Cancer has overtaken cardiovascular disease as the commonest cause of death in Scottish type 2 diabetes patients: A population-based study (The Ayrshire Diabetes Follow-up Cohort study)

Andrew Collier1,*, Carron Meney1, Mario Hair2, Lyall Cameron3, James G Boyle4
1Diabetes Day Center, 2NHS Ayrshire and Arran, University Hospital, 3Primary Care Quality and Development, NHS Ayrshire and Arran, Ailsa Hospital, Ayr, and 4Glasgow Royal Infirmary, Glasgow, UK

Keywords
Cancer, Mortality risk, Type 2 diabetes

*Correspondence
Andrew Collier
Tel.: +44-1292-610555
Fax: +44-1292-614540
E-mail address: andrew.collier@aaaht.scot.nhs.uk

J Diabetes Investig 2020; 11: 55–61
doi: 10.1111/jdi.13067

ABSTRACT
Aims/Introduction: The increased mortality risk associated with diabetes is well established. The aim of the present study was to determine the causes of death of people with type 2 diabetes in Ayrshire and Arran, Scotland, between 2009 and 2014, and compare them with the national mortality rates.

Materials and Methods: The primary causes of death were collated. The causes of death were clustered into nine categories: heart disease, stroke, infection, renal failure, respiratory disorders, cancer, mental health, decompensated diabetes and other. The total rates were compared with national rates using the standardized mortality ratio (SMR), and then individually with heart disease, cerebrovascular disease and cancer.

Results: There were 2116 deaths with the SMR, and 145 of those were caused by type 2 diabetes (n = 16,643; 95% confidence interval 139–152; P < 0.01). The SMR was >100 in all age bands, particularly in the younger age bands (P < 0.01). The SMR was consistently higher for women (P < 0.01). The SMR for heart disease was significantly >100 for both sexes in all age bands <65 years (P < 0.05). There was no difference in mortality causes related to the duration of diabetes. The most common cause of death was cancer (27.8%), followed by heart disease (24.1%). The SMR for cancer deaths was significantly elevated in women (120, 95% CI 104–137; P < 0.05).

Conclusions: This study confirmed increased mortality risk in type 2 diabetes patients, and suggests that where cardiovascular risk factors are being treated aggressively, cancer takes on a greater importance in the cause of death. Should greater consideration now be given for cancer as a complication of diabetes?

INTRODUCTION
The increase in mortality risk associated with diabetes is well established1–16. Mortality rates among people with type 2 diabetes compared with the general population appear to vary significantly depending on the glycemic control, age, duration of diabetes, renal complications and ethnicity1–16. The ultimate goal of the treatment of patients with type 2 diabetes is to improve the quality of life and to reduce the mortality rate to a level comparable to individuals without diabetes. The patterns of mortality appear to be changing, and a significant decline in mortality from cardiovascular disease (CVD) in both the general and type 2 diabetes populations has been reported1–16. The excess in mortality among type 2 diabetes patients in the past has been mainly attributable to cardiovascular disease1–16, particularly myocardial infarction. The Steno-2 Study, carried out from 1993 to 201010,11, plus numerous other studies1–9,12–16 have shown that aggressive multifactorial cardiovascular treatment of type 2 diabetes patients significantly reduces the risk of...
CVD and death. Furthermore, a number of studies suggest that the gap between the diabetes and non-diabetes populations is narrowing. Improved diabetes-related medical care plus more aggressive treatment strategies based on targeting multiple risk factors have now been recommended and implemented in the clinical care of people with type 2 diabetes.

The aims of the present study were to investigate the age profile of the deaths among people with type 2 diabetes in Ayrshire and Arran, Scotland. The study compared the deaths with the standardized mortality ratio (SMR), the expected and actual number of deaths over the 5 years, and the standardized mortality ratio for each age band. We also investigated specific causes (heart disease, stroke and cancer) for men and women in each age banding. In addition, we determined the effect of the duration of diabetes on mortality risk (<5 years, 5–10 years and >10 years).

