.0 (9.4, 13.0)	35.2 (30.6, 39.9)
2007	28.1 (25.4, 31.2)	12.2 (10.3, 14.6)	43.5 (37.9, 49.6)	27.7 (25.3, 30.4)	11.0 (9.4, 12.9)	39.8 (34.6, 45.2)	31.2 (28.3, 34.5)	11.2 (9.5, 13.3)	36.0 (31.0, 41.3)
2008	28.3 (25.4, 31.6)	12.8 (10.7, 15.3)	45.1 (39.3, 51.7)	27.5 (24.9, 30.3)	11.4 (9.7, 13.4)	41.4 (35.9, 47.4)	30.8 (27.7, 34.1)	11.4 (9.5, 13.5)	36.9 (31.4, 42.5)
2009	27.6 (24.8, 30.7)	12.6 (10.6, 14.9)	45.6 (39.9, 52.1)	27.2 (24.7, 29.9)	11.5 (9.8, 13.5)	42.3 (36.9, 48.1)	29.7 (26.9, 32.9)	11.3 (9.6, 13.4)	38.0 (32.9, 43.3)
2010	25.6 (23.3, 28.2)	11.5 (9.9, 13.4)	44.9 (39.6, 51.0)	26.7 (24.6, 29.1)	11.3 (9.8, 13.0)	42.2 (37.5, 47.3)	28.1 (25.7, 30.6)	11.1 (9.5, 12.9)	39.5 (34.8, 44.0)
2011	22.8 (20.6, 25.2)	10.0 (8.4, 11.9)	44.0 (38.4, 50.4)	26.2 (24.0, 28.5)	10.8 (9.3, 12.4)	41.2 (36.6, 46.2)	26.2 (23.9, 28.8)	10.7 (9.1, 12.6)	40.9 (35.9, 45.6)
2012	20.6 (18.2, 23.2)	8.9 (7.4, 10.8)	43.5 (38.1, 50.6)	25.5 (23.0, 28.2)	10.2 (8.7, 12.0)	40.0 (34.8, 45.9)	25.2 (22.6, 28.1)	10.5 (8.7, 12.5)	41.5 (35.6, 47.1)
2013	20.0 (17.8, 22.4)	8.7 (7.3, 10.2)	43.4 (38.2, 50.0)	24.7 (22.4, 27.3)	9.8 (8.4, 11.4)	39.7 (34.9, 44.9)	26.0 (23.5, 28.7)	10.5 (8.9, 12.3)	40.4 (35.0, 45.3)
2014	21.0 (19.0, 23.2)	8.8 (7.4, 10.4)	41.9 (36.8, 48.5)	24.0 (22.0, 26.1)	9.7 (8.4, 11.1)	40.3 (35.6, 45.4)	28.2 (25.8, 30.8)	10.7 (9.2, 12.5)	38.1 (33.4, 42.4)
2015	22.0 (19.5, 24.7)	8.8 (7.2, 10.6)	39.9 (34.6, 46.9)	23.3 (21.0, 25.9)	9.6 (8.1, 11.4)	41.3 (36.2, 47.1)	29.5 (26.5, 32.7)	10.9 (9.1, 13.0)	36.9 (32.0, 42.2)
2016	21.2 (19.0, 23.7)	8.3 (7.0, 9.9)	39.3 (34.5, 45.1)	22.9 (20.8, 25.2)	9.6 (8.2, 11.2)	42.0 (37.3, 47.1)	27.5 (25.0, 30.2)	10.7 (9.1, 12.5)	38.8 (34.1, 43.9)
2017	19.2 (17.1, 21.5)	7.7 (6.3, 9.3)	40.1 (34.3, 47.0)	22.6 (20.5, 24.9)	9.6 (8.1, 11.3)	42.5 (37.0, 47.4)	23.6 (21.2, 26.3)	10.2 (8.5, 12.2)	43.2 (37.3, 49.5)
2018	17.0 (14.0, 20.5)	7.0 (5.2, 9.6)	41.5 (32.2, 52.3)	22.4 (19.0, 26.3)	9.6 (7.3, 12.5)	42.8 (33.9, 52.2)	19.8 (16.6, 23.7)	9.7 (7.3, 12.9)	49.0 (39.6, 60.7)

Period	IMD – 4th quintile			IMD – 5th quintile (Most deprived)		
	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion
1998	40.0 (30.3, 52.9)	10.1 (6.4, 15.8)	25.2 (17.9, 35.2)	33.6 (25.3, 44.5)	9.8 (6.1, 15.9)	29.2 (19.0, 41.8)
1999	39.6 (30.9, 50.7)	10.4 (6.9, 15.5)	26.1 (19.1, 35.3)	34.6 (26.9, 44.4)	10.1 (6.6, 15.5)	29.3 (19.9, 40.1)
2000	39.2 (31.5, 48.7)	10.6 (7.5, 15.1)	27.1 (20.5, 35.4)	35.6 (28.5, 44.3)	10.4 (7.1, 15.3)	29.3 (20.8, 38.7)
2001	38.8 (32.1, 46.8)	10.9 (8.0, 14.8)	28.1 (21.9, 35.5)	36.6 (30.2, 44.3)	10.7 (7.7, 15.0)	29.4 (21.8, 37.3)
2002	38.4 (32.7, 45.1)	11.2 (8.6, 14.5)	29.1 (23.5, 35.7)	37.7 (32.0, 44.3)	11.1 (8.3, 14.8)	29.4 (22.9, 35.8)
2003	38.0 (33.2, 43.5)	11.5 (9.2, 14.3)	30.1 (25.0, 35.8)	38.8 (33.8, 44.5)	11.4 (8.9, 14.6)	29.5 (23.8, 34.7)
2004	37.6 (33.6, 42.1)	11.7 (9.7, 14.2)	31.2 (26.5, 36.0)	39.9 (35.4, 44.7)	11.8 (9.6, 14.5)	29.5 (24.5, 34.2)
2005	37.2 (33.7, 41.0)	12.0 (10.2, 14.2)	32.4 (28.0, 36.5)	41.0 (37.2, 45.3)	12.1 (10.1, 14.5)	29.6 (25.1, 33.9)
2006	36.8 (33.6, 40.4)	12.3 (10.5, 14.5)	33.5 (29.2, 37.9)	42.2 (38.5, 46.3)	12.5 (10.6, 14.8)	29.6 (25.3, 33.7)
2007	36.4 (33.0, 40.0)	12.6 (10.7, 14.8)	34.7 (29.9, 39.6)	43.3 (39.3, 47.6)	12.9 (10.9, 15.3)	29.8 (25.4, 34.2)
2008	35.6 (32.2, 39.4)	12.7 (10.7, 15.1)	35.7 (30.8, 41.2)	43.5 (39.4, 48.0)	13.2 (11.1, 15.8)	30.5 (25.8, 35.3)
2009	34.3 (31.1, 37.9)	12.5 (10.7, 14.7)	36.5 (31.7, 41.9)	42.3 (38.4, 46.5)	13.5 (11.3, 16.1)	32.0 (27.1, 37.3)
2010	32.5 (29.8, 35.4)	12.0 (10.4, 13.8)	36.8 (32.6, 41.3)	39.2 (36.0, 42.6)	13.6 (11.7, 15.9)	34.8 (30.5, 40.0)
2011	30.3 (27.7, 33.2)	11.2 (9.6, 13.0)	36.8 (32.3, 41.3)	35.4 (32.3, 38.7)	13.6 (11.7, 15.8)	38.4 (33.6, 43.6)
2012	28.9 (25.9, 32.1)	10.5 (8.8, 12.5)	36.5 (31.6, 41.6)	32.8 (29.5, 36.4)	13.3 (11.2, 15.9)	40.7 (35.2, 47.0)
2013	28.8 (26.1, 31.8)	10.3 (8.8, 12.0)	35.8 (31.5, 40.3)	32.9 (29.9, 36.1)	12.9 (10.9, 15.2)	39.3 (34.1, 45.0)
2014	30.0 (27.5, 32.8)	10.5 (9.0, 12.2)	34.9 (30.4, 39.1)	35.3 (32.3, 38.5)	12.4 (10.6, 14.4)	35.1 (30.9, 40.1)
2015	30.9 (27.8, 34.3)	10.7 (9.0, 12.7)	34.6 (29.7, 39.2)	37.2 (33.6, 41.2)	12.0 (10.0, 14.4)	32.3 (28.2, 37.4)
2016	30.0 (27.2, 33.0)	10.7 (9.1, 12.5)	35.7 (31.1, 40.9)	36.1 (33.0, 39.6)	11.9 (10.1, 14.0)	32.9 (28.6, 37.7)
2017	27.7 (25.0, 30.7)	10.5 (8.9, 12.5)	38.0 (32.8, 43.5)	33.2 (30.0, 36.7)	12.0 (10.1, 14.2)	36.1 (30.9, 41.3)
2018	25.3 (21.3, 30.0)	10.4 (7.9, 13.6)	41.0 (32.9, 50.3)	30.0 (25.5, 35.3)	12.1 (9.2, 15.9)	40.4 (31.4, 49.9)

