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Abstract

Background

Although diabetes has been associated with COVID-19 mortality, its scale and relationships with modifiable risk factors including hyperglycaemia and obesity in Type 1 and Type 2 diabetes remain unclear.

Methods

National diabetes and mortality data in England identified deaths in people with Type 1 and Type 2 diabetes weekly from 1st January 2017 to 1st May 2020. Cox proportional hazards analysis investigated the relationship between risk factors and COVID-19 related death in a cohort alive on 1st January 2020 and followed to 1st May 2020.

Findings

Weekly deaths in Type 1 and Type 2 diabetes more than doubled from the week ending 3rd April 2020 exceed

The National Diabetes Audit (NDA) collates data on nearly all people with diagnosed diabetes registered with a healthcare provider in England. Individuals are included

region of residence), clinical characteristics (HbA1c, duration of diagnosed diabetes, body mass index, eGFR, smoking status) and co-morbidities (history of myocardial infarction, stroke, heart failure and hypertension).

Statistical calculations were undertaken in SAS Enterprise Guide 7.1 (https://support.sas.com/en/software/enterprise-guide-support.html). All numbers taken directly from the National Diabetes Audit are rounded to the nearest five persons to protect confidentiality.

Information governance

The National Diabetes Audit (NDA) data are collected under the terms of section 254 of the Health and Social Care Act (HSCA) for England 2012. Data are not extracted if the person has registered their dissent from permission to use their record for secondary analysis. NHS England and NHS Digital are the joint data controller for the NDA data and this has been linked with ONS mortality data and hospital episode statistics data under the terms of section 254 of the HSCA.

Data linkage and analysis are undertaken within NHS Digital and further information can be found at https://digital.nhs.uk/data-

Between 1st January 2020 and 1st May 2020 71,160 deaths from all causes were registered in people with diabetes. A total of 9795 deaths (418 in people with Type 1 and 9377 in people with Type 2 diabetes) had COVID-19 included on the death certificate and 9341 (95.4%) had COVID-19 as the underlying cause of death.

Older age and male sex were associated with a higher risk of COVID-19 related mortality (see Table 2, Figure 2). In Type 1 diabetes, risk was higher in people of Black ethnicity (HR 1·68, 95% CI 1·23-2·29) compared to the white population, and was similarly elevated in those of Asian ethnicity (HR 1·79, 95% CI 1·21-2·63). The difference in risk for those of mixed ethnicity was not statistically significant. In Type 2 diabetes, the risk was greatest for people of Black ethnicity (HR 1·63 95% CI 1·50-1·77) compared to the white population, and there was only a small increase in risk in those of Asian ethnicity (HR 1·09, 95% CI 1·02-1·17) (See Figure 2).

There was a clear relationship between COVID-19 related death and socio-economic deprivation among people with diabetes of either type. The hazard ratio for COVID-19 related mortality for people with Type 1 diabetes in the most socioeconomically deprived quintile was 1·79 (95% CI 1·24 ï 2·57) compared to people living in the least deprived area, The comparable figure for Type 2 diabetes was a HR of 1·45 (95% CI 1·35-1·56).

The degree of hyperglycaemia was strongly associated with risk of death related to COVID-19 after adjusting for other risk factors. For people with Type 2 diabetes, those with an HbA1c of 59-74 mmol/mol had a hazard ratio of 1·23 (95% CI 1·15 ï 1·32) compared with people with an HbA1c of 48-53mmol/mol. In people with Type 2 diabetes and an HbA1c of Ó86mmol/mol the HR was 1·62 (95% CI 1·48-1·79). A similar overall pattern of association was seen in people with Type 1 diabetes, but the raised risk was only statistically significant in those with an HbA1c Ó86 mmol/mol (HR 2·19 95% CI 1·46-3·29) when compared to those with a HbA1c of 48-53 mmol/mol. The hazard ratio in people with Type 2 diabetes and a low HbA1c (<48mmol/mol) was 1·11 (95% CI 1·04 ï 1·18) and a similar, but non-statistically significant risk was seen in the equivalent glycaemic control group in people with Type 1 diabetes (HR 1·22 95% CI 0·78 ï 1·91).