**METHODS**

A total of 46 out of 55 general practices in National Health Service (NHS) Ayrshire and Arran, covering 85% of the total patient population (aged >18 years) of Ayrshire and Arran, contributed data from their practice computer systems. Data were provided both in 2009 and in 2014. There was no significant difference in the prevalence of diabetes between practices that did and did not provide data (5.5% vs 5.7%, \( \chi^2 = 3.3, P = 0.07 \)).

For the period under investigation, all conditions were coded in accordance with the International Classification of Diseases, 10th Revision. The General Practice EMIS data were linked to the national death records by the Information Services Division of NHS National Services Scotland. Generation of the linked dataset was approved by the Clinical Governance Department, NHS Ayrshire and Arran, and Caldicott Guardian approval was obtained from each general practice. The causes of death were attributed to one of nine categories: heart disease, stroke, infection, renal failure, respiratory disorders, cancer, mental health, decompensated diabetes and other.

The duration of diabetes was calculated as the time between diagnosis and either death or the study end date. SMR was calculated from Scottish mortality rates over the same period (estimated from National Records of Scotland Vital Events Reference Tables 2015) using the same age profile as the cohort. SMR confidence intervals were calculated using Byar’s method, which is accurate for observed frequencies of five or more. For smaller observed frequencies, an exact method based on the Poisson distribution was used. National data only gives mortality rates from specific causes (heart disease, cerebrovascular accidents and cancer) for each sex separately, so comparisons with national data are shown separately for men and women.

**RESULTS**

At the start of the study period in 2009, there were 10,679 people with type 2 diabetes in the cohort. At the end of the study in 2014, 1,764 people had died, giving a mortality rate over the 5-year period of 165.2 per 1,000 people. By comparison, the Scottish mortality rate over the same period, using the same age profile, was estimated as 113.7 per 1,000 patients. Hence, the SMR for people with type 2 diabetes in the cohort was 145. The SMR for people with type 2 diabetes was >100 (aged >35 years) and was greater in the earlier age bands, decreasing as age increased. Table 1 also shows separate SMRs for men and women. The SMR was consistently higher for women.

**Specific causes of death**

The distribution of cause of death by sex is shown in Table 2. The main cause of death was cancer (28%), followed by heart disease (24%). These two categories accounted for over half of all deaths. There was a statistically significant difference by sex.

---

**Table 1 | Standardized mortality ratio for type 2 diabetes patients over the 5-year study period by age**

| Age (years) | No. deaths/sample size | SMR (95% CI) | SMR (95% CI) | SMR (95% CI) |
|-------------|------------------------|--------------|--------------|--------------|
|             |                        | All‡         | Men          | Women        |
| <25         | 0/6                    |              |              |              |
| 25–34       | 2/88                   | 542 NS (61–1,006) | 157 NS (51–365) | 1,933 (242–7,224) |
| 35–44       | 14/495                 | 330 (180–553) | 190 (133–264) | 283 (182–422) |
| 45–54       | 60/1,547               | 232 (177–299) | 159 (132–189) | 220 (174–275) |
| 55–64       | 203/2,725              | 188 (163–216) | 154 (138–172) | 195 (171–222) |
| 65–74       | 563/3,319              | 176 (162–192) | 124 (111–137) | 137 (122–153) |
| 75–84       | 659/2,047              | 132 (122–143) | 102 NS (90–115) | 108 NS (89–128) |
| >85         | 263/452                | 102 NS (90–115) | 96 NS (81–113) | 96 NS (81–113) |
| Overall     | 1,764/10,679           | 145 (139–152) | 136 (128–145) | 148 (138–159) |

‡The 95%-confidence intervals (CI) were calculated using Byar’s method, which is accurate for observed frequencies of five or more. For smaller observed frequencies, an exact method based on the Poisson distribution was used. Scottish mortality rates estimated from National Records of Scotland Vital Events Reference Tables 2015 Table 5.1(b): Death rates, by sex and age, Scotland, 2001 to 2014 https://www.nrscotland.gov.uk/statistics-and-data/statistic s/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2015/section-5-deaths (accessed 15/11/17). NS, not significant.
Table 2 | Cause of death for patients with type 2 diabetes by sex