Proportion (%) and 95% confidence interval of cancer death out of all-cause death. Rates and 95% confidence interval are presented per 1000 person-years. IMD: index of multiple deprivation 2010.

ESM Table 5. Trends in all-cause and all cancer mortality rate and proportions of cancer death by body mass index

Period	Normal weight (BMI: 18.5-24.9 kg/m^2)			Overweight (BMI: 25-29.9 kg/m^2)		
	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion
1998	32.2 (24.4, 42.5)	9.8 (5.7, 16.9)	30.6 (19.0, 49.2)	30.7 (24.8, 38.0)	6.7 (4.6, 9.8)	22.0 (16.3, 29.0)
1999	32.5 (25.4, 41.5)	10.0 (6.2, 16.2)	30.9 (20.3, 47.5)	30.4 (25.1, 36.7)	7.1 (5.1, 10.0)	23.4 (18.0, 30.0)
2000	32.8 (26.5, 40.6)	10.2 (6.8, 15.5)	31.3 (21.7, 45.3)	30.0 (25.4, 35.5)	7.5 (5.6, 10.1)	25.0 (19.8, 31.2)
2001	33.1 (27.5, 39.7)	10.5 (7.3, 14.9)	31.6 (23.1, 43.2)	29.7 (25.7, 34.4)	7.9 (6.1, 10.3)	26.7 (21.8, 32.2)
2002	33.4 (28.6, 39.0)	10.7 (7.9, 14.4)	32.0 (24.3, 41.6)	29.4 (26.0, 33.3)	8.4 (6.7, 10.4)	28.5 (24.0, 33.5)
2003	33.7 (29.6, 38.4)	10.9 (8.5, 14.0)	32.3 (25.5, 40.6)	29.1 (26.2, 32.3)	8.9 (7.4, 10.7)	30.4 (26.2, 35.1)
2004	34.0 (30.5, 38.0)	11.1 (8.9, 13.9)	32.7 (26.6, 39.5)	28.8 (26.3, 31.4)	9.3 (8.0, 10.9)	32.5 (28.8, 36.7)
2005	34.3 (31.1, 38.0)	11.4 (9.2, 14.0)	33.1 (27.4, 39.4)	28.4 (26.3, 30.7)	9.9 (8.6, 11.3)	34.7 (31.0, 38.6)
2006	34.6 (31.3, 38.3)	11.6 (9.3, 14.4)	33.4 (27.8, 40.2)	28.1 (26.2, 30.2)	10.4 (9.2, 11.8)	37.0 (33.0, 41.2)
2007	34.6 (31.1, 38.6)	11.7 (9.3, 14.7)	33.7 (27.9, 41.1)	27.8 (25.8, 29.9)	11.0 (9.6, 12.5)	39.4 (35.0, 44.0)
2008	34.2 (30.7, 38.1)	11.6 (9.3, 14.5)	33.9 (28.0, 41.8)	27.4 (25.3, 29.6)	11.4 (9.9, 13.1)	41.6 (37.0, 46.7)
2009	33.0 (29.9, 36.5)	11.3 (9.2, 13.8)	34.1 (28.8, 41.4)	26.8 (24.8, 29.0)	11.5 (10.1, 13.2)	43.0 (38.4, 48.1)
2010	31.2 (28.4, 34.3)	10.8 (8.8, 13.3)	34.6 (29.1, 41.6)	26.0 (24.2, 27.8)	11.2 (10.0, 12.7)	43.3 (39.2, 47.5)
2011	29.5 (26.3, 33.0)	10.5 (8.3, 13.3)	35.5 (29.0, 44.1)	25.0 (23.3, 26.8)	10.7 (9.4, 12.1)	42.6 (38.1, 47.3)
2012	28.6 (25.5, 32.2)	10.6 (8.4, 13.2)	36.9 (30.2, 44.4)	24.3 (22.4, 26.4)	10.1 (8.7, 11.7)	41.6 (36.6, 47.1)
2013	29.0 (26.3, 32.0)	11.1 (9.1, 13.5)	38.2 (32.4, 44.8)	24.5 (22.6, 26.6)	9.9 (8.7, 11.3)	40.4 (35.9, 44.9)
2014	29.8 (26.7, 33.2)	11.7 (9.3, 14.6)	39.3 (32.4, 48.0)	25.5 (23.8, 27.4)	10.0 (8.8, 11.3)	39.0 (35.0, 43.3)
2015	29.8 (26.5, 33.4)	12.0 (9.6, 15.1)	40.3 (33.1, 49.3)	25.8 (23.7, 28.1)	9.9 (8.5, 11.5)	38.3 (33.4, 43.1)
2016	28.6 (25.9, 31.7)	11.9 (9.7, 14.6)	41.6 (35.1, 50.0)	23.8 (22.0, 25.8)	9.4 (8.2, 10.7)	39.4 (34.8, 43.8)
2017	27.0 (23.8, 30.7)	11.7 (9.0, 15.2)	43.2 (34.1, 54.0)	20.3 (18.7, 22.1)	8.6 (7.4, 10.0)	42.4 (37.2, 47.2)
2018	25.4 (21.0, 30.9)	11.4 (7.7, 16.9)	44.9 (32.0, 61.4)	16.9 (14.6, 19.6)	7.9 (6.2, 10.1)	46.4 (38.2, 55.8)