In this population of people with diabetes, there was a U-shaped relationship with body mass index. For those with Type 1 diabetes and a BMI of 20 kg/m

with normal renal function (eGFR Ó60). The relative risk in those with an eGFR of less than 15 was seven times that of people with normal renal function (HR 6·85 95% CI 4·65 ï 10·09). The comparable hazard ratios for people with Type 2 diabetes were 1·75 (95% CI 1·64-1·86) and 4·83 (95% CI 4·28-5·46) respectively.

A history of having a previous hospital stay for stroke and heart failure was associated with increased COVID-19 related mortality risk in both people with Type 1 and Type 2 diabetes (see Table 2). However, neither a history of myocardial infarction or having been prescribed anti-hypertensive drugs were associated with statistically significant increases in risk.

After adjustment for other risk factors, being a current smoker was associated with lower COVID-19 related mortality in the population of people with Type 2 diabetes (HR 0·63 95% CI 0·57 ï 0·69).

Discussion

Using data from the entire population of people with Type 1 and Type 2 diabetes in England, we have demonstrated that after the emergence of the COVID-19 epidemic in this country, there has been a rapid and sizeable increase in deaths from all-causes occurring in people with both Type 1 and Type 2 diabetes. The weekly number of deaths exceeded standard control limits (three standard deviations) five weeks after the first recorded death related to COVID-19 in the UK. The scale of the increased number of weekly deaths is sizeable with more than twice the number of people with diabetes dying each week after April 3rd 2020 than would be expected at this time of year. The data suggest that during this period approximately 2500 to 3000 more deaths per week have occurred in the population of people with diabetes.

In the population of people with Type 1 and Type 1 10.4 Tf1 0 0 1 239.53 614.17 Tm0 g0 G[( )] T480008869 -0.8869 -BTT480

mechanistic explanations for the association of glycaemia and COVID-19 mortality. People with diabetes are at known increased risk of many serious infections[6] and poor glycaemic control has previously been associated with serious infections and hospitalisation[7]. Hyperglycaemia is known to impair host defences including granulocyte and macrophage function that are more important in bacterial infection.

The association of BMI with risk of COVID-19 related death in the diabetes population was U-shaped. The risk was greatest for those with very high BMI with the nadir of risk being in those with a BMI 25-29·9 kg/m^2. The higher risk seen in people with lower BMI could be linked to the effect of confounding by factors that are associated with weight loss which have either not been considered in our analysis (unmeasured confounding) or for which we have only imperfectly adjusted (residual confounding). The elevated risk of COVID-19 in people with diabetes and severe obesity is marked and adds to evidence that obesity is an important risk factor for death from COVID-19 for which a number of possible mechanisms have been postulated[17].

We also observed independent associations of age, sex, ethnicity, socioeconomic status, smoking status (but in the opposite direction to that usually found in studies of mortality), and some comorbidities (renal impairment, heart failure, stroke) in people with both Type 1 and Type 2 diabetes.

Several of the associations with death related to COVID-19 in these data are with non-modifiable risk factors

This study also uses all deaths as the end point which helps to overcome concerns about measures of disease severity when just assessing deaths in hospital. The limitations of using admissions to hospital or to ICU as surrogates for disease severity, or indeed using data on deaths to assess the independent impact of diabetes status on infection with COVID-19 have been highlighted[15].

Conclusion

In conclusion, we have demonstrated that there has been a rapid and sizeable increase in deaths occurring in people with diabetes since the beginning of the COVID-19 epidemic in England. Using a cohort approach including the total populations of people with Type 1 and Type 2 diabetes in England, we have shown independent associations with deaths registered with COVID-19 and the potentially modifiable risk factors of HbA1c and BMI, as well as with risk factors which are not clinically modifiable such as age, sex, ethnicity, deprivation and pre-existing co-morbidities.

Funding

NHS England & Improvement and NHS Digital provided resources for these analyses.

Authors contributions

Tables and Figures

Figure 1a: Weekly number of deaths in people with Type 1 diabetes in England January 2017-April 2020

Figure 1b: Weekly number of deaths in people with Type 2 diabetes

Body mass index								
BMI <20	20,065	7·6%	22	5·3%	43,570	1·5%	428	4·6%

Figure 2: Forest plots showing adjusted hazard ratios for COVID-19 related death in people with Type 1 (n=265,090) and Type 2 diabetes (n=2,889,210) in England up until May 1st 2020·