| Cause of death                              | Men       | Women     | Total     |
|---------------------------------------------|-----------|-----------|-----------|
| Cancer                                      | 29.6% (342) | 25.6% (246) | 27.8% (588) |
| Heart disease                               | 25.7% (297) | 22.1% (212) | 24.1% (509) |
| Respiratory                                 | 12.4% (143) | 13.8% (133) | 13.0% (276) |
| Stroke                                      | 7.6% (88)  | 9.6% (92)  | 8.5% (180)  |
| Sepsis                                      | 5.0% (58)  | 7.0% (67)  | 5.9% (125)  |
| Decompensated diabetes                      | 4.2% (48)  | 4.7% (45)  | 4.4% (93)   |
| Mental health                               | 3.1% (36)  | 5.1% (49)  | 4.0% (85)   |
| Renal failure                               | 2.3% (27)  | 2.8% (27)  | 2.6% (54)   |
| Accident/liver/neurological/other           | 10.0% (116) | 9.4% (90)  | 9.7% (206)  |
| Total                                       | 1,155     | 961       | 2,116     |

(P = 0.02), with more male deaths from cancer and heart disease, and more female deaths in all other categories.

Heart disease
The SMR for patients with type 2 diabetes deaths from heart disease was >100 for both sexes in all age bands (>35 years), except the oldest (≥85 years). In men, however, the increase in SMR was not significant in the 35–54 years age groups. SMRs generally decreased with age and were consistently higher for women (Table 3).

Stroke
The number of deaths from stroke was small. The SMRs for people with type 2 diabetes deaths from stroke was significantly >100 only for ages 55–74 years for both men and women. SMRs generally decreased with age, and the overall SMRs were similar for both men and women (Table 3).

Cancer
The overall SMR for men with type 2 diabetes was not significantly different from the national population. For women with type 2 diabetes, the overall SMR was higher. Within the age bands, there was no clear pattern, but for both men and women the SMRs for the 65–74 years age band were significantly higher. The SMR for men aged >85 years was below the national population (Table 3).

Effect of duration of type 2 diabetes on SMR
Within the study period (2009–2014), 12.7% (2116) of people with type 2 diabetes died, this included 352 patients who were newly diagnosed within the study period: mortality was 10.1% (632) for those with duration of type 2 diabetes of <5 years; mortality was 14.7% (786) for those with duration of type 2 diabetes between 5 and 10 years; 175. SMRs for women aged <10 years were again highest in those with diabetes between 5 and 10 years for all causes except heart disease. The SMR for women with type 2 diabetes from heart disease was high for all diabetes durations, rising from 154 for those with diabetes for <5 years, to 214 for those with diabetes for >10 years.

DISCUSSION
The present study confirmed that all-cause mortality for people with type 2 diabetes remains higher than in the non-diabetes population. The SMR for women with type 2 diabetes was 148, and for men with type 2 diabetes was 136. These SMR results are very similar to the relative risk of mortality associated with type 2 diabetes compared with a diabetes-free population from a Scottish study published in 201623. The SMR in the present study was greater in the earlier age bands, decreasing as age increased, and was consistently higher in women than men. The commonest cause of death in our cohort was cancer, followed by heart disease and then respiratory conditions. The duration of diabetes did not impact on the causes of death.

The evidence base for managing type 2 diabetes and preventing complications has improved greatly1-16. Aggressive cardiovascular risk factor management, glycemic control studies and smoking cessation have shown better cardiovascular outcome1-16. In addition, there has been significant improvement in diabetes management in Scotland and the rest of the UK due to the Quality and Outcomes Framework payments made to general practitioners for the management of type 2 diabetes, hypertension, dyslipidemia and other chronic diseases24. Furthermore, the management of type 2 diabetes in general practice is very much guideline-driven17-19.