Period	Obese (BMI: 30-34.9 kg/m^2)			Severely obese (BMI: ≥35 kg/m^2)		
	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion
1998	35.8 (27.6, 46.6)	9.4 (6.3, 14.1)	26.2 (19.2, 35.0)	31.9 (21.9, 46.4)	3.6 (1.5, 8.4)	11.2 (4.8, 23.2)
1999	35.3 (27.9, 44.7)	9.7 (6.7, 13.9)	27.4 (20.6, 35.4)	32.2 (23.0, 45.2)	4.0 (1.8, 8.7)	12.4 (5.7, 23.8)
2000	34.8 (28.2, 42.9)	10.0 (7.2, 13.8)	28.7 (22.2, 35.9)	32.6 (24.1, 44.1)	4.5 (2.2, 9.0)	13.8 (6.9, 24.5)
2001	34.3 (28.6, 41.2)	10.3 (7.8, 13.6)	30.0 (23.9, 36.5)	33.0 (25.2, 43.1)	5.1 (2.7, 9.3)	15.3 (8.3, 25.4)
2002	33.8 (28.9, 39.6)	10.6 (8.3, 13.5)	31.3 (25.7, 37.2)	33.3 (26.4, 42.1)	5.7 (3.3, 9.7)	17.1 (9.9, 26.3)
2003	33.4 (29.1, 38.2)	10.9 (8.9, 13.4)	32.7 (27.6, 38.0)	33.7 (27.6, 41.1)	6.4 (4.0, 10.1)	18.9 (11.9, 27.3)
2004	32.9 (29.3, 36.8)	11.2 (9.4, 13.4)	34.2 (29.7, 39.0)	34.1 (28.8, 40.3)	7.2 (4.9, 10.5)	21.1 (14.1, 28.7)
2005	32.4 (29.4, 35.7)	11.6 (9.9, 13.5)	35.7 (31.7, 40.2)	34.4 (29.9, 39.7)	8.1 (5.9, 11.1)	23.4 (16.9, 30.0)
2006	31.9 (29.3, 34.8)	11.9 (10.4, 13.7)	37.4 (33.5, 41.5)	34.8 (30.9, 39.2)	9.1 (7.0, 11.8)	26.0 (19.8, 31.9)
2007	31.5 (29.0, 34.2)	12.3 (10.7, 14.1)	39.0 (35.2, 42.9)	35.2 (31.6, 39.1)	10.2 (8.1, 12.7)	28.9 (23.1, 34.6)
2008	31.0 (28.3, 33.8)	12.5 (10.9, 14.4)	40.5 (36.6, 44.8)	35.5 (32.0, 39.5)	11.4 (9.2, 14.2)	32.1 (26.1, 38.3)
2009	30.1 (27.5, 33.1)	12.5 (10.8, 14.4)	41.5 (37.5, 46.0)	35.7 (31.9, 39.9)	12.6 (10.0, 15.8)	35.2 (27.9, 42.1)
2010	28.9 (26.5, 31.5)	12.0 (10.5, 13.7)	41.6 (38.0, 45.8)	35.4 (31.7, 39.6)	13.3 (10.6, 16.7)	37.4 (30.1, 44.6)
2011	27.1 (25.1, 29.3)	11.0 (9.8, 12.5)	40.8 (37.2, 44.9)	34.5 (31.3, 38.1)	13.1 (10.7, 16.0)	37.9 (31.3, 44.6)
2012	25.2 (23.0, 27.6)	10.1 (8.7, 11.6)	39.9 (35.5, 44.8)	33.0 (30.0, 36.2)	11.9 (9.7, 14.6)	36.2 (30.2, 42.3)
2013	24.0 (21.7, 26.5)	9.5 (8.2, 11.1)	39.8 (35.4, 44.8)	31.5 (28.1, 35.4)	10.7 (8.3, 13.7)	33.9 (27.0, 41.3)
2014	23.9 (22.0, 26.1)	9.7 (8.6, 11.0)	40.6 (36.4, 44.6)	31.2 (28.0, 34.7)	10.2 (8.2, 12.8)	32.8 (27.0, 39.3)
2015	24.5 (22.3, 27.0)	10.1 (8.7, 11.7)	41.3 (36.4, 46.0)	32.0 (29.0, 35.3)	10.6 (8.5, 13.2)	33.1 (27.1, 40.2)
2016	24.6 (22.3, 27.1)	10.2 (8.9, 11.8)	41.7 (37.2, 47.0)	32.2 (28.7, 36.0)	11.1 (8.8, 14.1)	34.7 (28.4, 42.2)
2017	23.8 (21.7, 26.1)	10.0 (8.7, 11.5)	42.0 (37.7, 46.5)	30.7 (27.8, 33.8)	11.5 (9.4, 14.1)	37.6 (31.3, 43.5)
2018	22.7 (19.4, 26.6)	9.6 (7.7, 12.1)	42.4 (35.2, 50.0)	28.6 (24.2, 33.8)	11.8 (8.4, 16.6)	41.4 (29.7, 53.7)

Proportion (%) and 95% confidence interval of cancer death out of all-cause death.

Rates and 95% confidence interval are presented per 1000 person-years.

BMI: body mass index. Subjects with underweight (BMI: <18.5 kg/m^2) were not included in this analysis.

ESM Table 6. Trends in all-cause and all cancer mortality rate and proportions of cancer death by smoking status

