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Metformin and survival of people with type 2 diabetes and pleural mesothelioma: A population-based retrospective cohort study

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ABSTRACT

Objectives: This study aimed to investigate the effect of metformin on survival of people with type 2 diabetes and pleural mesothelioma.
Materials and methods: We conducted a retrospective cohort study of people with type 2 diabetes diagnosed with pleural or unspecified mesothelioma between 1993 and 2014 using linked Scottish population-based diabetes and cancer datasets. Kaplan-Meier plots, log-rank tests, and Cox proportional hazards regression models were used to describe the association between use of metformin and all-cause mortality following diagnosis of pleural mesothelioma.
Results: There were 300 people with type 2 diabetes and pleural or unspecified mesothelioma of whom 148 had ever used metformin and 290 died during follow up. The median survival time was 8.8 months and 6.5 months for metformin users and non-users respectively ($p = 0.37$, log-rank test). After adjusting for age, sex, diabetes duration, socio-economic status, and other anti-diabetic medications the hazard ratio for mortality associated with metformin was 0.99 (95% confidence intervals: 0.76–1.28; $p = 0.92$). Similar non-statistically significant associations were obtained in sensitivity analyses based on metformin use in year prior to diagnosis of mesothelioma, use of metformin for more than one year, in people below the mean age at diagnosis of mesothelioma (74 years) and 74 years of age or older, limitation to pleural mesothelioma and following further adjustment for body mass index and smoking.
Conclusion: There was no evidence that metformin improved survival among people with type 2 diabetes and pleural mesothelioma or to support trials of metformin in people with mesothelioma.

1. Introduction

Pleural mesothelioma is a rare and aggressive cancer of the pleura, and is mainly caused by exposure to asbestos with a mean latency time between 30 and 40 years in most people [1–3]. Its worldwide incidence has increased dramatically since the 1950s and is predicted to peak between 2015 and 2030 in industrialized countries [4]. The cancer is rapidly fatal and most affected patients die within one year of diagnosis with a median survival of about 9–12 months [5,6]. At present, long-term survival for pleural mesothelioma are extremely rare [7].

Epidemiologic evidence indicates that diabetes is strongly associated with both cancer incidence and mortality [8,9]. It is believed that approximately 8–18% of cancer patients have concurrent diabetes, and pre-existing diabetes increases the risk of death by as much as 41% in cancer patients [10,11]. Metformin is a widely prescribed oral hypoglycemic agent that is currently used as the first-line pharmacological therapy for type 2 diabetes [12]. Studies have suggested that metformin may have anti-cancer effects and its prescription has been reported to be associated with improved survival in the treatment of diabetic patients with several types of cancers [13–15]. Several studies of the association between metformin and cancer have been influenced by bias, such as immortal time bias, time-window bias and time-lag bias, but trials of metformin in lung cancer are in progress [16]. For lung cancer, it is reported that metformin inhibits NSCLC tumour growth

Abbreviations: SCI-diabetes, Scottish care information-diabetes; NHS, national health service; NRS, national records Scotland; SES, socioeconomic status; SIMD, Scottish index of multiple deprivation; BMI, body mass index.

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and enhances the effects of radiotherapy and chemotherapy, but enhanced radiosensitivity in SCLC associated with metformin was found only in vitro [17–19]. Currently, metformin has been suggested to be a clinically useful adjunct to radiotherapy and chemotherapy in NSCLC and most studies have indicated that the prognosis of lung cancer patients with diabetes treated with metformin was improved, though the results are still inconsistent between different studies [20–25].

To date, there have been no studies reporting the association between metformin use and survival following pleural mesothelioma. This study aimed to investigate the effect of metformin on survival following pleural mesothelioma in people with type 2 diabetes in Scotland. We hypothesized that metformin use would be associated with improved survival as compared with non-use in people with type 2 diabetes and pleural mesothelioma.