The recent Asia Pacific Cohort Studies Collaboration meta-analysis25 involving nearly 1 million participants showed that after controlling for major vascular risk factors, diabetes roughly
### Table 3 | Standardized mortality ratio for heart disease, stroke and cancer by age band and sex for patients with type 2 diabetes

| Age (years) | SMR (95% CI) | SMR (95% CI) | SMR (95% CI) |
|-------------|--------------|--------------|--------------|
|             | Heart disease | Stroke       | Cancer       |
| <25         |               |              |              |
| 25–34       |               |              |              |
| 35–44       |               |              |              |
| 45–54       |               |              |              |
| 55–64       |               |              |              |
| 65–74       |               |              |              |
| 75–84       |               |              |              |
| ≥85         |               |              |              |
| Overall     |               |              |              |

*The 95% confidence intervals (CI) calculated using Byar’s method*, which is accurate for observed frequencies of five or more. For smaller observed frequencies, an exact method based on the Poisson distribution is used. *Scottish mortality rates estimated from National Records of Scotland Vital Events Reference Tables 2015: Death rates, by sex and age, Scotland, 2001 to 2014 from ischemic heart disease (Table 6.8) https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2015/section-6-deaths-causes (accessed 16/11/17). *Scottish mortality rates estimated from National Records of Scotland Vital Events Reference Tables 2015: Death rates, by sex and age, Scotland, 2001 to 2014 from cerebrovascular disease (Table 6.9) https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2015/section-6-deaths-causes (accessed 16/11/17). *Scottish mortality rates estimated from National Records of Scotland Vital Events Reference Tables 2015: Death rates, by sex and age, Scotland, 2001 to 2014 from malignant neoplasms (all sites) (Table 6.6) https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2015/section-6-deaths-causes (accessed 16/11/17). NS, not significant; SMR, standardized mortality ratio.

### Table 4 | Cause of death by duration of diabetes diagnosis

| Cause of death              | Duration of DM diagnosis | Total |
|-----------------------------|--------------------------|-------|
|                             | <5 years                 | 5–10 years | ≥10 years |
| Cancer                      | 31.3% (198)              | 29.0% (228) | 23.2% (162) | 27.8% (588) |
| Heart disease               | 22.5% (142)              | 25.2% (198) | 24.2% (169) | 24.1% (509) |
| Respiratory                 | 14.9% (94)               | 11.5% (90)  | 13.2% (92)  | 13.0% (276) |
| Stroke                      | 7.1% (45)                | 8.7% (68)   | 9.6% (67)   | 8.5% (180)  |
| Sepsis                      | 4.9% (31)                | 6.2% (49)   | 6.4% (45)   | 5.9% (125)  |
| Decompensated diabetes      | 3.5% (22)                | 3.9% (31)   | 5.7% (40)   | 4.4% (93)   |
| Mental health               | 4.1% (26)                | 3.9% (31)   | 4.0% (28)   | 4.0% (85)   |
| Renal failure               | 1.7% (11)                | 2.5% (20)   | 3.3% (28)   | 2.6% (54)   |
| Accident/liver/neurological/other | 10.0% (63)          | 9.0% (71)   | 10.3% (72)  | 9.7% (206)  |
| Total                       | 632                      | 786         | 698          | 2116        |

DM, diabetes.
The researchers found that diabetes conferred an increased risk of mortality for all age groups studied, particularly in women. The risk conferred by diabetes was especially high among women aged 35–59 years, with a nearly sixfold higher occlusive vascular death rate in this age group. Absolute vascular death rates were higher for men with diabetes than for women with diabetes. As women without diabetes have the best prognosis, diabetes conferred a higher relative risk among women than among men. In that meta-analysis, the death relative risks for cancer mortality were considerably smaller (relative risk 1.17) than for vascular causes, and did not differ between men and women with diabetes.

Cancer is the second leading cause of death worldwide, and is recognized in the UK and USA to be more common in men than women. The present study is the first study to show that cancer is the major contributing cause of the increase in all-cause mortality seen in type 2 diabetes patients in the UK. In men with type 2 diabetes, the increase in cancer SMR was not significantly greater than in men without diabetes. In women with type 2 diabetes, the increase in cancer SMR was significantly greater than in women without diabetes. This might reflect both an increase in cancer prevalence and an improvement in the management and outcome of cardiovascular disease in women with type 2 diabetes.