Period	Current smoker			Non-smoker			Ex-smoker		
	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion	All-cause	All cancer	Proportion
1998	40.0 (29.5, 54.3)	8.8 (4.8, 16.1)	22.0 (12.9, 33.6)	24.9 (20.6, 30.2)	8.1 (5.8, 11.3)	32.4 (24.3, 41.0)	36.3 (28.9, 45.5)	8.5 (5.8, 12.6)	23.5 (16.7, 31.6)
1999	41.0 (31.3, 53.7)	9.4 (5.5, 16.1)	22.8 (14.2, 33.5)	24.8 (20.9, 29.4)	8.2 (6.1, 11.1)	33.1 (25.6, 40.6)	36.0 (29.4, 44.1)	8.8 (6.2, 12.5)	24.6 (18.1, 32.2)
2000	42.0 (33.2, 53.3)	10.0 (6.2, 16.0)	23.7 (15.7, 33.3)	24.6 (21.2, 28.6)	8.4 (6.4, 10.9)	33.9 (26.9, 40.4)	35.7 (29.8, 42.7)	9.2 (6.7, 12.5)	25.8 (19.8, 32.6)
2001	43.1 (35.1, 52.8)	10.6 (7.1, 16.0)	24.7 (17.1, 33.1)	24.5 (21.5, 27.9)	8.5 (6.8, 10.7)	34.7 (28.4, 40.4)	35.4 (30.2, 41.4)	9.6 (7.3, 12.5)	27.0 (21.4, 33.3)
2002	44.1 (37.1, 52.5)	11.3 (8.0, 16.0)	25.6 (18.8, 33.1)	24.4 (21.8, 27.2)	8.6 (7.1, 10.5)	35.5 (29.8, 40.5)	35.1 (30.7, 40.2)	9.9 (7.9, 12.5)	28.3 (23.3, 34.1)
2003	45.2 (39.1, 52.3)	12.1 (9.0, 16.2)	26.7 (20.6, 33.1)	24.2 (22.1, 26.6)	8.8 (7.5, 10.4)	36.3 (31.2, 40.6)	34.8 (31.0, 39.1)	10.3 (8.5, 12.6)	29.6 (25.0, 34.9)
2004	46.3 (41.0, 52.4)	12.8 (10.1, 16.4)	27.7 (22.3, 33.3)	24.1 (22.3, 26.0)	8.9 (7.8, 10.3)	37.1 (32.7, 41.0)	34.5 (31.4, 38.1)	10.7 (9.1, 12.7)	31.0 (27.1, 35.7)
2005	47.5 (42.7, 52.8)	13.7 (11.1, 16.9)	28.8 (24.4, 34.0)	24.0 (22.4, 25.6)	9.1 (8.0, 10.3)	38.0 (34.0, 41.9)	34.3 (31.6, 37.2)	11.1 (9.7, 12.9)	32.5 (28.7, 37.0)
2006	48.7 (44.0, 53.8)	14.6 (12.0, 17.7)	30.0 (25.4, 35.1)	23.8 (22.3, 25.4)	9.3 (8.2, 10.5)	38.8 (34.7, 43.0)	34.0 (31.6, 36.6)	11.6 (10.2, 13.2)	34.1 (30.3, 38.1)
2007	49.7 (44.7, 55.3)	15.5 (12.7, 19.0)	31.2 (25.9, 37.0)	23.6 (22.1, 25.3)	9.4 (8.2, 10.7)	39.7 (35.5, 44.1)	33.7 (31.4, 36.2)	12.0 (10.6, 13.6)	35.7 (32.0, 39.6)
2008	50.3 (45.0, 56.2)	16.4 (13.2, 20.2)	32.5 (26.7, 39.4)	23.2 (21.6, 24.9)	9.4 (8.2, 10.7)	40.4 (35.9, 45.1)	33.3 (30.9, 36.0)	12.4 (10.9, 14.2)	37.2 (33.5, 41.4)
2009	50.2 (45.2, 55.8)	17.1 (14.0, 21.0)	34.1 (28.4, 40.8)	22.4 (20.9, 24.0)	9.2 (8.1, 10.5)	41.2 (36.9, 45.6)	32.7 (30.2, 35.4)	12.5 (10.9, 14.3)	38.3 (34.2, 42.7)
2010	49.1 (44.8, 53.8)	17.6 (14.7, 21.0)	35.9 (31.1, 41.3)	21.1 (19.8, 22.4)	8.8 (7.9, 9.9)	41.8 (37.9, 45.9)	31.6 (29.4, 34.0)	12.2 (10.8, 13.8)	38.5 (34.7, 42.6)
2011	47.3 (43.0, 52.1)	17.8 (14.8, 21.3)	37.6 (32.6, 43.4)	19.6 (18.3, 20.9)	8.3 (7.3, 9.4)	42.4 (37.8, 47.1)	30.1 (28.2, 32.2)	11.4 (10.2, 12.8)	38.0 (34.4, 41.6)
2012	45.8 (41.0, 51.2)	17.7 (14.4, 21.9)	38.7 (32.6, 46.2)	18.4 (17.0, 19.9)	7.8 (6.8, 9.0)	42.3 (36.8, 47.5)	28.6 (26.5, 30.9)	10.7 (9.3, 12.2)	37.2 (33.3, 41.6)
2013	45.3 (41.0, 50.1)	17.5 (14.4, 21.1)	38.5 (32.5, 44.8)	18.1 (16.8, 19.4)	7.4 (6.5, 8.4)	40.9 (36.5, 45.3)	28.0 (25.8, 30.5)	10.3 (9.0, 11.8)	36.9 (33.0, 41.1)
2014	45.8 (41.8, 50.2)	17.1 (14.4, 20.4)	37.4 (31.8, 43.4)	18.5 (17.3, 19.7)	7.1 (6.2, 8.0)	38.4 (34.3, 43.1)	28.8 (26.9, 30.8)	10.6 (9.5, 11.9)	36.9 (33.3, 40.5)
2015	46.2 (41.4, 51.4)	16.9 (13.8, 20.8)	36.7 (30.7, 44.2)	18.6 (17.2, 20.2)	6.8 (5.9, 7.9)	36.7 (32.3, 41.8)	29.7 (27.4, 32.1)	11.0 (9.6, 12.6)	37.0 (33.2, 41.6)
2016	45.6 (41.4, 50.3)	16.9 (14.1, 20.4)	37.2 (31.6, 43.6)	17.6 (16.4, 18.9)	6.6 (5.8, 7.5)	37.3 (33.4, 41.8)	29.1 (26.9, 31.4)	10.9 (9.6, 12.4)	37.5 (33.9, 41.7)
2017	44.3 (40.1, 49.0)	17.1 (14.2, 20.7)	38.6 (31.9, 44.1)	15.9 (14.7, 17.2)	6.3 (5.5, 7.3)	39.8 (35.3, 44.5)	27.0 (25.0, 29.1)	10.4 (9.1, 11.9)	38.6 (35.0, 42.5)
2018	42.9 (36.5, 50.5)	17.4 (12.8, 23.5)	40.5 (31.0, 51.1)	14.1 (12.4, 16.0)	6.1 (4.8, 7.7)	43.1 (35.1, 52.0)	24.6 (21.6, 28.1)	9.9 (7.9, 12.3)	40.0 (34.0, 47.0)

Proportion (%) and 95% confidence interval of cancer death out of all-cause death.

Rates and 95% confidence interval are presented per 1000 person-years.

ESM Table 7. Annual percentage change and average annual percentage change in cancer-specific mortality rates (four most common cancers)