2. Material and methods

2.1. Study design and data collection

We performed a retrospective cohort study of 300 people with type 2 diabetes diagnosed with pleural (ICD10 code C45.0) or unspecified (C45.9) mesothelioma between 1993 and 2014 in Scotland, of whom 39 cases had mesothelioma at unspecified sites. During this period there were 15 cases of peritoneal mesothelioma that were not included in the analysis due to the small numbers. Our initial assumption was that the majority of people with unspecified mesothelioma would have pleural mesothelioma.

Population-based data are available for people diagnosed with diabetes in Scotland (2014 population 5.3 million) from the Scottish Care Information-Diabetes (SCI-Diabetes) database (previously known as SCI-DC), an electronic patient record of National Health Service (NHS) Scotland patients with diabetes [26]. The database has existed at a national level since 2000 and contains information for over 99% of diagnosed patients with diabetes in Scotland, including detailed demographic and clinical information relevant to diabetes care. The Scottish Cancer Registry was set up in 1958 and has been managed by Information Services Division of NHS National Services Scotland since 1997. The registry receives notification of cancer from hospital patient administration systems, screening datasets, death records from National Records of Scotland (NRS), private hospitals and community prescribing, covering all residents in Scotland that have had a diagnosis of cancer.

An area-based measure of socioeconomic status (SES) can be assigned to patients with diabetes on the basis of where they live by using the Scottish Index of Multiple Deprivation 2012 (SIMD) (see http://scotland.gov.uk/Topics/Statistics/SIMD for more information). The 2012 version of the SIMD combines seven domains of employment, income, health, education, geographic access to service, crime and housing. The overall index is a weighted sum of these seven domain scores for each datazone, a Census derived geographic area with a population between 500 and 1000. Quintiles of the index were defined at a national level, and Q1 and Q5 were used to identify the most and least deprived fifths of the population, respectively.

The data used in this study were obtained from a 2014 extract of the SCI-Diabetes database, which were then linked to the Scottish Cancer Registry and Scottish Mortality Records using a unique patient identifier, the Community Health Index. Approval for the generation and analysis of the linked dataset was obtained from the SCI-Diabetes steering committee, the Scottish multicenter research ethics committee, the Privacy Advisory Committee of NHS National Service Scotland, and Caldicott guardians of all NHS Boards in Scotland. The linked data contained information on patients' sex, age at diagnosis of mesothelioma, body mass index (BMI), smoking status, date of diagnosis of mesothelioma, date of diagnosis of diabetes, anatomical sub-site of mesothelioma, type of diabetes, and date of death. Patients with diabetes had their BMI measured on repeated occasions, and the BMI used in the study was the one recorded prior and closest to diagnosis with mesothelioma. Patients' smoking history was recorded as never, former and current at the closest point in time before mesothelioma was diagnosed. Mesothelioma diagnoses were identified in the cancer registry from International Classification of Disease tenth revision (ICD-10) code C45. Type of diabetes was confirmed by an algorithm using age at diagnosis and use and timing of treatment with oral hypoglycaemic agents and insulin [27]. Exposure to metformin, insulin, sulphonylureas and other diabetes treatments including acarbose, exenatide, linagliptin, liraglutide, miglitol, nateglinide, pioglitazone, repaglinide, rosiglitazone, saxagliptin, sitagliptin and vildagliptin, was defined as ever exposure to the medication prior to diagnosis with mesothelioma.

Survival was measured from date of mesothelioma diagnosis until the earliest of date of death or 13th June 2014, the latest date of death recorded in the 2014 SCI-Diabetes extract.

2.2. Statistical analysis

The baseline demographic and clinical characteristics of people at the diagnosis of mesothelioma were compared between metformin users and non-users using *t*-tests for continuous data and chi-square tests for categorical data. Survival curves for the two groups were estimated using the Kaplan-Meier method and compared by a log-rank test. Both univariate and multivariate Cox proportional hazards models were fitted to assess the association between metformin use and overall survival and to evaluate potential independent predictors of survival by estimating hazard ratios (HR) with 95% confidence intervals (CI). The variables included in the Cox proportional hazards models were age, sex, diabetes duration, metformin (ever or never), insulin (ever or never), sulphonylureas (ever or never), other anti-diabetic medications (ever or never) and SIMD (in quintiles labeled 1 (most deprived) to 5 (least deprived)). Patients alive at the end of follow-up were censored. The proportional hazards assumption in the Cox model was explored using the Cox time-dependent covariate test by adding an additional term representing the interaction of metformin status with survival time to the Cox model.