Obesity, type 2 diabetes and cancer appear to be linked. A recently published meta-analysis, including 20 million individuals, showed that diabetes is a risk factor for all-site cancer for both men and women, and the excess risk of cancer, as in the present study, was greater for women than men. Type 2 diabetes and cancer have many modifiable risk factors in common, including obesity, physical activity, diet, alcohol, smoking and long latency periods before clinically manifesting. Type 2 diabetes appears to be an independent risk factor for pancreatic, endometrial, liver, colorectal, bladder and breast cancer. Possible mechanisms linking diabetes with cancer include hyperglycemia and hyperinsulinemia (endogenous or exogenous), plus alterations of the insulin-like growth factor system, chronic subclinical inflammation, abnormalities in sex hormone metabolism, adipokines and possibly antidiabetes medication used in the management of type 2 diabetes. In addition, hyperglycemia might induce oxidative stress, which could promote the formation and expression of advanced glycation products and their receptors. This interaction could activate numerous cell signaling pathways, which promote carcinogenesis and cell invasion. Furthermore, through multiple cellular signaling cascades, enhanced insulin and insulin-like growth factor could promote cell proliferation and growth. The sex differences for the associations of diabetes and some cancers (e.g., gastrointestinal) might be shown through several alternative underlying mechanisms. The sex differences could be attributable to poorer glycemic control in women, longer period of “prediabetes” in women and various sex hormone-binding globulins, which might affect the bioavailability of estrogen in both sexes and bioavailable

---

**Table 5** | Standardized mortality ratio by all causes and specific mortalities

| Duration of DM diagnosis | All causes<sup>§</sup>(95% CI) | Heart disease<sup>§</sup>(95% CI) | Stroke<sup>§</sup>(95% CI) | Cancer<sup>¶</sup>(95% CI) |
|--------------------------|-------------------------------|-----------------------------|-------------------|-------------------|
|                          | n = 2116                      | n = 404                     | n = 180           | n = 588           |

| Men                      |                               |                             |                   |                   |
|--------------------------|-------------------------------|-----------------------------|-------------------|-------------------|
| <5 years                 | 120 (107–1,330)               | 132 (103–1,167)             | 114 NS (73–1,172) | 115 NS (95–1,137) |
| 5–10 years               | 138 (125–1,151)               | 175 (143–1,212)             | 123 NS (82–1,176) | 113 NS (94–1,135) |
| 10 years                 | 106 NS (96–1,117)             | 118 NS (94–1,147)           | 126 NS (88–1,175) | 75 (61–1,92)      |

| Women                    |                               |                             |                   |                   |
|--------------------------|-------------------------------|-----------------------------|-------------------|-------------------|
| <5 years                 | 130 (116–1,146)               | 154 (107–1,212)             | 98 NS (62–1,149)  | 108 NS (85–1,134) |
| 5–10 years               | 143 (129–1,159)               | 195 (146–1,253)             | 148 (105–1,202)   | 126 (103–1,154)   |
| 10 years                 | 120 (107–1,134)               | 214 (165–2,274)             | 107 NS (73–1,153) | 78 (60–1,99)      |

<sup>§</sup>Scottish mortality rates estimated from National Records of Scotland Vital Events Reference Tables 2015: Death rates, by sex and age, Scotland, 2001 to 2014 https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2015/section-5-deaths/ (accessed 15/11/17).

<sup>¶</sup>Scottish mortality rates estimated from National Records of Scotland Vital Events Reference Tables 2015: Death rates, by sex and age, Scotland, 2001 to 2014 from ischemic heart disease (Table 6.8) https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2015/section-6-deaths-causes/ (accessed 16/11/17).
testosterone in women. In addition, the increased mortality as a result of cancer in type 2 diabetes patients has been attributed to the cancer treatments, underlying disease, anti-diabetes medication, plus acute and chronic complications of diabetes, such as renal and cardiovascular diseases.

Mortality rates and causes of death in patients with type 2 diabetes vary according to ethnicity. The mortality caused by CVD, which was the leading cause of death among diabetes patients in the USA, declined by 32% every 10 years among people with type 2 diabetes. The rate of decline of CVD death was significantly greater among those with type 2 diabetes than those without diabetes. Approximately 70% of the participants in that study were non-Hispanic white people, and the decrease of the death rate due to CVD was consistent with the results of studies undertaken in white people reported in other developed countries.

In Japan, however, the proportion of total deaths from cancer in patients with type 2 diabetes has continued to rise and exceeds that from vascular causes (proportion of deaths in patients with diabetes in 2001–2010: vascular disease 14.9%, cancer 38.3%) This increase in cancer death among type 2 diabetes patients has continued, despite the proportion of total deaths due to cancer in the general population slightly decreasing over this period.