	Period 1	APC, %	Period 2	APC, %	Period 3	APC, %	Period 4	APC, %	AAPC for whole period, %
Breast									
Age, years									
55	1998-2006	12.7 (11.6, 13.8)	2006-2009	8.7 (6.3, 11.1)	2009-2015	-3.1 (-3.5, -2.7)	2015-2018	-6.7 (-8.4, -5.0)	4.1 (3.6, 4.7)
65	1998-2008	9.5 (8.2, 10.7)	2008-2015	-5.9 (-6.8, -4.9)	2015-2018	-15.3 (-22.2, -7.9)	–	–	-0.1 (-1.4, 1.2)
75	1998-2008	3.6 (3.4, 3.8)	2008-2012	-8.3 (-8.9, -7.6)	2012-2015	9.9 (8.4, 11.5)	2015-2018	-12.7 (-13.6, -11.7)	-0.6 (-0.9, -0.3)
85	1998-2008	-0.2 (-0.3, -0.2)	2008-2012	2.7 (2.6, 2.8)	2012-2015	-7.2 (-7.4, -6.9)	2015-2018	1.4 (1.2, 1.6)	-0.5 (-0.5, -0.4)
Ethnicity									
White	1998-2009	8.6 (8.2, 9.0)	2009-2012	-10.7 (-12.5, -8.8)	2012-2015	1.8 (-0.8, 4.4)	2015-2018	-15.9 (-18.1, -13.7)	0.5 (-0.1, 1.1)
Others	1998-2008	-33.1 (-34.3, -32.0)	2008-2014	55.7 (8.6, 123.1)	2014-2018	-30.3 (-43.1, -14.6)	–	–	-13.1 (-21.8, -3.5)
Deprivation									
Least deprived	1998-2009	5.5 (5.0, 6.0)	2009-2012	-23.6 (-26.7, -20.3)	2012-2015	47.5 (40.7, 54.6)	2015-2018	-32.4 (-35.7, -29.0)	-1.1 (-2.2, 0.0)
Most deprived	1998-2008	-11.6 (-12.2, -11.0)	2008-2012	38.2 (33.8, 42.8)	2012-2016	-27.8 (-30.2, -25.3)	2016-2018	10.4 (-4.4, 27.5)	-5.1 (-6.6, -3.6)
BMI group, kg/m^2									
18.5-24.9	1998-2008	1.6 (1.4, 1.7)	2008-2011	-10.4 (-11.4, -9.5)	2011-2015	1.8 (1.1, 2.5)	2015-2018	-27.6 (-29.1, -26.0)	-5.2 (-5.5, -4.9)
25.0-29.9	1998-2006	7.8 (6.0, 9.6)	2006-2009	4.1 (-0.8, 9.3)	2009-2012	-12.1 (-16.7, -7.3)	2012-2018	-2.7 (-4.4, -1.0)	0.8 (-0.4, 2.1)
30.0-34.9	1998-2009	21.7 (20.8, 22.7)	2009-2012	-21.9 (-24.0, -19.7)	2012-2015	16.5 (12.8, 20.4)	2015-2018	-30.6 (-33.4, -27.7)	4.0 (3.1, 4.9)
≥35.0	1998-2007	6.3 (5.7, 7.0)	2007-2010	1.5 (-0.9, 4.0)	2010-2015	-10.5 (-11.3, -9.6)	2015-2018	-28.9 (-33.9, -23.6)	-4.8 (-5.8, -3.8)
Smoking status									
Current smoker	1998-2008	1.8 (1.4, 2.1)	2008-2014	-6.8 (-7.4, -6.2)	2014-2018	-22.1 (-24.6, -19.5)	–	–	-6.1 (-6.6, -5.5)
Ex-smoker	1998-2009	11.0 (10.2, 11.8)	2009-2012	-25.2 (-28.5, -21.7)	2012-2015	26.3 (18.9, 34.2)	2015-2018	-26.4 (-30.9, -21.7)	0.3 (-1.0, 1.6)
Non-smoker	1998-2008	7.6 (7.4, 7.8)	2008-2011	-1.6 (-2.3, -0.9)	2011-2018	-10.7 (-10.9, -10.5)	–	–	-0.5 (-0.7, -0.4)
Prostate									
Age, years									
55	1998-2012	-5.0 (-5.1, -4.9)	2012-2016	19.3 (18.5, 20.2)	2016-2018	-26.5 (-28.4, -24.6)	–	–	-3.1 (-3.3, -2.8)
65	1998-2012	-1.4 (-1.5, -1.4)	2012-2016	13.1 (12.6, 13.6)	2016-2018	-23.3 (-24.6, -22.0)	–	–	-1.2 (-1.4, -1.0)
75	1998-2011	1.6 (1.5, 1.7)	2011-2016	5.0 (4.7, 5.4)	2016-2018	-14.1 (-15.6, -12.4)	–	–	0.8 (0.6, 1.0)
85	1998-2009	8.1 (7.9, 8.2)	2009-2013	2.9 (2.5, 3.2)	2013-2016	9.2 (8.7, 9.8)	2016-2018	-6.8 (-7.4, -6.2)	5.6 (5.5, 5.7)
Ethnicity									
White	1998-2012	3.6 (3.6, 3.6)	2012-2016	10.0 (9.9, 10.2)	2016-2018	-17.4 (-17.7, -17.0)	–	–	2.5 (2.5, 2.6)
Others	1998-2008	42.4 (15.9, 75.0)	2008-2018	-15.2 (-21.0, -8.9)	–	–	–	–	9.9 (-0.6, 21.6)
Deprivation									
Least deprived	1998-2008	-7.8 (-8.1, -7.4)	2008-2014	5.6 (4.6, 6.5)	2014-2018	-20.3 (-22.7, -17.9)	–	–	-6.7 (-7.3, -6.1)
Most deprived	1998-2009	7.2 (6.6, 7.8)	2009-2012	-27.9 (-31.4, -24.3)	2012-2016	42.4 (37.9, 47.1)	2016-2018	-38.2 (-43.1, -32.8)	1.2 (0.0, 2.4)
BMI group, kg/m^2									
18.5-24.9	1998-2012	7.7 (7.5, 8.0)	2012-2015	25.2 (23.7, 26.7)	2015-2018	-26.1 (-27.6, -24.5)	–	–	4.1 (3.8, 4.5)
25.0-29.9	1998-2008	-9.6 (-9.7, -9.5)	2008-2011	-0.9 (-2.7, 1.0)	2011-2015	13.3 (12.6, 14.1)	2015-2018	-10.4 (-11.2, -9.5)	-4.2 (-4.5, -3.9)
30.0-34.9	1998-2010	2.3 (2.2, 2.4)	2010-2013	-6.0 (-6.9, -5.1)	2013-2016	0.7 (-0.5, 1.9)	2016-2018	-4.0 (-5.6, -2.3)	0.1 (-0.1, 0.4)
≥35.0	1998-2015	24.2 (22.2, 26.2)	2015-2018	-25.3 (-32.6, -17.3)	–	–	–	–	15.1 (12.9, 17.3)
Smoking status									
Current smoker	1998-2009	3.7 (3.5, 3.9)	2009-2013	15.9 (15.5, 16.4)	2013-2016	-5.3 (-5.8, -4.8)	2016-2018	-11.4 (-12.4, -10.4)	3.0 (2.8, 3.1)
Ex-smoker	1998-2008	8.5 (8.3, 8.8)	2008-2011	5.9 (5.0, 6.8)	2011-2016	-2.1 (-2.3, -1.8)	2016-2018	-6.8 (-8.1, -5.4)	3.8 (3.6, 4.0)
Non-smoker	1998-2012	-6.1 (-6.7, -5.5)	2012-2016	29.0 (22.0, 36.5)	2016-2018	-37.8 (-50.0, -22.6)	–	–	-4.0 (-6.1, -1.8)
Lung									
Age, years									
55	1998-2010	8.5 (8.4, 8.7)	2010-2013	0.6 (-0.2, 1.3)	2013-2018	-16.9 (-17.2, -16.5)	–	–	0.4 (0.2, 0.5)
65	1998-2009	3.5 (3.5, 3.6)	2009-2012	1.2 (1.0, 1.4)	2012-2015	-8.6 (-8.9, -8.4)	2015-2018	-0.4 (-0.6, -0.2)	0.7 (0.6, 0.7)
75	1998-2009	8.6 (8.4, 8.9)	2009-2012	-3.8 (-4.8, -2.8)	2012-2015	2.0 (0.9, 3.2)	2015-2018	-9.8 (-10.7, -8.9)	2.8 (2.5, 3.0)
85	1998-2009	5.7 (5.5, 5.9)	2009-2012	-3.9 (-4.9, -2.8)	2012-2015	7.5 (6.4, 8.6)	2015-2018	-14.0 (-14.7, -13.2)	1.3 (1.1, 1.6)
Gender									
Men	1998-2006	3.6 (3.5, 3.7)	2006-2009	2.3 (2.0, 2.6)	2009-2013	-4.2 (-4.3, -4.1)	2013-2018	-0.2 (-0.3, -0.1)	0.9 (0.8, 0.9)