2.3. Sensitivity analyses

Sensitivity analyses were carried out to explore the effects of excluding unspecified mesothelioma, duration of metformin prescriptions (>1 year and $\leq$1 year), age below and above the mean at diagnosis of mesothelioma (<74 years and $\geq$74 years) and missing data for BMI or smoking status on survival of patients to confirm whether it was appropriate to report the primary analysis based on the pleural or unspecified mesothelioma population regardless of duration of metformin treatment, age group, or the availability of BMI or smoking status. All analyses were conducted using SPSS version 21 and a two-tailed p-value < 0.05 was considered statistically significant.

3. Results

Among 300 people with a diagnosis of pleural or unspecified mesothelioma, 148 (49.3%) were identified as having been ever prescribed metformin prior to diagnosis with mesothelioma. Demographic and clinical characteristics by metformin exposure status are described in Table 1. The mean (SD) age and duration of diabetes (SD) of the whole cohort was 74 (7.8) years and 8 (6.1) years, respectively. 4.7% of patients' records suggested that

Table 1
Demographic and Clinical Characteristics of Patients Close to Diagnosis of Pleural or Unspecified Mesothelioma for People Ever and Never Prescribed Metformin Prior to Diagnosis with Mesothelioma in Scotland 1993–2014.

Variable	Metformin prescription record (n = 148)	No record of metformin prescription (n = 152)	*P*-value
Sex			0.56
Male	124 (83.8%)	131 (86.2%)	
Female	24 (16.2%)	21 (13.8%)	
Age (years)			
Average (mean ± SD)	74 ± 6.9	74 ± 8.6	0.95
BMI (kg/m^2)			
Average (mean ± SD)	29 ± 3.8	27 ± 4.1	<0.001
Normal (<25)	20 (14.4%)	36 (29.3%)	0.002
Overweight (25–30)	65 (46.8%)	59 (48.0%)	
Obese (≥30)	54 (38.8%)	28 (22.8%)	
Smoking status			0.52
Never	53 (37.9%)	38 (31.1%)	
Former	66 (47.1%)	63 (51.6%)	
Current	21 (15.0%)	21 (17.2%)	
Diabetes duration (years) (mean ± SD)	9.7 ± 5.9	6.4 ± 5.9	<0.001
Anti-diabetic medication			
Insulin	11 (7.4%)	3 (2.0%)	0.03
Sulphonylureas	82 (55.4%)	50 (32.9%)	<0.001
Others	41 (27.7%)	6 (3.9%)	<0.001
SIMD			0.45
1 (most deprived)	47 (31.8%)	44 (28.9%)	
2	24 (16.2%)	34 (22.4%)	
3	31 (20.9%)	22 (14.5%)	
4	25 (16.9%)	29 (19.1%)	
5 (least deprived)	21 (14.2%)	23 (15.1%)	

BMI and smoking data were missing for 9 and 8 people in the metformin group and 29 and 30 people in the non-metformin group, respectively.

Table 2
Hazard Ratios (HR) Estimated from Univariate and Multivariate Cox Proportional Hazards Models for All-Cause Mortality among People with Pleural or Unspecified Mesothelioma and Type 2 Diabetes in Scotland 1993–2014.