One of the major strengths of the present study was the accuracy of the general practice data collected. Limitations in using death certificate data are well recognized with most of the attention being focused on whether or not the death certificates in people with diabetes refer to the diabetes. In the present study we knew which individuals had type 2 diabetes and therefore diabetes did not have to appear on the death certificate. The present study had a number of limitations. The study was not large enough to investigate the types of cancer associated with type 2 diabetes. In addition, we were unable to determine the pre-morbid body mass index, level of glycemic control, the diabetes complications plus the antidiabetic medication that the patients were taking.

Understanding the primary cause of excess mortality in type 2 diabetes patients is important in order to determine the interventions needed to decrease mortality rates. Further intervention is still required to reduce CVD death in both men and women. Why cancer death is more common in women with type 2 diabetes compared with women without diabetes is not clear and requires further investigation. Obesity appears to increase the risk of both diabetes and cancer, making lifestyle change even more important. Should greater consideration be given for cancer as a complication of diabetes and screening integrated into the follow up of patients with type 2 diabetes, particularly women? The present study was undertaken in a relatively deprived area of Scotland, where the uptake of antihypertensive medication and statin therapy is high, and the population predominantly Caucasian (>98%). Further work is required to investigate the links between diabetes and cancer, types of cancer, and the role of modifiable and non-modifiable risk factors, including hyperinsulinemia, hyperglycemia, antidiabetes medication, obesity and ethnicity.

ACKNOWLEDGMENT
The statistical analysis was funded by AstraZeneca.

DISCLOSURE
AC has received speaker fees from Sanofi, Novo, Lilly, AstraZeneca, Norgine and Bayer, and educational grants from Lilly, AstraZeneca, Norgine and Bayer. CM has received speaker fees from Sanofi, and a travel grant from Sanofi and AstraZeneca. JB has received speaker fees from Sanofi, Novo, Lilly and AstraZeneca. The other authors declare no conflict of interest.

REFERENCES
1. Mulnier HE, Seaman HE, Raleigh VS, et al. Mortality in people with type 2 diabetes in the UK. Diabetic Med 2006; 23: 516–521.
2. Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among U. S. adults with and without diabetes between 1997 and 2006. Diabetes Care 2006; 35: 1252–1257.
3. Seshasai SR, Kaptoge S, Thompson A, et al. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364: 829–841.
4. Tancredi M, Rosengren A, Svensson A-M, et al. Excess mortality among persons with Type 2 diabetes. N Engl J Med 2015; 373: 1720–1732.
5. Lind M, Garcia-Rodriguez LA, Booth GL, et al. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. Diabetologia 2013; 56: 2601–2608.
6. Thomas R, Palumbo P, Melton U, et al. Trends in the mortality burden associated with diabetes mellitus: a population-based study in Rochester, Minn, 1970-1994. Arch Intern Med 2003; 163: 445–451.
7. Preis SR, Pencina ML, Hwang SJ, et al. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. Circulation 2009; 120: 212–220.
8. Gregg EW, Cheng YJ, Srinivasan M, et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national and vital statistics data. Lancet 2018; 391: 2430–2440.
9. Ford ES. Trends in the risk for coronary heart disease among adults with diagnosed diabetes in the U.S.: findings from the National Health and Nutrition Examination Survey, 1999-2008. Diabetes Care 2011; 34: 1337–1343.
10. Olafsdottir E, Aspelund T, Sigurdsson G, et al. Similar decline in mortality rate of older persons with and without type 2 diabetes between 1993 and 2004 the Icelandic population-based Reykjavik and AGES-Reykjavik cohort studies. BMC Public Health 2013; 3: 36.
11. Mensah GA, Wei GS, Sorlie PD, et al. Decline in cardiovascular mortality: possible causes and implications. Circ Res 2017; 120: 366–380.

12. Harding JL, Shaw JE, Peeters A, et al. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997-2010. Diabetes Care 2015; 38: 2579–2586.