	Period 1	APC, %	Period 2	APC, %	Period 3	APC, %	Period 4	APC, %	AAPC for whole period, %
Women	1998-2009	8.9 (8.9, 9.0)	2009-2012	2.0 (1.6, 2.3)	2012-2015	-5.0 (-5.3, -4.6)	2015-2018	-0.4 (-0.6, -0.1)	4.3 (4.2, 4.4)
Ethnicity									
White	1998-2007	7.3 (7.2, 7.4)	2007-2010	5.0 (4.6, 5.5)	2010-2015	-2.3 (-2.4, -2.2)	2015-2018	0.7 (0.4, 0.9)	3.5 (3.4, 3.6)
Others	1998-2010	-17.7 (-17.8, -17.7)	2010-2013	-6.1 (-9.4, -2.7)	2013-2016	28.8 (25.2, 32.6)	2016-2018	-6.6 (-9.1, -4.1)	-9.1 (-9.7, -8.5)
Deprivation									
Least deprived	1998-2008	10.7 (10.5, 11.0)	2008-2011	5.7 (5.0, 6.5)	2011-2015	-17.7 (-18.2, -17.3)	2015-2018	-0.7 (-1.7, 0.4)	1.9 (1.7, 2.2)
Most deprived	1998-2008	7.7 (7.6, 7.9)	2008-2012	9.8 (9.6, 10.0)	2012-2016	-5.9 (-6.1, -5.7)	2016-2018	2.7 (2.1, 3.2)	4.8 (4.7, 4.9)
BMI group, kg/m²									
18.5-24.9	1998-2008	11.1 (10.7, 11.4)	2008-2012	-8.2 (-8.8, -7.5)	2012-2015	10.1 (8.6, 11.6)	2015-2018	-13.3 (-14.3, -12.3)	2.9 (2.6, 3.2)
25.0-29.9	1998-2009	1.8 (1.7, 1.8)	2009-2012	-0.5 (-0.7, -0.3)	2012-2018	-5.0 (-5.0, -4.9)	–	–	-0.6 (-0.7, -0.6)
30.0-34.9	1998-2008	2.1 (1.7, 2.5)	2008-2015	5.3 (5.0, 5.6)	2015-2018	-17.7 (-19.0, -16.4)	–	–	-0.1 (-0.4, 0.2)
≥35.0	1998-2009	33.5 (24.7, 43.0)	2009-2013	-17.6 (-24.2, -10.3)	2013-2018	20.2 (16.3, 24.2)	–	–	18.1 (13.7, 22.7)
Smoking status									
Current smoker	1998-2009	5.5 (4.7, 6.3)	2009-2012	12.6 (8.5, 16.9)	2012-2018	-6.8 (-7.6, -6.1)	–	–	2.6 (1.9, 3.3)
Ex-smoker	1998-2009	13.8 (13.5, 14.1)	2009-2013	-9.7 (-10.3, -9.2)	2013-2018	1.8 (1.4, 2.2)	–	–	5.7 (5.5, 5.9)
Non-smoker	1998-2008	-13.4 (-13.4, -13.4)	2008-2011	-11.9 (-12.2, -11.6)	2011-2015	3.8 (3.6, 4.0)	2015-2018	-19.8 (-20.1, -19.4)	-11.0 (-11.1, -10.9)
Colorectal									
Age, years									
55	1998-2006	10.1 (9.0, 11.3)	2006-2009	3.7 (0.8, 6.7)	2009-2012	-15.0 (-17.9, -11.9)	2012-2018	3.8 (2.9, 4.7)	3.1 (2.4, 3.9)
65	1998-2007	3.7 (3.6, 3.9)	2007-2010	-0.7 (-1.4, 0.1)	2010-2015	-8.3 (-8.6, -8.1)	2015-2018	14.2 (13.5, 14.9)	1.4 (1.2, 1.5)
75	1998-2006	3.5 (3.2, 3.8)	2006-2009	0.9 (-0.3, 2.1)	2009-2013	-8.7 (-9.4, -8.1)	2013-2018	-0.7 (-1.1, -0.2)	-0.5 (-0.7, -0.2)
85	1998-2008	5.4 (5.2, 5.5)	2008-2012	-0.6 (-0.9, -0.2)	2012-2015	2.5 (1.8, 3.1)	2015-2018	-7.4 (-7.8, -6.9)	1.7 (1.6, 1.9)
Gender									
Men	1998-2008	0.4 (0.3, 0.4)	2008-2011	-1.7 (-2.0, -1.4)	2011-2015	-9.2 (-9.3, -9.0)	2015-2018	1.0 (0.7, 1.3)	-1.8 (-1.9, -1.8)
Women	1998-2006	9.4 (8.0, 10.8)	2006-2009	4.6 (0.7, 8.6)	2009-2014	-12.4 (-13.9, -11.0)	2014-2018	23.6 (21.5, 25.7)	5.3 (4.4, 6.2)
Ethnicity									
White									
Others	1998-2009	3.7 (3.6, 3.8)	2009-2012	-1.2 (-1.9, -0.5)	2012-2015	-11.6 (-12.5, -10.8)	2015-2018	14.2 (13.5, 14.8)	2.0 (1.8, 2.2)
Deprivation	1998-2010	-10.1 (-10.1, -10.1)	2010-2013	20.1 (19.8, 20.4)	2013-2016	-24.9 (-25.1, -24.7)	2016-2018	21.2 (20.8, 21.7)	-5.8 (-5.9, -5.8)
Least deprived									
Most deprived	1998-2008	-1.6 (-1.7, -1.5)	2008-2011	3.0 (2.4, 3.6)	2011-2015	-20.3 (-20.7, -19.9)	2015-2018	15.2 (14.4, 16.0)	-2.7 (-2.9, -2.6)
BMI group, kg/m²	1998-2008	14.9 (14.3, 15.5)	2008-2011	6.5 (5.0, 8.0)	2011-2015	-18.2 (-19.1, -17.4)	2015-2018	51.3 (50.1, 52.6)	10.6 (10.2, 11.0)
18.5-24.9									
25.0-29.9	1998-2007	-9.6 (-10.0, -9.2)	2007-2015	6.7 (6.2, 7.3)	2015-2018	11.1 (9.6, 12.6)	–	–	-0.3 (-0.7, 0.0)
30.0-34.9	1998-2008	5.0 (4.9, 5.1)	2008-2011	-2.3 (-2.9, -1.8)	2011-2015	-15.9 (-16.3, -15.4)	2015-2018	12.1 (11.3, 12.9)	0.3 (0.2, 0.5)
≥35.0	1998-2009	0.8 (0.5, 1.0)	2009-2013	-8.0 (-9.1, -6.9)	2013-2018	-0.3 (-1.1, 0.5)	–	–	-1.3 (-1.6, -1.0)
Smoking status	1998-2012	1.7 (1.6, 1.8)	2012-2016	-7.0 (-7.7, -6.3)	2016-2018	46.6 (45.1, 48.2)	–	–	3.6 (3.4, 3.8)
Current smoker									
Ex-smoker	1998-2008	-1.4 (-1.5, -1.3)	2008-2012	8.1 (7.5, 8.6)	2012-2015	-17.4 (-18.3, -16.5)	2015-2018	30.2 (29.6, 30.9)	2.0 (1.8, 2.2)
Non-smoker	1998-2008	0.2 (0.0, 0.5)	2008-2015	-4.1 (-4.5, -3.8)	2015-2018	19.9 (18.7, 21.1)	–	–	1.4 (1.1, 1.6)

APC: Annual Percentage Change; **AAPC**: Average Annual Percentage Change. –: Not applicable. Different number of segments for each stratum (period 1 to 4) are identified by Joinpoint regressions**.**