	Univariate		Multivariate	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male vs. female)	1.02 (0.74, 1.42)	0.88	1.06 (0.76, 1.49)	0.72
Age (per year increase)	1.03 (1.01, 1.05)	<0.001	1.03 (1.02, 1.05)	<0.001
Diabetes duration (per year increase)	0.998 (0.996, 1.000)	0.027	0.997 (0.995, 1.000)	0.018
Anti-diabetic medication				
Metformin (ever vs. never)	0.90 (0.71, 1.14)	0.37	0.99 (0.76, 1.28)	0.92
Insulin (ever vs. never)	0.95 (0.53, 1.69)	0.85	1.28 (0.65, 2.50)	0.48
Sulphonylureas (ever vs. never)	1.06 (0.84, 1.34)	0.63	1.18 (0.91, 1.52)	0.21
Others (ever vs. never)	0.82 (0.60, 1.14)	0.24	0.87 (0.58, 1.30)	0.50
SIMD				
1 (most deprived)	1.0		1.0	
2	1.05 (0.75, 1.47)	0.76	1.04 (0.74, 1.46)	0.84
3	0.85 (0.60, 1.21)	0.36	0.90 (0.62, 1.31)	0.58
4	1.05 (0.74, 1.48)	0.79	1.11 (0.79, 1.57)	0.55
5 (least deprived)	0.91 (0.63, 1.32)	0.62	0.93 (0.64, 1.36)	0.72

they had received insulin monotherapy, 44.0% had been prescribed sulphonylureas, 15.7% had ever received prescriptions for other anti-diabetic medications and 33.3% had no record of receiving any type of anti-diabetic medication. Data for BMI and smoking status were missing for 38 people. Most of the patients were men (85.0%) and a history of smoking was common (57.0%). Statistically significant differences in characteristics between people prescribed metformin and those not prescribed metformin included higher BMI (29 ± 3.8 kg/m^2 compared to 27 ± 4.1 kg/m^2; $p < 0.001$), longer diabetes duration (9.7 ± 5.9 years compared to 6.4 ± 5.9 years; $p < 0.001$), and higher prevalence of prescription of insulin (7.4% compared to 2.0%; $p = 0.03$), sulphonylureas (53.9% compared to 33.3%; $p < 0.001$) and other anti-diabetic medications (24.5% compared to 2.2%; $p < 0.001$).

A date of death was available for 290 patients, and 10 patients were censored at the end of follow-up. The median follow-up duration was 7.5 months for the whole cohort. Metformin users had a higher median overall survival (8.8 months; 95% CI: 7.6–10.0) compared with non-users (6.5 months; 95% CI: 5.3–7.7), however the difference in survival between the two groups was not statistically significant (log-rank test $p = 0.37$) (Fig. 1).

A univariate Cox proportional hazards analysis showed that there was no significant difference (HR = 0.90; 95% CI: 0.71–1.14; $p = 0.37$) in all-cause mortality between metformin users and non-users, and the results were similar when adjusted for age, sex, diabetes duration, anti-diabetic medications and SIMD (adjusted HR = 0.99; 95% CI: 0.76–1.28; $p = 0.92$) (Table 2). In addition, both unadjusted and adjusted Cox proportional hazards analyses indicated that age and diabetes duration were significant predictors of all-cause mortality in the study population, with an adjusted HR of 1.03 (95% CI: 1.02–1.05; $p < 0.001$) per year of age and an adjusted HR of 0.997 (95% CI: 0.995–1.000; $p = 0.018$) per year of duration of type 2 diabetes. The Cox time-dependent covariate test suggested that the proportional hazard assumption was met for the model with $p = 0.86$ for the term representing the interaction of metformin status with survival.

In analyses stratified by duration of metformin use, 119 patients had metformin duration more than one year and 29 patients used metformin for one year or less. Neither long-term (>1 year) nor