13. Gæde P, Lund-Andersen H, Parving HH, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008; 358: 580–591.

14. Faerch K, Carstensen B, Almdal TP, et al. Improved survival among patients with complicated type 2 diabetes in Denmark: a prospective study (2002–2010). J Clin Endocrinol Metab 2014; 99: E642–E664.

15. Tsunekawa S, Kamiya H, Nakamura J. Different trends in causes of death in patients with diabetes between Japan and the USA. J Diabetes Investig 2019; 10: 571–573.

16. Nakamura J, Kamiya H, Haneda M, et al. Causes of death in Japanese patients with diabetes based on the results of a survey of 45,708 cases during 2001-2010: Report of the Committee on causes of Death in Diabetes Mellitus. J Diabetes Investig 2017; 8: 397–410.

17. American Diabetes Association. Standards of medical care in diabetes – 2018. Diabetes Care 2018; 41(Suppl 1): S38–S50.

18. SIGN guideline 116: management of diabetes. sign.ac.uk/ guidelines/fulltext/116. ISBN 978 1 905813 58 2 (March 2010).

19. Type 2 diabetes in adults: management NICE guideline [NG28] Published date: December 2015 Last updated: May 2017. Available from: https://www.nice.org.uk/guidance/ng2820 Accessed November 2, 2018.

20. WHO. International classification of diseases. 11th Revision (ICD-11).

21. Breslow NE, Day NE. Statistical Methods in Cancer Research, Volume II: The Design and Analysis of Cohort Studies. IARC Sci Publ. 1987:1–406.

22. Goldblatt P. Longitudinal Study, Mortality and Social Organisation. Series LS no 6. HMSO London, 1990. Table 3.7, p58.

23. Read SH, Kerssens JJ, McAllister DA, et al. on behalf of the Scottish Diabetes Research Network Epidemiology Group Trends in type 2 diabetes incidence and mortality in Scotland between 2004 and 2013. Diabetologia 2016; 59: 2106–2121.

24. British Medical Association and NHS Employers. Quality and Outcomes Framework guidance for GMS contract 2009/10. Available from: http://www.lmc.org.uk/visagework/guidance/2009/qofguidance200910 mar09.pdf Accessed June 9, 2018.

25. Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980793 adults from 68 prospective studies. Lancet Diabetes Endocrinol 2018; 6: 538–546.

26. GBD 2015 Mortality and Causes of Death Collaboration. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015; a systematic analysis for the Global burden of Disease Study 2015. Lancet 2016; 388: 1459–1544.

27. Dorak MT, Karpuozoglu E. Gender differences in cancer susceptibility: an inadequately addressed issue. Front Genet 2012; 3: 268.

28. Giovannucci E, Harlan DM, Archer MA, et al. Diabetes and cancer. A consensus report. Diabetes Care 2010; 33: 1674–1685.

29. Ohkuma T, Peters SAE, Woodward M. Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events. Diabetologia 2018; 61: 2140–2154.

30. van Kruitjeldijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev 2009; 18: 2569–2578.

31. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer 2009; 9: 798–809.

32. Fang H-J, Shan S-b, Zhou Y-h, et al. Diabetes and the risk of gastrointestinal cancer compared with men: a meta-analysis of cohort studies. BMC Cancer 2018; 18: 422–439.

33. Rojas A, González I, Morales E, et al. Diabetes and cancer: looking at the multiligand/RAGE axis. World J Diabetes 2011; 2: 108–113.

34. Abe R, Yamagishi S. AGE-RAGE system and carcinogenesis. Curr Pharm Des 2008; 14: 940–945.

35. Adachi Y, Yamamoto H, Ohashi H, et al. A candidate targeting molecule of insulin-like growth factor-I receptor for gastrointestinal cancers. World J Gastroenterol 2010; 16: 5779–5789.

36. Lorenzi M, Montisano DF, Toledo S, et al. High glucose induces DNA damage in cultured human endothelial cells. J Clin Invest 1986; 77: 322–325, 335.

37. Brenner H. Limitations of the death certificate only index as a measure of incompleteness of cancer registration. Br J Cancer 1995; 72: 506–510.

38. Scottish Diabetes Survey 2017. Available from: https://www.diabetes.org.uk/statistics/diabetes-prevalence-2017 Accessed May 5, 2018.