ESM Table 8. Annual percentage change and average annual percentage change in cancer-specific mortality rates (four type 2 diabetes-related cancers)

|	Period 1	APC, %	Period 2	APC, %	Period 3	APC, %	Period 4	APC, %	AAPC for whole period, %
Pancreas									
Age, years									
55	1998-2007	6.7 (6.4, 6.9)	2007-2010	0.1 (-0.9, 1.1)	2010-2014	-9.3 (-9.9, -8.7)	2014-2018	5.2 (4.5, 5.9)	2.0 (1.8, 2.2)
65	1998-2008	15.0 (14.1, 15.9)	2008-2012	-7.1 (-8.6, -5.6)	2012-2018	2.6 (1.9, 3.3)	–	–	6.5 (6.0, 7.0)
75	1998-2008	9.5 (9.2, 9.9)	2008-2014	-6.8 (-7.2, -6.5)	2014-2018	0.7 (-0.2, 1.7)	–	–	2.6 (2.4, 2.9)
85	1998-2008	12.3 (12.1, 12.6)	2008-2011	-1.6 (-2.4, -0.8)	2011-2015	4.3 (3.9, 4.7)	2015-2018	-3.0 (-3.4, -2.5)	6.1 (6.0, 6.3)
Gender									
Men	1998-2005	12.1 (11.5, 12.6)	2005-2008	7.9 (6.7, 9.1)	2008-2013	-9.7 (-10.0, -9.3)	2013-2018	-0.1 (-0.6, 0.4)	2.6 (2.3, 2.8)
Women	1998-2008	15.1 (14.8, 15.4)	2008-2012	-2.0 (-2.5, -1.5)	2012-2015	1.3 (0.3, 2.3)	2015-2018	-8.5 (-9.3, -7.8)	5.6 (5.4, 5.9)
Ethnicity									
White	1998-2008	21.5 (19.8, 23.3)	2008-2012	-8.2 (-10.3, -6.1)	2012-2018	1.3 (0.2, 2.3)	–	–	8.8 (7.9, 9.7)
Others	1998-2010	-3.2 (-3.3, -3.2)	2010-2014	-8.8 (-9.1, -8.5)	2014-2018	6.4 (6.1, 6.6)	–	–	-2.6 (-2.6, -2.5)
Deprivation									
Least deprived	1998-2006	27.2 (25.7, 28.7)	2006-2009	11.4 (9.5, 13.4)	2009-2014	-16.0 (-16.6, -15.4)	2014-2018	11.4 (10.1, 12.6)	9.5 (8.9, 10.0)
Most deprived	1998-2008	1.7 (1.5, 1.9)	2008-2012	8.0 (7.5, 8.6)	2012-2015	-7.2 (-8.1, -6.3)	2015-2018	17.2 (16.6, 17.9)	3.7 (3.5, 3.9)
BMI group, kg/m²									
18.5-24.9	1998-2006	0.4 (0.1, 0.6)	2006-2010	18.4 (17.6, 19.2)	2010-2014	-15.0 (-15.6, -14.4)	2014-2018	-5.7 (-6.6, -4.8)	-0.9 (-1.1, -0.6)
25.0-29.9	1998-2008	23.5 (22.4, 24.5)	2008-2013	-10.5 (-11.2, -9.7)	2013-2018	3.2 (2.3, 4.2)	–	–	9.0 (8.4, 9.5)
30.0-34.9	1998-2009	6.7 (6.1, 7.4)	2009-2012	-11.2 (-14.5, -7.9)	2012-2018	6.3 (5.4, 7.1)	–	–	3.7 (3.1, 4.3)
≥35.0	1998-2010	0.8 (0.3, 1.3)	2010-2013	31.0 (27.0, 35.1)	2013-2018	-15.9 (-16.6, -15.1)	–	–	0.2 (-0.3, 0.8)
Smoking status									
Current smoker	1998-2008	36.1 (33.5, 38.8)	2008-2014	-8.9 (-9.6, -8.2)	2014-2018	2.9 (1.2, 4.7)	–	–	14.1 (13.0, 15.2)
Ex-smoker	1998-2008	6.5 (6.2, 6.7)	2008-2012	-7.6 (-8.2, -7.0)	2012-2015	10.0 (8.7, 11.3)	2015-2018	-9.6 (-10.4, -8.8)	1.5 (1.2, 1.7)
Non-smoker	1998-2008	11.6 (11.3, 11.9)	2008-2012	-10.3 (-10.9, -9.6)	2012-2015	7.7 (5.9, 9.4)	2015-2018	-2.9 (-3.9, -1.9)	4.1 (3.7, 4.4)
Liver									
Age, years old									
55	1998-2009	6.9 (6.6, 7.2)	2009-2013	17.5 (16.9, 18.1)	2013-2016	-12.5 (-13.3, -11.8)	2016-2018	-2.2 (-3.8, -0.6)	4.8 (4.5, 5.0)
65	1998-2015	5.8 (5.5, 6.1)	2015-2018	-18.6 (-21.8, -15.2)	–	–	–	–	1.7 (1.1, 2.4)
75	1998-2009	12.3 (11.4, 13.2)	2009-2013	-15.1 (-16.9, -13.2)	2013-2016	24.7 (18.7, 30.9)	2016-2018	-20.6 (-26.1, -14.7)	4.2 (3.1, 5.3)
85	1998-2009	5.8 (5.5, 6.1)	2009-2014	-1.5 (-2.0, -0.9)	2014-2018	5.6 (5.1, 6.2)	–	–	3.9 (3.7, 4.1)
Gender									
Men	1998-2009	4.4 (4.2, 4.7)	2009-2013	-15.2 (-16.1, -14.3)	2013-2016	17.3 (14.6, 20.1)	2016-2018	-14.7 (-17.3, -11.9)	-0.1 (-0.6, 0.4)
Women	1998-2010	32.8 (31.9, 33.8)	2010-2013	-19.1 (-20.1, -18.1)	2013-2016	34.9 (32.8, 37.0)	2016-2018	-34.5 (-36.6, -32.4)	15.2 (14.5, 15.8)
Ethnicity									
White	1998-2010	9.0 (8.6, 9.4)	2010-2013	-12.4 (-14.3, -10.4)	2013-2016	20.5 (17.8, 23.2)	2016-2018	-29.7 (-33.1, -26.1)	2.5 (1.8, 3.2)
Others	1998-2010	24.1 (23.1, 25.0)	2010-2013	-55.2 (-60.4, -49.3)	2013-2016	121.3 (-12.2, 457.3)	2016-2018	-41.8 (-57.3, -20.7)	7.7 (-5.1, 22.1)
Deprivation									
Least deprived	1998-2010	11.5 (11.4, 11.5)	2010-2013	4.3 (4.1, 4.5)	2013-2016	27.7 (27.6, 27.9)	2016-2018	-50.5 (-50.9, -50.1)	3.9 (3.8, 3.9)
Most deprived	1998-2007	29.9 (29.1, 30.7)	2007-2010	14.4 (13.7, 15.1)	2010-2014	-32.0 (-32.5, -31.4)	2014-2018	24.2 (23.3, 25.0)	11.0 (10.6, 11.3)
BMI group, kg/m²									
18.5-24.9	1998-2015	18.9 (14.6, 23.3)	2015-2018	-37.8 (-62.1, 2.0)	–	–	–	–	7.9 (0.1, 16.2)
25.0-29.9	1998-2009	6.5 (6.3, 6.7)	2009-2012	-17.9 (-19.0, -16.8)	2012-2015	23.9 (21.7, 26.2)	2015-2018	-22.9 (-24.2, -21.5)	-0.2 (-0.6, 0.2)
30.0-34.9	1998-2018	5.5 (2.6, 8.4)	–	–	–	–	–	–	5.5 (2.6, 8.4)
≥35.0	1998-2008	12.3 (10.9, 13.6)	2008-2011	7.1 (4.1, 10.2)	2011-2014	-18.3 (-21.2, -15.3)	2014-2018	-3.5 (-5.7, -1.3)	3.1 (2.2, 4.1)
Smoking status									
Current smoker	1998-2009	-4.3 (-4.7, -3.9)	2009-2013	15.4 (13.4, 17.5)	2013-2016	-15.5 (-18.6, -12.4)	2016-2018	50.8 (46.6, 55.1)	2.0 (1.4, 2.7)
Ex-smoker	1998-2012	-5.2 (-5.3, -5.0)	2012-2016	12.3 (11.2, 13.5)	2016-2018	-31.1 (-34.2, -27.9)	–	–	-5.0 (-5.4, -4.5)
Non-smoker	1998-2010	21.3 (19.9, 22.6)	2010-2013	-27.2 (-30.2, -24.1)	2013-2016	28.7 (21.9, 35.9)	2016-2018	-42.3 (-51.7, -31.1)	5.2 (3.3, 7.2)
Gallbladder									