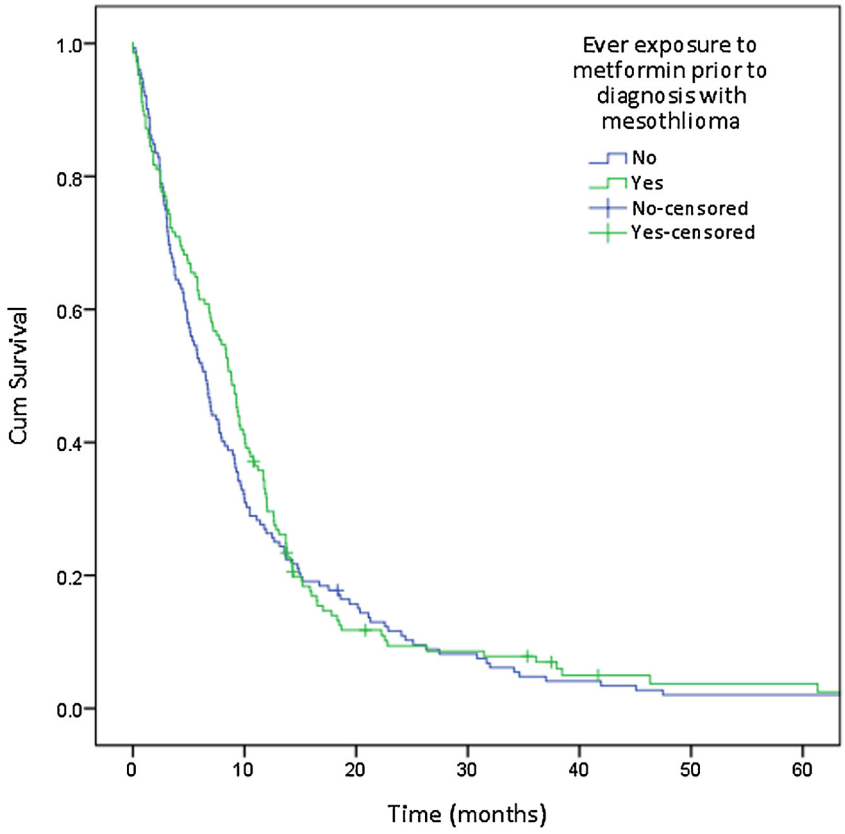

Fig. 1. Kaplan-Meier survival curves for metformin users and non-users. P-value (log-rank test) was 0.37.

Table 3
Duration of Metformin Use and Survival of People with Pleural or Unspecified Mesothelioma and Type 2 Diabetes in Scotland 1993–2014.

Metformin use	No. of patients	Median survival (month)	HR[a] (95% CI)	*p*-Value
Never	152	6.5	1	
≤1 year	29	9.5	0.86 (0.56, 1.31)	0.48
>1 year	119	8.5	1.04 (0.79, 1.37)	0.79

[a] Adjusted for age, sex, diabetes duration, anti-diabetic medication and SIMD.

short-term (≤1 year) metformin use had a statistically significant effect on all-cause mortality (Table 3).

Sensitivity analyses gave similar findings for survival when defining exposure as metformin use in one year prior to diagnosis of mesothelioma (adjusted HR = 0.92; 95% CI: 0.71–1.18; $p = 0.49$), in people aged less than 74 years (adjusted HR = 1.12; 95% CI: 0.76–1.66; $p = 0.57$) or people aged 74 years or older (adjusted HR = 0.79; 95% CI: 0.55–1.16; $p = 0.23$), or excluding people with mesothelioma at unspecified sites (adjusted HR = 0.89; 95% CI: 0.68–1.17; $p = 0.41$) and further adjusting for BMI or smoking status (HR = 0.91; 95% CI: 0.68–1.23; $p = 0.55$) among the sub-set of people with available data. As a consequence we believe the results of the primary analysis were robust in regard to these characteristics.

4. Discussion

In this retrospective cohort study of 300 cases of pleural or unspecified mesothelioma among people with type 2 diabetes in Scotland with a median follow-up of 7.5 months, we found that there was no statistically significant association between metformin use and survival of people with type 2 diabetes and pleural mesothelioma.

To our knowledge, this is the first study to examine the association between metformin use and survival following pleural mesothelioma among people with type 2 diabetes. The age-standardized incidence rate of mesothelioma in Scotland was 1.8/100,000 in 2013 [28]. Although the sample size of the study is not large, this is unavoidable due to the rare incidence of mesothelioma. The UK has the highest burden of mesothelioma in the world [29]. As a consequence, using Scottish data has more power than studies performed in many other countries because at present it is not possible to link prescribing data to cancer registry data at a population level in England. We included people with mesothelioma at unspecified sites and who had missing data for BMI or smoking status to keep the study sample size as large as possible and sensitivity analyses showed that this made little difference to estimates of the effect of metformin on survival. Furthermore, restriction of the study to people with type 2 diabetes reduced the risk of confounding by type of diabetes. Many observational studies in pharmacoepidemiology have been influenced by time-related bias [16]. We defined the exposure as metformin ever used prior to diagnosis of pleural mesothelioma, and measured patients' survival time starting from the diagnosis of pleural mesothelioma, thus, immortal time bias should not be a potential issue, in contrast to studies whose starting point is the diagnosis of diabetes. Additionally, the cohort study design avoided time-window bias which usually arises in case-control studies [30].

Despite our efforts to make this study comprehensive, limitations need to be noted. Firstly, the present study had a relatively small sample size and therefore provides imprecise estimates of effect size. This means that metformin could be associated with anything between a 23.6% reduction and a 27.5% increase in the hazard of mortality compared to those not treated with metformin.

Secondly, due to the use of routine health care records, data for the study were not complete. Thus, bias from an absence of

data on potential confounding factors is possible. Data on mesothelioma stage or histological sub-type were not available in the present study. Lack of adjustment for mesothelioma stage may have underestimated the association between metformin and survival if patients who received metformin prescription had a more advanced stage of pleural mesothelioma at diagnosis. Furthermore, Lee et al., found that the effect of metformin on survival in colorectal cancer was only statistically significant in patients with stage 3 tumours [29]. Without information on mesothelioma stage, it is uncertain whether a beneficial effect of metformin might have been observed for tumours of a specific stage. Some published studies suggest that metformin may work by preventing tumour progression, so that ever- or never- use of metformin may be less relevant than cumulative metformin use [31–33]. In this study, efforts were also made to extend measures of metformin use beyond a simple ever- or never-use classification to determine whether more sophisticated exposure measures might be feasible. Furthermore, Spillane and colleagues found significant associations between metformin exposure and colorectal cancer-specific mortality was only for high-intensity exclusive metformin use [34]. However the limited power of our study means that further stratification of the exposure data was not possible. Assessment of deprivation was based on the 2011 version of SIMD while the earliest mesothelioma case was recorded in 1994. As a result, the classification of socioeconomic status may not reflect the situation in 1994.

Additionally, assessment of BMI and smoking status was based on the most recently recorded value prior to the diagnosis of pleural mesothelioma, which may not have reflected values at the point of mesothelioma diagnosis. This could have contributed to residual confounding of the association between metformin exposure and survival outcomes by these factors.

Although the risk of selection bias was minimized by including all patients recorded in administrative databases for almost the whole population of Scotland, the findings may not apply to people with mesothelioma in other populations, including people without diabetes. The patient cohort had an average age of 74 years at the diagnosis of pleural mesothelioma, which was four years older than the mean age at death described in a previous study, and also a higher proportion of male patients were included in this study with male to female ratio of about 5.7:1 compared with the previously reported ratio of 3.6:1 [35]. It is not clear whether the findings of this study would apply outside Scotland. Other limitations include the lack of information on comorbidities, glucose control, and mesothelioma treatments in the dataset. As a result the possibility of confounding by these factors remains.

All forms of asbestos cause pleural mesothelioma, and there is no safe level of exposure to asbestos [2,36,37]. Even if metformin has a survival benefit in pleural mesothelioma as found in other studies, the prevention of asbestos exposure is likely to be much more important in reducing mortality. Currently, asbestos is banned in 55 countries including most developed countries. However, the world's production and consumption of asbestos is increasing at an alarming rate, with more than 70% of production in developing countries [38]. The only way to eliminate asbestos-related diseases is to eliminate the use of all forms of asbestos as exposure to asbestos cannot be adequately controlled by technology or by regulation of work practices. Achieving a universal ban on the use of asbestos is still challenging due to the significant contributions that the asbestos industry makes to the economy, especially in developing countries where it continues to be used in the construction and manufacturing sectors [39,40].

5. Conclusions

The results of our study suggest that metformin use was not associated with improvement in survival of people with type 2 diabetes and pleural mesothelioma. As yet, there is no evidence to support trials of metformin in people with mesothelioma.

Conflicts of interest

The authors declare no conflicts of interest.

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