	Period 1	APC, %	Period 2	APC, %	Period 3	APC, %	Period 4	APC, %	AAPC for whole period, %
Age, years old									
65	1998-2013	-14.6 (-14.7, -14.6)	2013-2016	113.1 (112.1, 114.1)	2016-2018	-84.4 (-85.2, -83.6)	–	–	-17.4 (-17.8, -17.0)
75	1998-2010	-24.8 (-25.5, -24.0)	2010-2014	40.1 (15.4, 70.2)	2014-2018	-1.5 (-8.7, 6.2)	–	–	-10.1 (-13.5, -6.6)
85	1998-2012	-0.9 (-1.1, -0.8)	2012-2015	40.3 (38.6, 42.1)	2015-2018	-27.7 (-37.4, -16.4)	–	–	-0.4 (-2.4, 1.6)
Endometrium									
Age, years old									
55	1998-2009	-5.7 (-6.2, -5.1)	2009-2013	21.1 (17.9, 24.4)	2013-2018	-23.9 (-26.0, -21.7)	–	–	-6.0 (-6.8, -5.2)
65	1998-2007	14.1 (13.6, 14.6)	2007-2010	8.7 (7.6, 9.8)	2010-2014	-3.5 (-3.9, -3.0)	2014-2018	5.8 (5.5, 6.2)	7.9 (7.7, 8.2)
75	1998-2009	9.8 (9.2, 10.4)	2009-2013	-24.8 (-26.8, -22.8)	2013-2018	22.4 (20.6, 24.1)	–	–	4.6 (3.9, 5.3)
85	1998-2009	23.4 (22.9, 24.0)	2009-2013	1.0 (0.5, 1.4)	2013-2016	22.7 (22.1, 23.4)	2016-2018	-11.6 (-12.2, -11.0)	14.6 (14.3, 14.9)

Due to small numbers of events, stratified analyses were not possible for gallbladder and endometrial cancer mortality while rate for gallbladder cancer mortality in 55-year-old subjects was not estimable.

APC: Annual Percentage Change; **AAPC**: Average Annual Percentage Change. –: Not applicable. Different number of segments for each stratum (period 1 to 4) are identified by Joinpoint regressions**.**

ESM Figure 1. Study participants selection flowchart
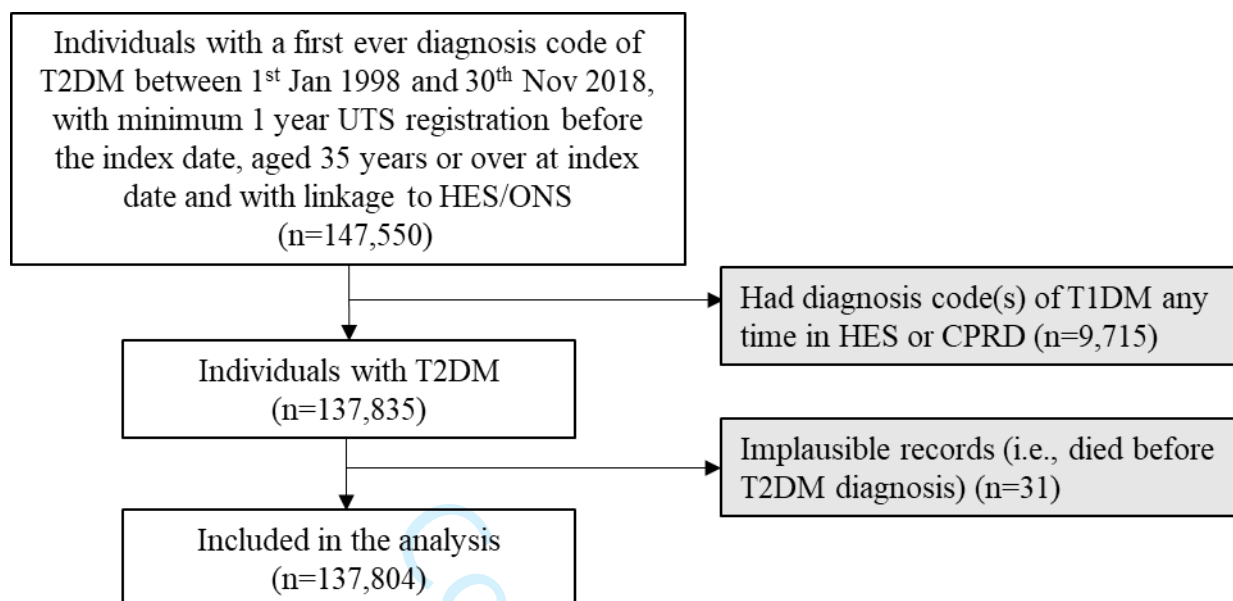
T2DM: type 2 diabetes; T1DM: type 1 diabetes; UTS: up-to-standard date; HES: Hospital Episodes Statistics; ONS: Office for National Statistics.

The index date was the first diagnosis date of type 2 diabetes.

RECORD checklist

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1, 3
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			4
Objectives	3	State specific objectives, including any prespecified hypotheses			4
Methods					
Study Design	4	Present key elements of study design early in the paper			5, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			5, 6
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	5-7, ESM fig. 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	5, 6, Github ID: supingling
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			5, 6
Bias	9	Describe any efforts to address potential sources of bias			NA
Study size	10	Explain how the study size was arrived at			7, ESM fig. 1

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses			6
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	5, 14
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	5, 6
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	7, ESM fig. 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			7, Table 1
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time			7, Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized			7-9, Table 3, Table 4, Figure 1-4, ESM Table 1-8

			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17		Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses		7-9, Table 3, Table 4, Figure 1-4, ESM Table 1-8
Discussion					
Key results	18		Summarise key results with reference to study objectives		10
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	11-12
Interpretation	20		Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		10-13
Generalisability	21		Discuss the generalisability (external validity) of the study results		11-12
Other Information					
Funding	22		Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		14
Accessibility of protocol, raw data, and programming code			..	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	14

Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015.

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